inputs from ON and OFF bipolar cells encode the local increase or decrease in light intensity impinging on the retina. Second, electrical synapses rapidly and reliably broadcast the timing of the leading AP to neighboring cDSGCs. Third, dendritic voltage-gated Na^+ channels enable active backpropagation of the leading AP into the dendrites of the prejunctional cell and the amplification of both the chemical synaptic input and GJ-mediated spikelet in the post-junctional cell.

So what role could this complex interplay of synaptic and dendritic mechanisms subserve in visual processing? The link between these synaptic and dendritic mechanisms and encoding was cemented in a final series of experiments, in which the authors used different patterns of illumination and varied the contrast to investigate which aspects of the visual stimulus are encoded in temporal correlations and firing rate. When two illumination spots were separated by a gap, fine-scale temporal correlations disappeared, suggesting that these correlations report changes in illumination on a fine spatial scale. Decreasing the contrast of the bar-shaped visual stimulus or introducing a spatial gap in the stimulus both resulted in a decrease in firing rate, indicating that these two stimuli were indistinguishable in the firing rate response. However, these visual features could be discriminated with spike correlations: relative spike correlations were higher at lower contrasts, but were reduced with the introduction of a gap into the stimulus. Moreover, unlike in the case of firing rate, fine-scale correlations were present when the visual stimuli moved in both the preferred and the non-preferred direction. Indeed, the authors show that the strength of fine-scale synchrony mediated by GJs is inversely correlated to the firing rate of cDSGCs, contrary to that expected when correlations arise from firing rate[15]. Fine-scale synchrony in the spikes arising from local cDSGCs therefore conveys information that is distinct from the firing rate. Thus, electrical and chemical synaptic inputs operate in concert with nonlinear dendrites to convert distinct features of the visual scene into complementary codes.

Electrical synaptic input provides an early readout of the activation state of dendrites in the cDSGC network during ON and OFF responses. By synchronizing the spikes of cDSGC whose dendrites are in a similarly activated state, they may enhance the temporal fidelity of the onset spikes in the cDSGC population response. The presence of electrical and chemical synapses and active dendrites in output neurons of the retina may therefore enable more information to be read out rapidly and represented in a way that downstream networks can transmit and decipher quickly, potentially enabling animals to perceive changes in the visual scenes more rapidly. It will be interesting to explore whether electrically coupled networks in other brain regions use similar mechanisms to read out patterns of activated dendrites and convert them into a synchronous population code.

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ERKquake in Noonan syndrome: one step closer to personalized medicine

Mauro Costa-Mattioli

A study now provides proof of concept that restoration of Ras-Erk signaling during adulthood rescues cellular and cognitive phenotypes in mouse models of the genetic disorder Noonan syndrome.

Personalized medicine is often described as providing a given patient with the right drug at the right dose at the right time. NS is a genetic disorder that is acquired through dominant inheritance[1]. Originally described by Jacqueline Noonan in 1963, NS has an estimated prevalence of 1 in 1,000–2,500 individuals[2]. Although the syndrome is caused by several germline mutations impinging on the Ras-Erk signaling pathway, mutations in the *PTPN11* gene, which encodes the phosphatase SHP2, account for approximately 50% of cases[3]. A variety of signs and symptoms are characteristic of NS, including short stature, cardiac and hematopoietic problems, auditory deficits, feeding difficulties, and problems with social and emotional competence[2]. Approximately 30–50% of individuals with NS show intellectual disability[3,4]. However, the precise neurobiological mechanisms underlying the cognitive impairment in NS remain unknown. Consequently, no treatment is yet available.

In this issue of *Nature Neuroscience*, Lee *et al.*[5] show that mouse models of NS exhibit impaired long-lasting changes in hippocampal synaptic strength and long-term memory that are similar to the memory impairment seen in human patients. In addition, in a compelling set of multidisciplinary experiments, the authors also show that restoration of the abnormally high Ras-Erk signaling during adulthood, with either a mitogen-activated protein kinase kinase (MEK) inhibitor or an FDA-approved drug that blocks Ras-Erk signaling, rescues the NS-like cellular and cognitive phenotypes in these mice.

Mice expressing NS-associated *Ptpn11* mutations have been crucial tools in helping investigators to understand the pathological and molecular underpinnings of NS, specifically those related to cardiac defects and short stature. These mutations, $Ptpn11^{N308D/+}$ and $Ptpn11^{D61G/+}$, result in gain-of-function

