

Alexey Ponomarenko* and Tatiana Korotkova*

To eat? To sleep? To run? Coordination of innate behaviors by lateral hypothalamus

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Abstract: Lateral hypothalamus (LH) is crucial for the regulation of innate behaviors, including food intake, sleep, wakefulness and locomotion. Pathologies of LH are associated with widespread sleep and eating disorders. Recent progress in several technologies, including optogenetics, multisite high-density neuronal recordings and Ca²⁺ imaging in behaving mice have enabled cell-type specific readout of activity in hypothalamus, as well as identification and manipulation of defined neuronal populations and their projections with high temporal resolution. Here we summarize recent studies characterizing the functions of orexin/hypocretin-, GABA- and MCH (melanin-concentrating hormone)-expressing LH neurons in innate behaviors. Further, we describe how top-down inputs convey information from other forebrain regions to LH and regulate innate behaviors. We then elucidate how spontaneous or optogenetically induced changes of neuronal activity in hypothalamic circuits are translated into behavior.

Keywords: Optogenetics; neuronal recording; BEHAVIOR; network oscillations; HYPOTHALAMUS

Innate behaviors, their disorders and neural substrates

Coordination of innate behaviors is instrumental for survival: a sufficient level of arousal is necessary to perform food-seeking and consumption, while hyperactivity might prevent goal-directed behavior, necessary for successful food-seeking. On the other hand, the ability to stop feeding and start locomotion is crucial to escape threats, e.g. if

a predator appears. Pathologies of innate behaviors lead to sleep and eating disorders, which are widespread in all age groups. Eating disorders are difficult to treat and extremely dangerous, displaying the highest mortality rate of all psychiatric disorders (Kaye et al., 2009). Remarkably, changes of innate behaviors are usually not isolated: patients suffering from narcolepsy or chronic sleep restriction have an increased risk of developing obesity; obesity patients have disrupted sleep patterns (Broussard and Van Cauter, 2016); the majority of patients suffering from anorexia nervosa exhibit excessive physical activity (Davis et al., 1997). Thus, understanding of neuronal regulation of innate behaviors also gains insights into mechanisms of eating and sleep disorders.

One of the key brain regions, instrumental for feeding, sleep and locomotion, is hypothalamus (Saper et al., 1997; Morton et al., 2014; Waterson and Horvath, 2015). An indication of functional specializations in hypothalamus stems from classical studies, showing that lesions or electrical stimulation of distinct parts of hypothalamus, designated as discrete anatomical “centers”, results in dramatic changes of drinking, feeding, sleep and other innate behaviors (Stellar, 1954; Sinnamon, 1993). The concept of hypothalamic “centers” has been, however, challenged by findings of their considerable redundancy, overlap and ambiguous anatomical localization, partially due to a relatively low anatomical specificity of manipulation techniques (reviewed by (Berridge, 2004)). Further, recent genetic studies revealed the presence of neurochemically distinct cell populations in hypothalamic areas, implicated in the control of feeding, sleep (Steculorum et al., 2015; Steiger et al., 2011; Bonnavion et al., 2016) and defensive (Lin et al., 2011) behaviors. Also in the lateral hypothalamus (LH), in addition to “fast” neurotransmitters (glutamate or GABA), cells co-express neuropeptides, including orexins/hypocretins or MCH (melanin-concentrating hormone) (reviewed in (Bonnavion et al., 2016; Schone and Burdakov, 2012)). Administration of these neuropeptides as well as studies in mutant mice showed that each of these neuronal groups plays a unique, complementary role in regulation of sleep, feeding and locomotion. For instance, orexins have been implicated in vigilance state control, feeding, exploratory activity and reward processing (reviewed in (Li and Lecea, 2014)). A causal involve-

Corresponding authors: Alexey Ponomarenko, Behavioural Neurodynamics Group, Leibniz Institute for Molecular Pharmacology (FMP)/NeuroCure Cluster of Excellence, Berlin, Germany, Mail: ponomarenko@fmp-berlin.de

Tatiana Korotkova, The Max Planck Institute for Metabolism Research, Cologne, Germany; Behavioural Neurodynamics Group, Leibniz Institute for Molecular Pharmacology (FMP)/NeuroCure Cluster of Excellence, Berlin, Germany, Mail: tatiana.korotkova@sf.mpg.de

ment of these neuronal populations in behavior has been further revealed by ablation, opto- and chemogenetic manipulation and readouts of neuronal activity. Recent physiological and genetic manipulations of hypothalamic neuronal populations, including pro-opiomelanocortin (POMC), MCH, Agouti-related protein (AGRP) and orexins, vesicular GABA transporter-expressing (VGAT) cells, and their connections within and outside hypothalamus have led to further elaboration of the models of neural circuits, which enable feeding, foraging and vigilance state control (reviewed in (Bonnayon et al., 2016)).

