Attentional flexibility in the thalamus: now we're getting SOMwhere

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Loss of the receptor tyrosine kinase ErbB4 in somatostatin (SOM) inhibitory neurons of the thalamic reticular nucleus (TRN) enhances top-down cortical feedback, improving feature detection at the cost of reduced ability to switch attention. The study furthers our understanding of the circuit mechanisms underlying TRN function.

As you strap on your skates in preparation for your trip to work, consider the complex task before you. You need to stay in your lane, maneuver around joggers and watch out for animals that cross your path. Pay too little attention to the path and you may end up in the ditch. Having trouble switching your attention from the jogger? Hello squirrel and a bad start to the day. The ability to select relevant environmental stimuli from among less relevant features is clearly a critical adaptive behavior. Equally important is the ability to transition attention from one feature to another in a dynamic environment in which the relative importance of varied features is constantly in flux. These two behaviors, feature detection and attentional switching, are opposed to each other, such that enhanced feature detection might perturb the ability to transition focus to a new target and enhanced switching might interfere with feature detection. In this issue of *Nature Neuroscience*, Ahrens *et al.*[1] span genes, circuits and behavior to make a compelling case that the receptor tyrosine kinase ErbB4 is responsible for regulating the sensitivity of the thalamic reticular nucleus (TRN) to cortical inputs. In so doing, ErbB4 expression tunes the balance between attention and behavioral flexibility.

The TRN is a key player in attention[2,3] and sensory detection[4,5]. The unique position and intrathalamic inhibitory connectivity of the TRN place these cells in an ideal position to regulate incoming sensory information[6]. Consequently, the TRN has been called the gatekeeper of the thalamus[6], as it may selectively reduce or enhance specific sensory stimuli depending on an integration of top-down and bottom-up inputs. However, the cell types and signaling molecules in the TRN that participate in this regulation are not well understood. Ahrens *et al.*[1] find that ErbB4 normally acts to reduce the strength of cortical inputs onto the somatostatin-positive (SOM^+) subset of TRN cells. Reducing ErbB4 expression in these cells leads to increased cortico-TRN excitation and divergent behavioral consequences in tasks involving attention.

The authors began with the observation that ErbB4 is selectively expressed in the SOM^+ cells of the TRN, but not other forebrain regions. This unique expression profile was exploited using a SOM-Cre conditional knockout approach to reduce ErbB4 expression in SOM^+ cells in the TRN. Given the importance of the TRN in sensory and attentional processes and the association of ErbB4 with schizophrenia[7,8], a psychiatric disorder involving altered attention, might the loss of ErbB4 in SOM^+ TRN neurons affect performance in behavioral tasks that rely on attention? With this SOM-TRN-ErbB4 knockout mouse in hand, the authors proceeded to address this question with a set of innovative behavioral tasks that required animals to engage in feature detection and attentional switching. Animals were first trained to associate the position of a light or the presence of particular tones with the position of a reward. For example, a light to the right indicates a reward to the right and a light to the left indicates a reward to the left, whereas a 20-kHz tone indicates a reward to the right and an 8-kHz tone indicates a reward to the left. Once trained, the animals were presented with a two-alternative choice task that required selection from among competing sensory inputs. In the auditory/auditory task, animals were presented with the target tone (either 8 or 20 kHz) in addition to distractor tones at other frequencies. Surprisingly, SOM-ErbB4 knockout enhanced performance in this task, suggesting that a loss of ErbB4 leads to an enhancement in feature detection.

Ahrens *et al.*[1] then mixed things up a bit in the visual/auditory task by changing the reward payout to only follow the light and not the tone while presenting both auditory and visual cues, which sometimes agreed (were congruent) and sometimes disagreed (were incongruent). For example, in an incongruent trial, the light indicated reward to the left and the tone indicated reward to the right. Would the super-detector ErbB4-deficient animals be able to effectively switch attention from the previously relevant tone stimuli to favor the light cues? In contrast with their enhanced performance in the feature detection experiment, SOM-ErbB4 knockout animals were actually impaired in their ability to discard the previously relevant stimulus (in this case, the tone) for the informative stimulus (the light), suggesting a deficit in attentional switching.

