

## COMMENTARY

# Thalamic Relay or Cortico-Thalamic Processing? Old Question, New Answers

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**What are the functions implemented by neurons in the sensory nuclei of the thalamus? It seems that this question has accompanied cortical and thalamic studies since their onset some 6 decades ago. Over the years, the simplistic, traditional view of thalamic neurons as mere relays of sensory information has given way to more sophisticated views, of which several alternative hypotheses have been proposed. This commentary briefly reviews the 2 current major hypotheses and shows how a new, pioneering experiment, published in *Cerebral Cortex* by Groh, Acsady and colleagues, discriminates between them. The commentary further elaborates on the thalamo-cortical processing suggested by the new findings, the general sensory-motor scheme to which these findings may be relevant, and the possible roles such thalamo-cortical processing may have in sensory-motor control.**

**Keywords:** gating, relay, thalamo-cortical loop, thalamus, whisking control

### Introduction

The thalamus has long been a riddle to neuroscientists. Many researchers of the cerebral cortex view the thalamus as a simple relay station. The origins of this view are likely to be found in the once prevailing notion that information processing in the brain begins in the cortex, and that subcortical systems primarily serve as communication pathways between the cerebral cortex and the external environment. It was thus assumed that the role of neuronal stations found along these pathways is probably to improve signal quality, as is done by relay stations of engineered communication systems. As is true of all relay stations, these relay stations are not expected to change the content of the information they relay. In the brain, relay functions have traditionally been attributed to brainstem and thalamic nuclei. This view has been modified as thalamic neurons were shown to exhibit dynamic control over information relay (Basso et al. 2005). Now, an illuminating study by Groh et al. (2013) takes this trend a significant step forward by showing that thalamic processing is not limited to information relay, at least in the whiskers-related portion of the posterior nucleus (Pom).

One robust form of signal transformation performed by thalamic neurons has been known for a while. Thalamo-cortical neurons switch between 2 modes of information transfer characterized by their typical firing patterns: bursting and tonic (McCormick and von Krosigk 1992; Sherman and Guillery 1996). Following a quiescent period, thalamic neurons are shifted to a hyperpolarized, sensitive mode, in which input-output relationships are not linear and are characterized by the frequent occurrence of high-frequency bursts. Following sensory stimulation or a change in the state of the brain, thalamo-cortical neurons shift to a more depolarized and less sensitive mode, in which input-output relationships are more linear and

firing is typically tonic. The hyper-sensitivity and the nonlinear transformation that occur in the bursting mode are suitable for detecting environmental changes, whereas the linear transformation that occurs in the tonic mode is suitable for perceptual processing. Thus, thalamic nuclei can dynamically switch between detection and perception modes, providing the thalamus with the capability of implementing a “searchlight of attention,” that is, perceiving one part of the environment while decreasing detection thresholds in the other parts. Importantly, because it is highly nonlinear, the transformation of sensory information that occurs in the thalamic bursting mode cannot serve perceptual processing; thalamic spikes in this mode provide information about the occurrence of a change in the environment and not about the nature of that change.

Additional clues about the possible functions of thalamic nuclei come from their connectivity schemes. For example, thalamic neurons receive massive innervation from cortical outputs. In some thalamic nuclei, cortical inputs comprise the vast majority of inputs to thalamo-cortical neurons. Thalamic nuclei also receive inputs from virtually all motor outputs of the cerebral cortex. Motor outputs emerge from the deep layers of the entire cortical sheet, including primary sensory cortical areas. These motor outputs send collaterals to specific thalamic nuclei (Guillery and Sherman 2002). Thus, not only do thalamic neurons receive massive sensory-related cortical inputs, but they also receive significant amounts of motor-related information.