Innate behaviors are conserved across species, their monitoring allows straightforward experimental designs in mice, where most molecular biological tools are available. Their application for brain-behavior analysis is further facilitated by links of specific behaviors to genetically distinct populations of hypothalamic neurons. At the same time, studies of innate behaviors pose a unique set of challenges, leading to new research horizons. Firstly, unlike other basal ganglia and cortical areas, hypothalamic connectivity has been only recently revealed and is still being elaborated using genetic anatomical tools. Secondly, data about intrinsic dynamics of hypothalamic networks *in vivo* are largely unavailable. Thirdly, since innate behaviors and their coordination are crucial for survival, their specific phases, i.e. initiation, execution and termination, eventually not only satisfy homeostatic needs, but are also tightly adjusted to a variety of environmental stimuli. For instance, initiation of feeding includes food approach, which can be more or less exploratory, depending on the familiarity of food locations in the environment. This involves prior associative learning and retrieval of information encoded by multiple forebrain regions involved in cognition. Similarly, termination of feeding by ventral striatal inputs to the lateral hypothalamus is a classic example of a top-down sentinel control, which terminates ingestion depending on environmental threats (O'Connor et al., 2015; Kelley et al., 2005). Embedding of innate patterns into complex adaptive behaviors involves function-specific readout of network dynamics, operating in other forebrain regions, by the lateral hypothalamus (Carus-Cadavieco et al., 2017).

Manipulation and monitoring of neural circuits

Recent progress in several technologies, including optogenetics, chemogenetics, Ca²⁺ imaging and multisite high-density neuronal recordings in behaving mice have

enabled readout of activity of multiple cells in hypothalamus in behaving animals, as well as identification and manipulation of defined neuronal populations and their projections with high temporal resolution. The development and implementation of genetically encoded Ca²⁺ indicators, such as GCaMP, which emit fluorescent signal upon Ca²⁺ binding, allows optical monitoring of changes in intracellular Ca²⁺ concentrations, associated with fluctuations of neuronal activity. Implanting a microendoscopic lens (gradient-refractive-index (GRIN) lenses attached on either end of a relay lens) further enables simultaneous visualization of multiple single cells (Ziv et al., 2013) even in deep brain regions (Resendez et al., 2016). Electrophysiological recordings in behaving mice allow directly measuring of neuronal activity at high temporal resolution and collecting high yields of recorded cells using movable multisite electrodes which dimensions compare to a size of a neuron. Multitrodes (e.g. tetrodes and silicon probes) enable to better distinguish neurons in close proximity to each other, using a principle of triangulation (McNaughton et al., 1983; Buzsaki et al., 2015). The electrodes may be mounted on a microdrive, implanted and gradually advanced during several weeks of recordings to maximize number of neurons recorded.

The combination of electrophysiological recordings in behaving mice with optogenetics enables identification of cells of interest, since these cells respond to a laser pulse with a short latency, and may have their spontaneous activity monitored. Control of neuronal activity using excitatory or inhibitory opsins (light-sensitive channels or pumps) (Boyden et al., 2005; Wietek et al., 2014; Gunaydin et al., 2010; Zhang et al., 2007) further permits study of the causal role of a particular cell group. To target cell groups selectively, Cre-dependent opsins are introduced in a brain region of interest in Cre-recombinase driver mouse lines (Tye and Deisseroth, 2012). By combining monitoring of neuronal activity and rhythmic optogenetic stimulation of brain regions and cells, directly involved in the generation of network oscillations in particular brain circuits, mechanisms and causal role of synchronization across behaviors can be investigated (Buzsaki et al., 2015; Bender et al., 2015; Yamamoto et al., 2014; Dupont et al., 2006; Draguhn et al., 1998; Wulff et al., 2009; Korotkova et al., 2010; Behrens et al., 2005; Korotkova and Ponomarenko, 2017). Readout of neuronal activity in a circuit in behaving animals prior to optogenetic manipulations allows establish a correlative link between specific behaviors and changes in neuronal activity. Subsequent optogenetic manipulation of the same circuit enables to study whether this relationship is causal. Finally, simultaneous readout of optogenetically induced changes of neuronal activity

ensures that protocols chosen for optogenetic manipulations recapitulate physiological patterns of neuronal activity.