Although SOM^+ TRN neurons consistently express ErbB4, small numbers of SOM^+ cells in other brain regions show sporadic expression. Might then the behavioral consequences of loss of ErbB4 expression in SOM^+ cells be explained by potential off-target (non-TRN) deficits in ErbB4? The authors developed an impressive genetic approach to rule out this possibility. They introduced an *FRT*-Stop-*Cre* construct into *Som-Flp*; $ErbB4^{loxP/loxP}$ animals so that only cells that contain both *Flp* and *Cre* undergo deletion of ErbB4. Cell-type specificity was achieved by SOM-Flp expression and region specificity was achieved by local injection

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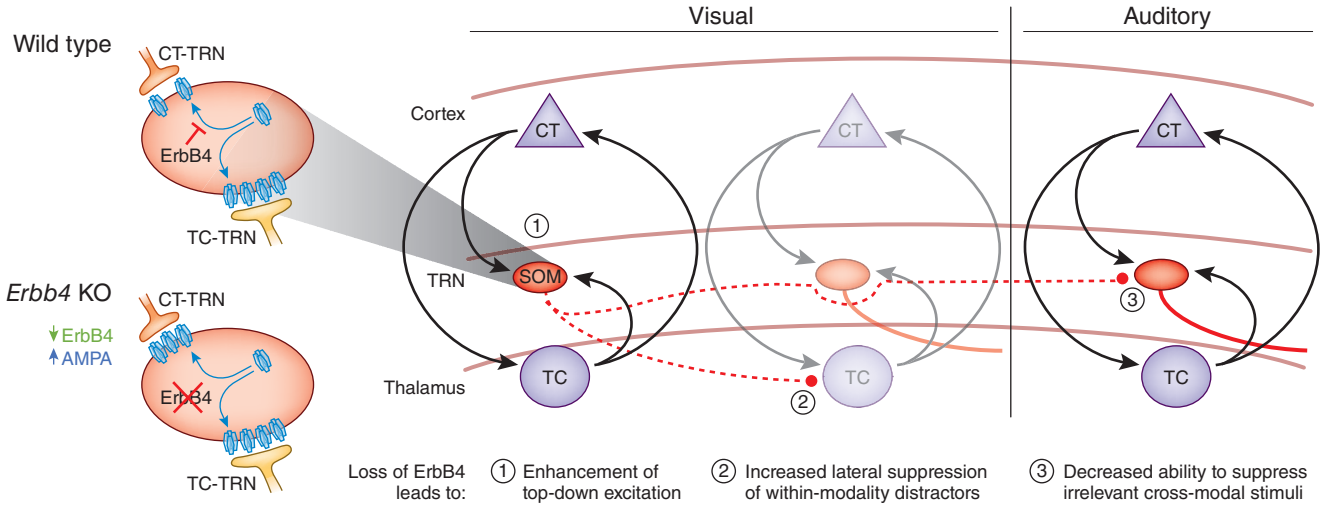

Figure 1 Integrating thalamic ErbB4 function across synapses, circuits and behavior: a hypothetical model. A series of corticothalamic loops are represented in visual and auditory regions. Corticothalamic (CT, purple triangles) and thalamocortical (TC, purple circles) neurons form excitatory synaptic connections in each thalamocortical loop, and neurons of the thalamic reticular nucleus (TRN, red ovals) form inhibitory synaptic connections across loops. Dashed lines indicate possible TRN connectivity in and across visual and auditory sensory regions. ErbB4 reduces the strength of AMPA currents at CT-TRN synapses in the SOM$^+$ subset of TRN cells (inset). Knockout (KO) of ErbB4 specifically strengthens the CT-TRN synapse (1), but not the TC-TRN synapse, enhancing top-down attentional feedback. In this model, lateral inhibition by TRN at the level of the TC cells (2) inhibits the passage of distracting sensory information by TC relay cells en route to the cortex, leading to suppression of within-modality distractors and enhanced performance in feature detection tasks. However, intra-TRN inhibition across sensory modalities may disinhibit thalamocortical circuits that are not relevant (3), leading to a reduced ability to switch attention across sensory modalities.

of an adeno-associated virus into TRN. These animals showed the same behavioral alterations as the SOM-ErbB4 knockout mice, highlighting the importance of ErbB4 exclusively in SOM$^+$ TRN cells.