So, what are the secrets of the thalamus? Is it primarily a relay/switching system or is it a processing station? One interesting hypothesis suggests that the thalamus is a multiway relay station. This hypothesis divides thalamic nuclei to first- and higher-order nuclei. The division is based on the relative strengths of their peripheral and cortical drives. Nuclei in which peripheral drives are significantly stronger than the cortical drives are termed first-order nuclei; these nuclei (such as the ventral posteromedial nucleus [VPM], and the lateral geniculate nucleus [LGN]) are considered to be primarily sensory relay stations. In contrast, the nuclei whose cortical drives are considered to be significantly stronger than their peripheral drives are termed higher-order nuclei, and are considered to be cortico-cortical relay stations. According to this model, the thalamic nuclei are all relay stations, but not all of them necessarily relay information between the periphery and the cortex. Rather, higher-order nuclei, such as the Pom or pulvinar, facilitate communication between various cortical stations (Sherman and Guillery 2002). Importantly, given the poor spatiotemporal resolution of the neuronal responses in these higher-order nuclei, the nature of the information that is supposed to be relayed via cortico-thalamo-cortical pathways is not yet clear (Basso et al. 2005).

An alternative hypothesis for thalamic function, the “closed-loop” hypothesis, assumes that the tight connectivity between the thalamus and cortex reflects the fact that thalamo-

cortical circuits form processing units. Anatomy indicates that neurons in the granular and subgranular layers of sensory cortices form anatomical loops with thalamic neurons (Fig. 1). For example, layer 4 neurons in S1 of the rat affect layer 6 neurons, which, in turn, affect the thalamo-cortical neurons in the VPM, which then drive layer 4 neurons. Similarly, layer 5a neurons affect layer 5b neurons, which, in turn, drive POM neurons, which then drive layer 5a neurons. Similar closed loops (i.e., circuits in which every signal constantly though not exclusively affects its source or sources) occur in the visual and auditory systems. As neuronal processing is often iterative, these closed loops can serve as a means by which thalamo-cortical networks converge upon reliable internal representations (Yu et al. 2013).

These 2 hypotheses predict different thalamic transformations. The multiway relay model predicts that a given thalamic neuron will relay information in one specific direction depending on its nucleus type: bottom-up (thalamo-cortical) in first-order and top-down (cortico-thalamic) in higher-order nuclei. The closed-loop model predicts that thalamic neurons will be sensitive to certain *relationships* between peripheral and cortical inputs. In the current issue of *Cerebral Cortex*, Groh et al. (2013) report an elegant study addressing exactly this issue in the POM of rats and mice. The elegance of their approach and the discriminatory power of their results suggest that this work, along with recent works (e.g., Groh et al. 2008), signals a paradigmatic shift in the study of thalamic functions. The new paradigm combines measurements at the level of individual synapses, selective neuronal stimulations, well-defined

stimulation protocols in vitro and in vivo, and integration between anatomy and physiology.

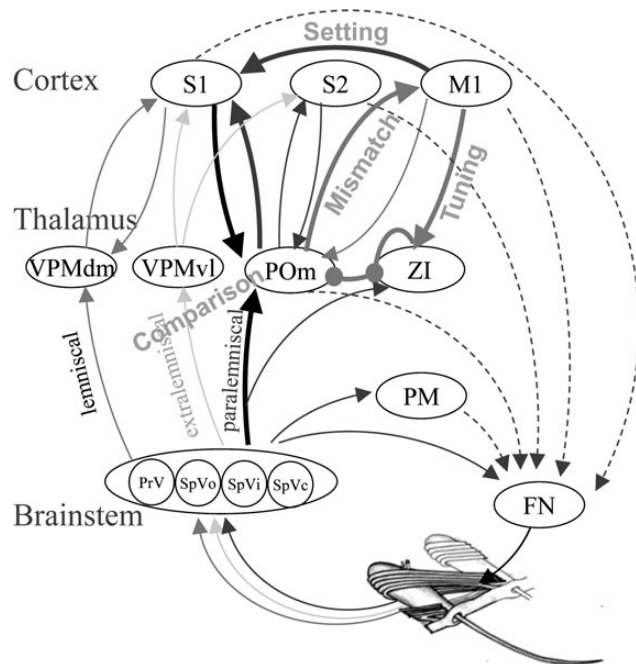
Using state-of-the-art methodology and integration of expertise from different labs, Groh et al. provide an unequivocal answer to the relay/processing question—POM neurons process and do not merely relay information. These researchers first show that peripheral and cortical “driver inputs,” that is, those forming strong giant synapses, converge in the POM, and that the membrane potential of POM neurons in the convergent zones follows both cortical and peripheral activities. Then, they show that this dual innervation, in fact, converges on individual POM neurons, where 2 giant synapses, one of each source, can be found within  $<1 \mu\text{m}$  of each other. Groh et al. found that this microarchitecture results in a temporal computation: POM neurons “report the relative timing between sensory events and ongoing cortical activity.” They revealed this function in vivo using optogenetics by selectively stimulating the projecting cortical neurons at various delays before and after vibrissal stimulations. The robustness of this revelation lies in its consistency across anatomical methods, preparation modes, and species (rats and mice).