Broad capabilities of neural network manipulation and monitoring can be optimally exploited when experimental designs, preparations and data analysis are well tailored to questions in focus. The choice of an optical actuator depends on a time scale of neuronal dynamics and on an investigated functional output, which can be matched to photocurrent parameters of opsins, ranging from ultrafast variants (Wietek et al., 2014; Gunaydin et al., 2010; Berndt et al., 2014) to step-function opsins featuring steady activation (Yizhar et al., 2011). Opto- and chemogenetic inhibition are further examples of tools optimal for brief and temporally discrete vs. more prolonged behavioral read-outs, respectively, like food seeking vs. food intake (Stachniak et al., 2014). Anatomical and cell-type specificity of optogenetic stimulation is defined to a large extent by features of Cre driver mouse lines and/or viral promoters used to drive opsin expression, by viral serotypes and titers as well as by injection techniques which together influence volume of the transduced brain tissue. Reliable protocols have been established for major neuronal types and their efficacy has been demonstrated by many reports (reviewed in (Lerner et al., 2016; Grunemann and Luthi, 2015)). Mice which express the same fluorophor (e.g. YFP) in same brain regions, and receive the same light stimulation are used to control for effects of light exposure and local heating on behavior and neuronal activity. In the following parts we will summarize recent studies showing functions of LH neurons in innate behaviors.

Causal role of orexin-, MCH- and VGAT-expressing LH neurons in regulation of sleep and wakefulness

Each of these three non-overlapping (Jennings et al., 2015) LH populations has a unique role in regulation of sleep (Fig. 1). Administration of orexins/hypocretins activates aminergic arousal-related nuclei (Brown et al., 2002; Eriksson et al., 2001; Korotkova et al., 2003; Bourgin et al., 2000) and induces arousal (Saper et al., 2010), whereas disturbances of orexin system due to mutations causes narcolepsy both in humans and animals (Kilduff and Peyron, 2000). Electrophysiological recordings of various LH cells (GABA-, orexin-, and MCH-expressing) showed that each of these subgroups exhibit a characteristic state-de-

pendent activity across sleep-wake cycle. Firing rate of orexin-expressing neurons is highest during active waking, and lowest during non-REM and REM sleep (Lee et al., 2005; Mileykovskiy et al., 2005). Optogenetic activation of orexin neurons increases the probability of waking from non-REM sleep as well as from REM sleep (Adamantidis et al., 2007).

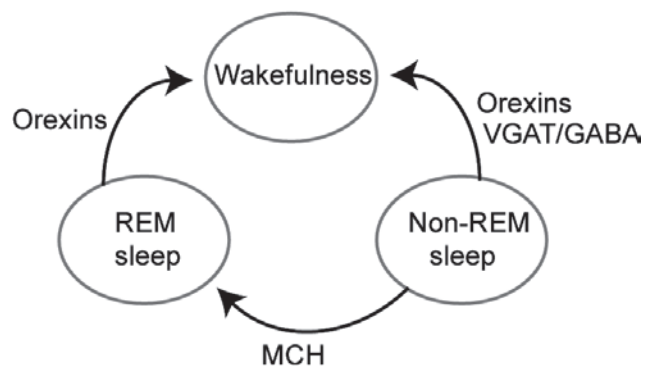


Fig. 1: Scheme illustrating effects of wake-active orexin, wake transitions-active VGAT/GABA and sleep-active MCH cell groups on transitions between non-REM sleep, REM sleep, and wakefulness.

VGAT (vesicular GABA transporter)-expressing LH GABA (VGAT/GABA) cells also change their activity across sleep-wake cycle. We optogenetically identified these cells using opsin expression in VGAT-Cre mice and found that they show a transient increase of firing rate during transitions from non-REM sleep to wakefulness (Herrera et al., 2016). In accordance with this finding, optical stimulation during non-REM sleep induced a rapid transition to wakefulness, stronger stimulation led to faster transitions. The waking upon VGAT/GABA LH cells activation occurred faster than upon activation of orexin-expressing LH cells (Adamantidis et al., 2007). The behavioral response was selective for non-REM sleep state, optogenetic activation of LH VGAT/GABA neurons during REM sleep did not lead to waking, suggesting that LH VGAT/GABA cells are part of neuronal circuit selectively modulating transitions from non-REM. Non-REM sleep differs from REM sleep in a number of crucial features (see (Brown et al., 2012) for extensive review), and these stages of sleep are controlled by different neuronal circuits (Saper et al., 2010; Lee and Dan, 2012). In accordance with effects of selective optogenetic activation, a more prolonged, chemogenetic, activation of LH VGAT/GABA cells, using the excitatory DREADDs (designer receptors exclusively activated by a designer drug (DREADD), (Armbruster et al., 2007)), promoted wakefulness, whereas chemogenetic inhibition increased sleep (Venner et al., 2016).