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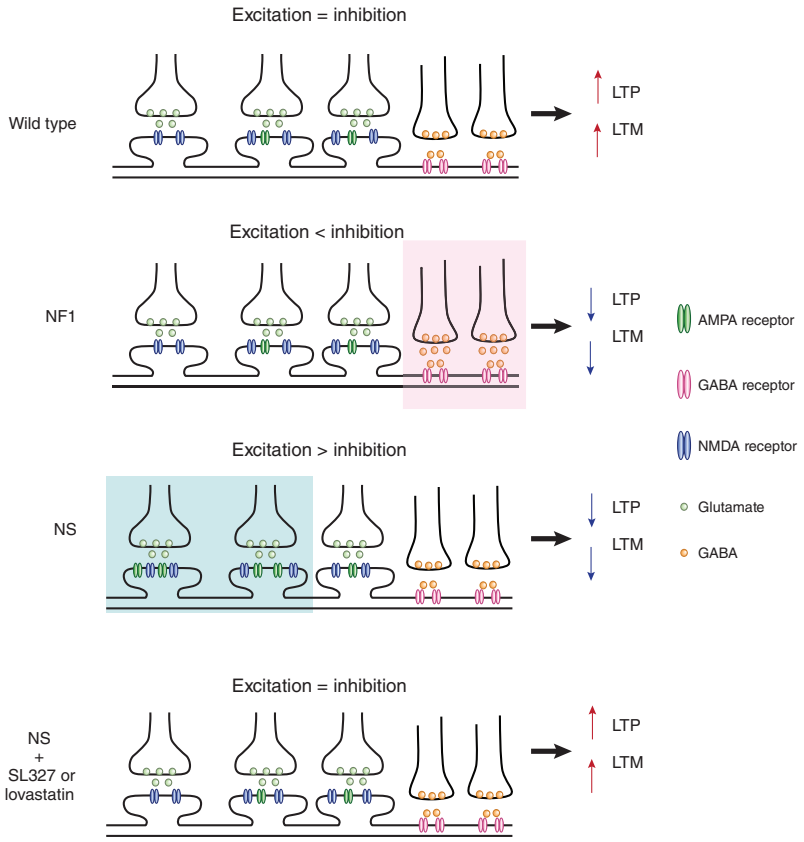

Figure 1 Excitation and inhibition imbalance, impaired LTP and long-term memory (LTM) are common features in RASopathies. Wild-type mice show a balance between excitation and inhibition. By contrast, in NS and NF1 mouse models, the inhibition and excitation balance is disrupted. Consequently, LTP and LTM are impaired. Whereas hyperactivation of Erk-Ras signaling in *Nf1*$^{+/-}$ mice causes an increase in inhibitory synaptic transmission, the increased Erk-Ras signaling in *Ptpn11* mutant mice boosts excitatory synaptic transmission. Treatment with SL372 or lovastatin restores the balance between excitation and inhibition and rescues the deficient LTP and LTM in NS mouse models. Pink shading highlights the increased inhibitory transmission at GABAergic synapses in NF1; blue shading highlights the enhanced excitatory synaptic transmission at glutamatergic synapses in NS.

alleles leading to upregulation of Ras-Erk signaling[6].

Given that NS patients exhibit problems in memory tasks known to require the hippocampus, a brain region crucial for spatial learning and memory in both humans and rodents[7], Lee *et al.*[5] first examined whether two NS mouse models (*Ptpn11*$^{N308D/+}$ and *Ptpn11*$^{D61G/+}$ mice) show any evidence of defective spatial learning and memory. Spatial memory was assessed in the Morris water maze, where mice swimming in a pool of opaque water search for a submerged platform.

Lee *et al.*[5] first tested the *Ptpn11*$^{N308D/+}$ mice. These had trouble forming long-term spatial memories, but, after extensive training, their performance was comparable to that of wild-type mice. Thus, they were able to learn the task, albeit at a substantially slower rate than normal mice. In addition, *Ptpn11*$^{N308D/+}$ mice were also impaired in another hippocampus-dependent behavioral task, in which animals learn that a given visual stimulus predicts a foot shock. The authors then examined the *Ptpn11*$^{D61G/+}$ mice, which carry a mutation that is known to cause a more severe phenotype than *Ptpn11*^{N308D}. These mice were dramatically impaired in spatial learning, and even overtraining failed to restore their memory.

It is widely believed that memory storage has a physical basis in long-lasting changes in synaptic strength[8]. For instance, high-frequency stimulation of a given neuronal pathway (for example, the Schaffer collateral and commissural axons in the hippocampus) leads to a sustained increase in the efficacy of their synaptic connections, resulting in a phenomenon known as long-term potentiation (LTP)[9]. The authors next determined whether LTP was altered in the hippocampus of *Ptpn11* mutant mice. Consistent with the idea that LTP underlies long-term memory storage, Lee *et al.*[5] found that both *Ptpn11*$^{N308D/+}$ and *Ptpn11*$^{D61G/+}$ mice show impaired LTP, with a greater impairment in the latter. These data provide conclusive evidence that hippocampal LTP and spatial long-term memory are deficient in the NS mouse models.

To specifically study the role of mutated Ptpn11 in adult synaptic plasticity and behavioral learning in the hippocampus, bypassing any possible developmental effects caused by the mutations, the authors selectively overexpressed the more pathogenic mutation (*Pptpn11*^{D61G}) in the hippocampus of control mice. Strikingly, virally mediated overexpression of PTPN11^{D61G} in the hippocampus of adult mice caused impairments in the learning performance of the mice, both in the Morris water maze and in a hippocampus-dependent behavioral task that tests the animal's ability to distinguish between new and familiar objects. Accordingly, overexpression of PTPN11^{D61G} blocked the induction of LTP by repeated stimulation. Furthermore, using single-cell recording techniques, the authors observed a selective increase in excitatory synaptic transmission in hippocampal neurons from both PTPN11^{D61G}-overexpressing mice and *Ptpn11*$^{D61G/+}$ mice (**Fig. 1**), which may account for the deficits in LTP and spatial memory in these NS mouse models.