With such strong inputs, a single POM cell becomes a basic computational element, whose most straight-forward functions are logical OR- and AND-gating. In an OR-gate, the output equals the binary sum of the inputs, whereas in an AND-gate the output equals the binary product of the inputs. Thus, an OR-gate cell can transfer any of its inputs, whereas an AND-gate cell will only transfer the conjunction of its 2 inputs. Importantly, single cells can shift from functioning as OR-gates to functioning as AND-gates by simply changing their firing threshold; a threshold that can be crossed by either of the 2 inputs yields an OR-function, whereas a threshold that can be crossed only by the sum of the 2 inputs (i.e., requiring simultaneous occurrence) implements an AND-function (Ahissar 1998).

Groh et al. show that POM neurons implement their temporal computation while operating as AND-gates—if a cell’s output depends on the product of both peripheral and cortical inputs, then this product is “1” only in a given time window when both inputs are effective (compare Groh’s Fig. 8 with Fig. 4 in Ahissar 1998). This, of course, may change in awake animals in which POM cells might be more depolarized. Still, POM circuitry allows for a dynamic, controllable change between OR- and AND-gating across brain states.

POM neurons receive strong inhibitory projections from a nearby nucleus, the zona incerta (ZI; Fig. 1; Bartho et al. 2002; Trageser and Keller 2004; Lavallee et al. 2005). The amount of inhibition exerted by ZI neurons is tightly controlled by the primary motor cortex (M1; Urbain and Deschenes 2007). Thus, M1 can control the transfer function of POM neurons and can shift them, for example, from functioning as OR-gates (light ZI inhibition) to AND-gates (heavy ZI inhibition). Using intracellular recordings, Groh et al. show that the transfer function of POM neurons is highly nonlinear—small differences around the threshold induce large differences in the output spiking rate. This strong nonlinearity renders the POM transfer function highly dependent on its inhibitory inputs from the ZI.

The AND-gate function demonstrated by Groh et al. enables POM neurons to implement processing that is crucial for motor control. Motor control of whisking appears to be hierarchically organized, so that the exact timing and the exact amplitude of individual whisk cycles are determined by low-order loops



**Figure 1.** Sensory-motor scheme of the vibrissal system. Sensory pathways are distinguished by gray levels. Top-down feedback connections and cortico-cortical connections are not depicted except for those relevant to the study by Groh et al. Motor pathways to the facial nucleus (FN) are represented by dashed lines (details are not shown). Not all pathways are shown. Excitatory connections are depicted by arrows and inhibitory connections by circles. The pathways relevant to the current discussion are plotted in bold lines. The pathways studied by Groh et al. are depicted in black. Gray bold titles indicate suggested functions of stations and pathways. FN, facial nucleus; PM, pre-motor nuclei. Follicle drawing courtesy of Sebastian Haidarliu.

involving mostly brainstem structures and pattern generators, whereas modulations of these variables during a whisking bout are determined by higher-order loops involving cortical stations (Hill et al. 2011; Huber et al. 2012). Efficient control involving such complex circuitry crucially depends on a feedback-based comparison of the intended and resulting motion (Ahissar and Kleinfeld 2003). The synaptic architecture in the POM, as revealed by Groh et al., completes a circuit that has all the ingredients required for comparing the intended and the resulting whisking frequency.