LH VGAT/GABA cells project to multiple sleep-related regions, including locus coeruleus, dorsal thalamus (Herrera et al., 2016) and ventral lateral preoptic area (VLPO) (Venner et al., 2016). Further, LH VGAT/GABA neurons massively project to the reticular thalamic nucleus (RTN) – an inhibitory nucleus innervating multiple thalamic nuclei. Optogenetic stimulation of LH GABA terminals in the RTN during non-REM sleep induced a rapid transition to wakefulness, thus reproducing sleep wake transitions upon activation of LH VGAT/GABA cells bodies. To characterize changes of RTN activity upon sleep-wake transitions, we recorded their firing across sleep-wake cycle. We found that the majority of TRN cells displayed state-dependent activity: the variability of their firing was lower (i.e. cells fired more regularly) during spontaneous waking than during non-REM sleep. Optical stimulation of LH VGAT/GABA-TRN GABA projections replicated these state-dependent changes of firing variability in RTN cells (Herrera et al., 2016). Further, optogenetic inhibition of this pathway prolonged the duration of non-REM sleep, showing the necessity of LH GABA-RTN pathway for normal transitions to wakefulness.

Classical models suggested LH to be an “arousal” center while preoptic area since studies of von Economo and Nauta (1946) considered to be a “sleep center”, as its lesions produced insomnia. Accordingly, sleep-active neurons were identified both in inhibitory neurons in VLPO and the median preoptic area, reviewed in (Saper et al., 2010). However, recent studies showed that LH also contains sleep-active neurons. MCH-expressing cells exhibited increased activity during REM sleep compared to non-REM sleep and were least active during wakefulness (Jones and Hassani, 2013). MCH administration in rats caused hypersomnia (Verret et al., 2003), while the MCH-R1 antagonist promoted wakefulness (Ahnaou et al., 2008). In agreement, ablation of MCH neurons by cell-specific expression of diphtheria toxin A increased wakefulness and decreased non-REM sleep duration (Tsunematsu et al., 2014). Optogenetic activation of MCH neurons extended the duration of REM sleep episodes, induced transitions from non-REM to REM sleep (Jego et al., 2013) and increased REM sleep time while decreased non-REM sleep time (Tsunematsu et al., 2014). A 24-hours optogenetic stimulation of MCH cells hastened sleep onset, reduced length of wake episodes and increased total time in non-REM and REM sleep (Konadhode et al., 2013). Another possible sleep-promoting population in LH are LH GABA cells, expressing the long form of the leptin receptor b (LepRb). Selective optogenetic stimulation of these cells led to a significant increase of latency to wake (Herrera et al., 2016). Thus, orexins-, MCH- and VGAT/GABA-express-

ing LH cells selectively regulate particular phases of sleep: orexins and VGAT being wake promoting, and MCH and LH LepRB- sleep-promoting.

Multifaceted mechanisms of feeding behavior

Changes of VGAT/GABA-, orexin- and MCH-expressing LH neurons' activity also influence feeding behavior. Optogenetic stimulation of LH VGAT/GABA neurons promotes voracious feeding while optogenetic inhibition of these cells reduces feeding even in food-deprived mice (Jennings et al., 2015). Similarly, selective activation of LH VGAT/GABA cells, projecting to the ventral tegmental area (VTA), a reward-related brain region, which is a major source of dopamine, leads to increase of sucrose-licking (Nieh et al., 2015), suggesting that reward system is involved in LH VGAT/GABA cells-mediated effects on feeding. Another pathway through which effects of LH VGAT/GABA cells may be mediated, are LH VGAT/GABA projections to hypothalamic paraventricular nucleus, since selective optogenetic stimulation of this pathway promotes feeding (Wu et al., 2015). Further, stimulation of LH VGAT/GABA at cells at different frequencies elicits differential effects on feeding and reward (Barbano et al., 2016), which might be explained by selective, frequency-dependent release of neuropeptides (Stuber and Wise, 2016), described also for other neurons (Schone and Burdakov, 2012). Interestingly, activation of LepRB-expressing LH cells, which also express GABA, shows an opposite effect to the activation of whole VGAT/GABA population, namely decreased feeding (Leininger et al., 2009). This suggests that LH VGAT/GABA cell group actually comprises several populations with distinct functions depending on co-expressing peptides or differential connections.

The role of orexins in feeding seems to be more multidirectional. Their administration stimulates eating (Inutsuka et al., 2014), and orexin cells are activated during hunger (Diano et al., 2003). Activity of orexin cell population, measured by fiber photometry, decreased within milliseconds after eating onset, and remained decreased during eating, in hungry as well as in satiated mice (Gonzalez et al., 2016), suggesting that orexin neurons might signal hunger till food becomes available. At the same time, chronic inactivation of orexin cells by cell-specific expression of diphtheria toxin A induced increased feeding (Gonzalez et al., 2016). Since disturbances of orexin system lead to narcolepsy, which is often accompanied by overweight, it could be suggested that normal patterns

and timing of sleep are important for feeding behavior, while typical for narcolepsy disturbed sleep timing, e.g. increased periods of arousal at times when mice eat most, lead to disturbed feeding behavior and obesity.