Given this relationship between feature detection versus switching performance and ErbB4 expression in SOM$^+$ TRN cells, how might the thalamocortical circuit be altered leading to the observed behavioral changes? Using an elegant set of optogenetic approaches to individually excite cortico-thalamic or thalamo-cortical inputs to TRN, the authors found a specific increase in the strength of excitatory postsynaptic currents in TRN arising from cortical synapses, and thus an enhancement in top-down influence. In turn, this enhancement leads to an increase in cortical feedback inhibition of the thalamus through TRN.

Notably, normalizing excitatory synaptic currents specifically in SOM-TRN cells was sufficient to reverse the behavioral alterations observed following the loss of ErbB4. Given that cortico-TRN synapses are specifically dependent on AMPA glutamate receptors containing the GluA4 subunit[9], the authors achieved pathway-specific AMPA receptor knockdown using a clever dominant-negative approach: overexpression of the C-terminal tail of GluA4. This experiment demonstrated that a loss of ErbB4 causes an AMPA-dependent enhancement in cortico-TRN synaptic excitation, which mediates the observed improvement in feature selection and impairment in attentional switching.

The challenge, however, lies in integrating these two major findings, one at the molecular level—specific strengthening of cortico-TRN synapses—and another at the behavioral level—changes in detection and attention. To this end, the authors present a speculative, yet intriguing, model of thalamocortical circuitry to explain their results. In this model, TRN mediates lateral inhibition to increase the salience of certain stimuli. In the case of within-modality feature detection, ErbB4-deficient TRN cells are primed to respond strongly to top-down cortical input resulting from increased synaptic GluA4 (**Fig. 1**). In this model TRN cells would in turn inhibit off-target 'relay cells' (**Fig. 1**), thereby reducing the activity of distractor inputs. This surround suppression feature of TRN inhibition of relay neurons is an attractive model for TRN-mediated enhancement of feature detection.

How then might the impaired attentional switching be explained in the context of this model? One possibility is that TRN cells may primarily form long-range, cross-modal synaptic connections in the TRN itself (**Fig. 1**) while bypassing local TRN cells. This leads to the possibility that strong TRN activation in one sensory modality might effectively reduce the salience of relevant information in other modalities by disinhibition of irrelevant inputs. If true, this would help to reconcile inconsistencies between studies that have found evidence of intra-TRN synaptic connections and those that have not. Extensive paired recordings of nearby TRN cells[10] and optogenetic stimulation of cortical regions projecting to TRN[11] have failed to find evidence of TRN-mediated chemical inhibition of TRN cells. However, at least one study mapping circuits by means of laser-scanning glutamate uncaging has suggested that longer range intra-TRN synaptic connections do in fact exist, whereas gap-junction coupling predominates local connectivity[12].

The TRN has historically been thought to uniformly and broadly provide inhibition to the thalamus[6,13]. However, the findings reported here and recently by others[14,15] are beginning to challenge this view. As opposed to an all-encompassing gatekeeper, it is now apparent that the TRN instead consists of many gatekeepers, each with different standing orders that sometimes conflict with one another. How exactly the thalamus is subdivided into distinct functional compartments is still very much an open question. Undoubtedly, as Ahrens *et al.*[1] have shown, the use of continually advancing genetic, physiological and molecular approaches to deconstruct these newly appreciated TRN subnetworks represents a new frontier in understanding the role of the thalamus in regulating perception and behavior.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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Change the neural code, change the message

Maarten Kamermans

The retina encodes visual information and sends it to the brain. We now learn that this neural code varies strongly with light adaptation. Does this mean a change in the message or a change in the way that the message is coded?