AND-gating in the POM enables it to report the temporal (or phase) difference between its 2 driving inputs: The larger the difference, the weaker the output. POM projects to layers 1, 2, and 5a of S1. If these projections inhibit, via interneurons, the back projections from layer 5b to POM, and if the layer 5b projecting neurons possess intrinsic oscillatory mechanisms (Silva et al. 1991; Ahissar et al. 1997), then, with the appropriate neuronal tuning, the POM–S1 loop may become a phase-locked loop (Ahissar et al. 1997; Ahissar and Kleinfeld 2003). A phase-locked loop is a negative feedback loop whose fixed point is a state in which the 2 inputs to the phase comparator (the POM in this case) oscillate at the same frequency (Ahissar 1998). The POM–S1 loop thus forces the cortical oscillations to track the frequency of whisking. The difference between the actual cortical frequency and its intrinsic reference frequency is coded by the phase difference and by the output firing rate of the POM (Ahissar 1998). If the reference frequency equals the intended whisking frequency, the POM's output codes the difference between the intended and actual whisking frequency. As M1 projects to S1 (Matyas et al. 2010; Petreanu et al. 2012; Zagha et al. 2013), the intended frequency coded in M1 could, indeed, be used to set the reference frequency in S1.

The output of the POM feeds back to M1 neurons, as well as to neurons of other motor stations (Cadusseau and Roger 1990; Deschenes et al. 1995; Smith et al. 2012), and can be used to correct motor commands (Fig. 1). If the intended and actual frequencies are the same, no correction is needed and the POM output is expected to be zero (note the distinction between phase and frequency here; as the difference between the frequencies of the 2 driving inputs to the POM decreases, the difference between their phases increases). As the error increases, the POM output is expected to increase and to remain high as long as the error exists. According to this scheme 'error-less' whisking, such as whisking in air in head-fixed conditions (e.g., Masri et al. 2008), is expected to generate weak POM activity whereas artificial whisking (e.g., Yu et al. 2006) is expected to generate strong POM activity. This circuit further predicts that POM output will reflect unexpected changes in whisking frequency during natural whisking due to either head movements or external perturbations.

Similar POM computations may be implemented for the control of other body movements (Diamond 1995). Moreover, the circuitry of POM does not limit its function to frequency or to phase comparison. It can be also used for whisker position comparison. Since whisker angle is coded by the population of peripheral "whisking cells" (Knutsen and Ahissar, 2009), specific wiring diagrams could result in the POM–S1 loop computing position difference rather than frequency difference. This would require that neurons in layer 5 of S1 encode the intended whisker angle, and that a matching connectivity occurs in the POM such that a given POM neuron receives cortical and peripheral inputs that code for the same (intended or actual)

whisker position. The actual position comparison can be implemented in various ways—we will leave that for future analyses, once relevant data will be available. We will only mention that, given the microscale pair-wise localization of peripheral and cortical synapses revealed by Groh et al., AND computations could also be performed along the dendrites (Polsky et al. 2004) of POM neurons, thereby making possible extremely detailed comparisons of intended and resulting motion variables.

Thus, the AND-gate function demonstrated by Groh et al. enables POM neurons to implement frequency or amplitude comparison functions. An OR-gate function, which can be obtained with low amounts of ZI inhibition, would not allow this comparative computation, and thus, it is not clear when, if ever, thalamic OR-gates would be used for perception. Obviously, it is expected to occur in POM cells operating in the detection mode. Still, the flexible modulation of POM firing threshold via the M1–ZI pathway should be instrumental in compensating for modulations in the excitability of the peripheral and cortical pathways to the POM. The M1 → ZI → POM pathway, thus, is expected to function within a POM → M1 → ZI → POM closed loop (Fig. 1), whose role is to keep POM outputs within a desired working range, as a component of whisking control.

Whether similar computations occur in other thalamic nuclei or in other species is not yet known. The dual-drive scheme revealed by Groh et al. is probably specific to the so-called higher-order thalamic nuclei. Thus, while neurons in the pulvinar or in the medial or dorsal sections of the medial geniculate body (MGB) may exhibit POM-like computations, possibly in relation to the control of eye movements or basilar membrane dynamics, neurons in the VPM, ventral posterolateral nucleus, ventral MGB, or LGN may exhibit computations of a different nature, possibly related to the perception of specific features of external objects. Importantly, the search for such mechanisms should take into account, in addition to the synaptic and cellular characteristics of the thalamic neurons, the computational and control framework within which the specific thalamic nucleus functions.

## Notes

*Conflict of Interest:* None declared.

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