MCH system is also feeding-promoting, although its effects on feeding are more mild than actions of LH VGAT/GABA cells. MCH administration increases feeding, and levels of MCH mRNA increase during hunger (Qu et al., 1996). MCH knockout mice eat less and are more sensitive to starvation, showing greater weight loss and mortality, in contrast to littermates, even after a short fasting period (Shimada et al., 1998). Deletion of MCH receptor 1 disrupts overeating in the presence of food cues (Sherwood et al., 2015). Mice lacking MCH neurons show a reduced preference for sucrose over the artificial sweetener sucralose, compared to normal mice, and they release less dopamine than control mice during sucrose consumption. Finally, optogenetic stimulation of MCH neurons reverses natural preference for sucrose over sucralose (Domingos et al., 2013) suggesting that MCH neurons participate in sensing the nutritional value of sugar.

Feeding is also regulated by multiple extra-LH inputs (Fig. 2). First, feeding-promoting hypothalamic nuclei send projections onto LH. Optogenetic stimulation of projections of AGRP-expressing cells, located in arcuate nucleus (Betley et al., 2013), elicits feeding. Second, several extrahypothalamic inputs selectively regulate feeding (for review see e.g. (Bonnavion et al., 2016; Stuber and Wise, 2016). Bed nucleus of the stria terminalis, a region regulating various components of anxiety (Kim et al., 2013), sends inhibitory projections onto glutamatergic (VGlu2-expressing) LH cells, and its stimulation increases feeding (as does inhibition of VGlut cells) (Jennings et al., 2013). In contrast, a top-down input from NAcc shell neurons onto LH VGAT/GABA cells abruptly stop ongoing feeding (O'Connor et al., 2015; Kelley et al., 2005). Synchronization of LH inputs interacts with intrinsic LH activity as indicated by the role of the inhibitory input from the lateral septum (LS). Gamma oscillatory activity of LS projections, coordinated with gamma oscillations in LH, makes LH neurons with different feeding-related activity fire at distinct oscillation phases. The separate signaling by these LH populations is associated with changes of their firing rates, opposite to changes observed during feeding-inducing optostimulation of LH VGAT/GABA cells. The gamma-rhythmic input to LH from somatostatin-positive LS cells elicits food approach without affecting food intake (Carus-Cadavieco et al., 2017). Thus, multiple groups of LH neurons as well as inputs onto those cells selectively and complementary regulate various aspects of feeding behavior.

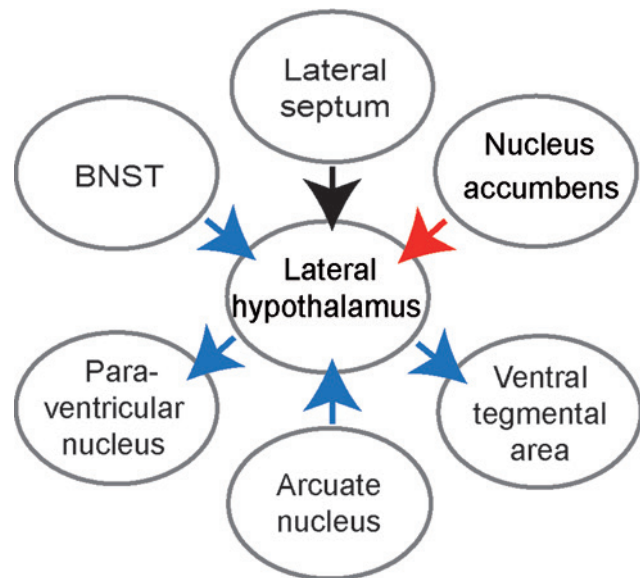


Fig. 2: Scheme showing effects of LH inputs and outputs on feeding. Blue arrows: activation of a given pathway increases feeding, red arrow: activation of a pathway decreases feeding; black arrow: activation elicits food approach. BNST – Bed nucleus of the stria terminalis.

Oscillatory top-down signals and role of LH in locomotion

Eating disorders are often accompanied by changes in locomotor activity: about 80% of anorexia nervosa patients engaging in compulsive, excessive exercise (Davis et al., 1997). Rodents also display hyperactivity after food restriction, so-called activity-based anorexia (ABA): rats on a restricted diet profoundly increase activity in a running wheel (Routtenberg and Kuznesof, 1967; Adan et al., 2011). From classical electrical stimulation studies it is known that stimulation of LH induces locomotion, and can induce walking-like behavior even in anaesthetized rats (Sinnamon, 1993). We found that the majority of recorded LH neurons, including GABA cells, displayed locomotion-dependent firing: they increased discharge during initiation of locomotion and maintained increased firing during spontaneous running (Bender et al., 2015). As a part of the diencephalic locomotor region, LH is connected with midbrain and brain stem locomotor circuits and upstream forebrain regions (Sinnamon, 1993), which can provide LH with experience-dependent interpretation of sensory inputs.