Although the retina is possibly the most extensively studied part of the brain, it still contains many mysteries. The retina is characterized by three basic features: two types of photoreceptors (rods for low light levels and cones for daylight conditions), ON and OFF pathways (signaling light increments and decrements, respectively), and antagonistic center/surround-organized receptive fields. These basic structures generate a complex neural code at the level of the ganglion cells, which carry the output of the retina to the brain, signaling information about, for instance, luminosity, contrast, color, direction of movement and orientation. The ability of the retina to perform this coding under an extraordinarily wide range of light levels is well known, and a plethora of the associated adaptational changes have been described. However, it has generally been assumed that the neural code itself is qualitatively stable. Two studies published in *Nature Neuroscience*[1,2] show that this view is much too simplistic. The retina seems to change its coding strategies by switching functions of retinal pathways. The implications for understanding the retinal neural code are profound.

Szikra *et al.*[1] found that rods, which were thought to function only at very low light levels, actually have a daytime job as well. Although rods did not respond directly to light under daylight conditions, they did relay cone signals to the bipolar cells. In this study, voltage responses of single rods in a whole-mount mouse retina were recorded while the retina was stimulated with a spot of light of various sizes, but with constant contrast, on backgrounds of different intensities.

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As expected, the authors found that rods hyperpolarized in response to the spot stimulus in dim background conditions. However, the surprise came when they increased the background intensity. One would expect rods to become saturated in these conditions and therefore be unresponsive, but, unexpectedly, the rods depolarized to spot stimuli for these high background intensities.

Depolarizing responses in photoreceptors have been shown before[3–5] and can be attributed to inhibition by horizontal cells. However, the general assumption that cones receive inhibition from horizontal cells driven by cones and rods receive inhibition from horizontal cells driven by rods does not fit the results of Szikra *et al.*[1]. In this case the depolarizing responses were found far outside the range of light intensities at which rods respond to light, suggesting that the cones were driving this response. The first indication that this was indeed the case came from the finding that the spectral sensitivity of the depolarizing response measured in rods was similar to that of cones.

Next, Szikra *et al.*[1] tested whether depolarizing responses of rods could be mediated by feedforward inhibition from cones via horizontal cells to rods. The depolarizing responses in rods were abolished when the photoreceptor input to horizontal cell was blocked, suggesting that they were indeed driven by horizontal cells. However, the authors went one step further and performed a particularly elegant optogenetic experiment in which they reversibly switched the functionality of horizontal cells on or off. When horizontal cells were switched off, the depolarizing responses disappeared, directly showing their involvement.

To resolve the origin of the depolarizing responses in rods, Szikra *et al.*[1] tried blocking the feedback signal from horizontal cells to photoreceptors pharmacologically. They first tested picrotoxin, a GABA receptor antagonist, but the depolarizing responses in rods remained. This is consistent with most feedback studies, which have ruled out the involvement of GABA[6,7]. The two leading alternative hypotheses for negative feedback from horizontal cells to photoreceptors, an ephaptic one[8] and a pH-based one[9], have recently been combined into one mechanism[10]. Application of the pH buffer HEPES at 10 mM inhibits feedback[9]. Szikra *et al.*[1] indeed found that the depolarizing responses were reduced after the application of HEPES. Interestingly, they did not see a complete block, suggesting that some component of feedback remains present. It will be of great interest to repeat these experiments in knockout mice lacking proteins that may be involved in the feedback pathway, such as pannexin 1 and connexin 57.

The results of this study illustrate one of the 'design principles' of the retina: it should encode information as efficiently as possible, using the least amount of energy. One way to achieve this is to use a minimal redundancy code and another is to use all available neurons in any adaptational state[11,12]. Szikra *et al.*[1] elegantly show how the retina reuses the neurons dedicated to rod vision during night time to mediate cone-driven surround responses in daytime (**Fig. 1**). They even present some evidence for the reverse: cone pathways might mediate rod-driven surrounds during night time (**Fig. 1**). The consequence is that the meaning of the signals flowing through the various ganglion pathways to higher brain areas might change with adaptation state.

Tikidji-Hamburyan *et al.*[2] illustrate this unexpected consequence in an astonishing way. Their findings suggest that such switches in retinal coding might be a general phenomenon. Using multi-electrode recordings in isolated mouse retinas, the authors found that most ganglion cells had distinctly different, but stable, response properties in different luminance conditions (**Fig. 1**). For instance, cells