A conceptual framework, helping to study regulation of innate behaviors, has been proposed by Swanson based on investigations of hypothalamic connections (Risold

and Swanson, 1996). Behavioral control columns comprise dedicated behavioral systems of hypothalamus together with their cortical and basal ganglia input regions. Rostrally to premammillary nuclei, this system is involved in ingestive, reproductive, and defensive behaviors, while more caudal parts drive exploratory behavior. Upstream, an important interface between hypothalamus and cortical regions is the lateral septal nucleus (LS). LS is anatomically and functionally distinct from the medial septum, which projects to hippocampus and rhinal cortices in the medial temporal lobe and plays a key role in controlling timing of network activity in these areas. Medial septum has little if any connectivity with LS. The LS is the main source of forebrain inputs to hypothalamus, and the main subcortical output area of hippocampus (Fig. 3). In the rat, each pyramidal cell in the CA3 area and most of CA1 pyramidal cells project to LS, additionally to projections to the entorhinal cortex. There is a strict topographical mapping between hippocampus, LS and hypothalamus, i.e. hippocampal areas project to distinct portions of the LS and along the medio-lateral axis of hypothalamus (Risold and Swanson, 1996). These connections provide basis for behavioral control columns, routing hippocampal signals to hypothalamic regions, involved in feeding, locomotion, arousal and other innate behaviors. Our group has recently investigated information processing and some of the physiological functions mediated by cortico-hypothalamic circuits.

When animals or humans find themselves in a specific location in the environment, a place cell in the hippocampus becomes active. This brain navigation system signals each spatial position by activating relatively few place cells and, together with a grid cell network of the medial entorhinal cortex, is a fine-tuned dynamic machinery which follows its own rhythm. Rhythmic ups and downs in the activity of a large number of place cells during running occur 5 to 10 times per second, making activity of cells and electrical signals recorded from hippocampus oscillate with an impressive regularity of the so called theta oscillation. Since their discovery almost 80 years ago (Jung, 1938) theta oscillations have been implicated in communication of hippocampus with cortical and subcortical regions during spatial navigation and memory processing (reviewed by (Buzsaki and Moser, 2013; Seidenbecher et al., 2003; Stempel et al., 2016; Bikaev and Manahan-Vaughan, 2008; Sirota et al., 2008)), motivational aspects of running, and in behavioral control of complex voluntary movements, including locomotion (Grastyan et al., 1965; Vanderwolf, 1969). Studies using electrophysiological monitoring, lesions or electrical

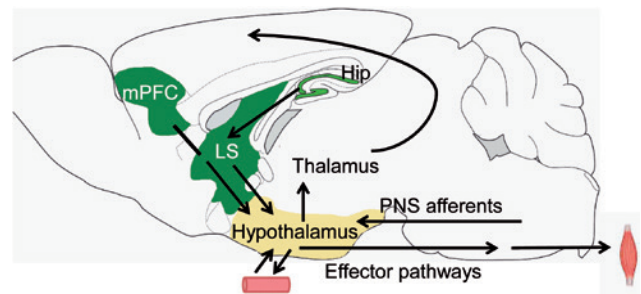


Fig. 3: Circuit diagram showing inputs to hypothalamus from medial prefrontal cortex (mPFC) and hippocampus (Hip), routed via lateral septum (LS) as well as hypothalamic outputs to forebrain, brain stem and secretory effector pathways via hypophysis. PNS – peripheral nervous system. The mouse brain image was modified from (Paxinos and Franklin, 2001).

stimulation indicated, however, a complex relationship between theta oscillations and locomotion.

Our laboratory used optogenetics to gain dynamic control over brain networks that pace theta oscillations in hippocampus. Using viral gene transfer and a light-sensitive protein, Channelrhodopsin-2, we targeted projections from the main pacemaker of the theta rhythm, medial septum, to the hippocampus. This way, brain synchronization could be selectively manipulated by an implanted optic fiber and microelectrode assembly in behaving mice with high temporal precision (Bender et al., 2015). The optogenetic entrainment regularized theta oscillations, i.e. rendered their frequency constant and the magnitude more regular while other aspects of information processing, including rhythmic discharge of pyramidal cells and place fields features, remained unchanged. Optogenetic control of theta oscillations released them from a multitude of influences normally generated by the interplay of brain state and sensory inputs and therefore opened a way to answering long-standing questions about the impact of hippocampal theta rhythmic activity on behavior (Grastyan et al., 1965; Vanderwolf, 1969). As the oscillation in hippocampus was optogenetically regularized, mice changed the way they moved through environment: they moved slower and with a more constant speed depending on the experimentally adjusted regularity of theta oscillations (Fig. 4 A,B).

How can hippocampal theta oscillations influence locomotion, initiation and pattern of which are controlled by hierarchically organized hypothalamic, midbrain and brain stem regions? One can view brain oscillations as traffic lights, which signal when neurons can fire and when they must stay silent; more regular oscillations resemble temporally coordinated traffic lights repeated with regular intervals. Hence, during regular theta rhythm ac-

tivity of many traffic participants – populations of place cells – is more consistent over time. Does this activity affect outbound connections of hippocampus to the lateral septum and hypothalamus? We found that theta-periodic signals operate also downstream from hippocampus, in the LS: many cells in this brain region see and respond to “green” and “red” lights, switching on and off in synchrony with theta oscillations in the hippocampus. Thus swift transmission of neural signals along this route relies on theta oscillations, coordinated between hippocampus and LS.

Would mice move differently if the neural signal traffic in the hippocampus to LS pathway or downstream, from LS to lateral hypothalamus, is inhibited or stimulated? Inhibition of hippocampus to LS communication became possible applying “red light” protein switches (halorhodopsin, an inhibitory optogenetic tool) in the axons of hippocampal pyramidal cells in LS. The mouse’s speed did not react to manipulations with theta oscillations in the hippocampus when the outbound signalling from hippocampus to lateral septum was optogenetically blocked (Fig. 4 C,D). Further, many cells in the lateral hypothalamus become more active when an animal starts running, and theta rhythmic stimulation of inhibitory LS-LH projections decreased running speed (Fig. 4 E,F). Thus, theta oscillations provide a natural physiological signal, which operates in hippocampus – LS – lateral hypothalamus pathway and supports rapid adjustments of exploratory behavior in response to changes of hippocampal, cognition-related dynamics.

Interestingly, earlier studies demonstrated that theta rhythmic activation of hippocampus – LS – ventral tegmental area pathway is sufficient for context-dependent reinstatement of reward seeking (Luo et al., 2011). These findings highlight a prospective on theta oscillations, complementary to their role as a global clock signal, organizing encoding of spatial and, more generally, behavioral sequences. Indeed, theta synchronization operates at time scales potentially relevant for multiple brain functions. While an animal’s path is signalled by place cells within single theta cycles, variations of theta synchronization at a slower scale (up to seconds) provide feedback from hippocampus to subcortical networks during locomotion and adjust its pattern. Since activity of place cells reflects animal experience, participation of pyramidal cells in synchronized ensembles can change depending on ongoing sensory input and thus determine spatiotemporal pattern of the oscillatory output (Bahner et al., 2011; Denker et al., 2011).

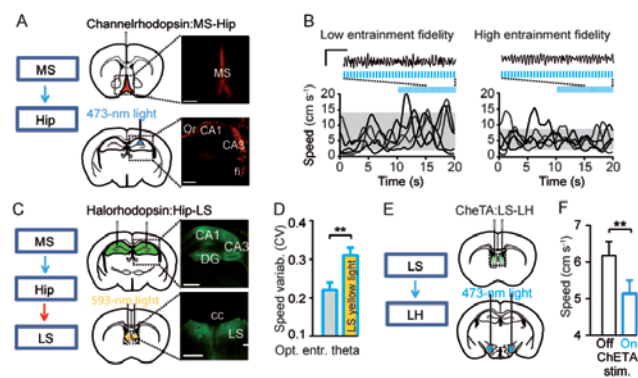


Fig. 4: Regulation of locomotion via hippocampus-lateral septum-lateral hypothalamus pathway by theta oscillations. **A.** Optogenetic control of theta oscillations in behaving mice. Injections of Cre-dependent ChR2 in medial septum (MS) of parvalbumin-Cre mice and light-induced stimulation of MS-hippocampus (Hip) projections. Expression of ChR2:tdTomato: neuronal somata in MS and axons in Hip. Scale bars: 500 μ m (left), 50 μ m (right). **B.** Representative local field potential signals, recorded from hippocampus, before and after the onset of stimulation (7Hz) with a low (<0.3; left) or high (>0.8; right) theta oscillations entrainment fidelity, grey shadows mark 10-90% ranges of speed distributions during stimulation, blue lines mark optostimulation. Scale bars: 1 s, 2 mV. Note that efficiently controlled theta oscillations are accompanied by reduced speed variability. **C.** Left: Scheme of experimental design for simultaneous optogenetic entrainment of theta oscillations in Hip and inhibition of hippocampal outputs to LS. Right: Injections and expression of halorhodopsin (eNpHR3.0) in hippocampal pyramidal cells (top), axonal immunofluorescence in LS; bilateral optic fibers implantation for light-induced inhibition of Hip-LS projections (right). Scale bars: 500 μ m (left), 50 μ m (right). **D.** Reduction of speed variability during optogenetic theta entrainment was prevented by simultaneous LS yellow light (593 nm) delivery (yellow bar, $p=0.007$, $N=8$ mice). **E.** Targeting of ChETA, a faster version of channelrhodopsin (Gunaydin et al., 2010) to GABAergic cells in lateral septum (LS) mice and light-induced stimulation of LS_{GABA}-LH projections. **F.** Optogenetic theta-frequency activation of LS-LH pathway decreases running speed ($P=0.003$, $N=7$ mice). Modified from (Bender et al., 2015).

Outlook

The results reviewed here suggest that innate behaviors provide a good model for functional investigation of neural circuits using a broad repertoire of genetic manipulation and physiological monitoring techniques in mice. Thanks to the integration of the core circuit for innate behaviors – hypothalamus – with sensory and associative cortices as well as basal ganglia, brain dynamics adaptively governing foraging, ingestion, vigilance state and other innate patterns can now be studied with high temporal resolution and anatomical specificity. These studies rely on quickly accumulating knowledge about connections be-

tween chemically and anatomically distinct classes of hypothalamic neurons as well as on anatomical mapping of their extrahypothalamic afferents and efferents. Further, investigation of intrinsic responses of hypothalamic cells to metabolic and hormonal signals together with recording and manipulation of their activity *in vivo* will provide detailed mechanistic information about hypothalamic integration. Future research will also address how hypothalamic networks read out information from upstream forebrain regions, providing new clues about a common language used by evolutionarily conserved subcortical and computationally advanced cortical networks (Gray and Singer, 1989; Yang et al., 2009; Herz et al., 2006). This will help understand organization of motivation behind exploratory stages of feeding, often executed in advance of nutritional deficits. Alterations of these processes highlight core symptoms of eating disorders and investigation of these circuits will lead to novel pathogenesis – oriented treatment strategies.

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Bionotes



Tatiana Korotkova

The Max Planck Institute for Metabolism Research, Cologne, Germany; Behavioural Neurodynamics Group, Leibniz Institute for Molecular Pharmacology (FMP)/NeuroCure Cluster of Excellence, Berlin, Germany
Mail: tatiana.korotkova@sf.mpg.de

Photo: Philipp Jester

Tatiana Korotkova studied biology with a focus on human and animal physiology in Lomonosov Moscow State University. During her Ph.D. in the lab of Prof. H.L. Haas in Düsseldorf she investigated actions of various hypothalamic neuropeptides on aminergic nuclei, particularly on dopaminergic system. As a postdoc in the lab of Prof. H. Monyer in Heidelberg, and later in a collaboration with Prof. T. J. Jentsch in Berlin she studied mechanisms of hippocampal network oscillations in behaving transgenic mice. Since 2012 T. Korotkova is a junior group leader at the Leibniz Institute of Molecular Pharmacology (FMP)/NeuroCure Cluster of Excellence in Berlin, since April 2017 – a Research group leader at the Max Planck Institute for Metabolism Research, Cologne, Germany. Her work focuses on functions of lateral hypothalamus in hunger and sleep. To unravel the roles of hypothalamic circuits in health and disease, she combines optogenetics with neuronal recordings in behaving mice. She was a holder of the DFG Graduate College 320 and Schering foundation research stipends, and was awarded the Junior Brain Prize by Lundbeck Foundation.



Alexey Ponomarenko

Behavioural Neurodynamics Group,
Leibniz Institute for Molecular Pharmacology (FMP)/NeuroCure Cluster of Excellence, Berlin, Germany
Mail: ponomarenko@fmp-berlin.de

Alexey Ponomarenko studied biology with a focus on physiology of humans and animals in Lomonosov Moscow State University. During his Ph.D. with Prof. H.L. Haas in Düsseldorf he studied fast network oscillations in hippocampus and amygdala using electrophysiological recordings in behaving rats. He then learned *in vivo* stereotrode recordings in the laboratory of Prof. G. Buzsáki (Rutgers University, USA). During postdoctoral training with Prof. H. Monyer in Heidelberg and following joint studies with Prof. T. J. Jentsch in Berlin, he implemented neuronal recordings in genetic mouse models and studied network mechanisms of hippocampal oscillations and spatial representations. Since 2009 A. Ponomarenko leads a junior group at the FMP Institute/NeuroCure Cluster of Excellence in Berlin. He uses optogenetics and high-density electrophysiology to manipulate synchronization between cortical and subcortical regions and to explore its function in innate behaviors. He is a holder of Arthur A. Hancock Young Investigator Award in the European Histamine Research Society.