Given that overexpression of PTPN11^{D61G} in the hippocampus resulted in increased Erk activity and that proper regulation of Ras-Erk signaling is required for spatial long-term memory and LTP[10,11], Lee *et al.*[5] wondered whether blockade of Erk activity would be sufficient to rescue the behavioral and cellular cognitive deficits in these animals. To address this question, they first injected mice overexpressing PTPN11^{D61G} with a low dose of the MEK inhibitor SL327. Remarkably, reducing Erk activity reversed the hippocampus-dependent memory deficit evident in the Morris water maze and object recognition tasks, as well as the impaired LTP and increased excitability in adult PTPN11^{D61G}-overexpressing mice (**Fig. 1**). Furthermore, when adult whole-body knock-in *Ptpn11*$^{D61G/+}$ mice (which also showed enhanced hippocampal Erk activity) were treated with SL327, their severe memory deficits disappeared.

To further support the notion that the Ras-Erk hyperactivation is responsible for the cognitive impairment in these NS mouse models, the authors switched strategies and treated *Ptpn11*$^{D61G/+}$ mice with the FDA-approved blood-brain-barrier permeant drug lovastatin. Although lovastatin is a 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitor in the statin family of drugs and, in the clinic, has been mostly used to lower cholesterol and treat cardiovascular disease, there is evidence

that lovastatin can decrease Ras-mediated Erk activation in the brain[12]. Treating adult *Ptpn11*$^{D61G/+}$ mice with lovastatin not only normalized Erk activity, but fully rescued their severe learning and memory and LTP deficits. Remarkably, the lovastatin-treated *Ptpn11*$^{D61G/+}$ mice performed as well as wild-type mice, and lovastatin was not observed to have any detrimental effect in wild-type mice.

These synergistic and elegant experiments by Lee *et al.*[5] provide strong evidence that the hippocampus-dependent memory impairment in NS mouse models is caused by hyperactivation of Ras-Erk signaling. More importantly, they suggest that it may be possible to reverse this neurodevelopmental disorder even during adulthood. The study by Lee *et al.*[5] builds on previous work from the same laboratory on other RASopathies (disorders caused by changes in Ras activity). In a series of groundbreaking studies, Silva's research group has shown that normalization of Ras-Erk signaling in *Nf1*$^{+/-}$ mice, a mouse model of neurofibromatosis 1 (NF1), rescues the long-term memory and LTP deficits[13,14]. Unlike NS mouse models, which show exaggerated excitatory synaptic transmission[5], *Nf1* deficiency leads to increased GABAergic synaptic transmission[13,14]. Thus, it will be interesting to determine precisely how hyperactivation of Ras-Erk signaling differentially controls GABAergic and glutamatergic synaptic transmission in NF1 and NS, respectively.

The overall disruption in the balance between excitation and inhibition caused by mutations in *Nf1* or *Ptpn11* (**Fig. 1**) and the fact that epileptic seizures have been observed in NS and NF1 patients raise some interesting questions. First, do NS and NF1 mouse models exhibit electrographic seizures? If so, what exactly is their contribution to the cognitive phenotype? In addition, could Erk or Ras inhibitors suppress the seizure phenotype? Disruption in the balance between excitation and inhibition is a common synaptic feature of mouse models of autism spectrum disorders. Thus, it would be also interesting to assess whether NF1 and NS mouse models show behavioral endophenotypes that are associated with autism, including deficits in social behavior and stereotypic repetitive behaviors, and whether those are caused by abnormally high Erk-Ras signaling. Finally, the solid findings with *Nf1*$^{+/-}$ mice and lovastatin have already led to early clinical trials[15]. Given the very encouraging preclinical findings presented by Lee *et al.*[5], personalized treatment of NS patients with MEK inhibitors or statin-based drugs may ultimately follow.

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Replay to remember: a boost from dopamine

Laura A Ewell & Stefan Leutgeb

A study links transient activation of the brain's reward system during a novel experience to frequent reactivation of memory traces during sleep and shows that artificial activation of the reward circuit can strengthen memories.

We all know that some experiences stand out in our memories, whereas others seem to not be there at all. Certain conditions, such as novelty, seem to promote memory. For example, think about the detailed memories when you travel to a new destination as opposed to the scarce memories from a regular commute. What is different about the brain dynamics during novel experiences? Novelty promotes the release of the neurotransmitter dopamine[1], which is canonically thought of as a reward signal, but has more recently been implicated in signaling a mismatch between reality and one's expectation of reality[2,3]. Novel experiences may represent the most extreme mismatch of this sort. To study the influence of dopamine release during novelty in memory augmentation, McNamara *et al.*[4] used optogenetics to precisely control the activity of dopaminergic neurons. They then read out the effects of the manipulation with large-scale neural population recordings of hippocampal neuronal activity patterns. By combining these approaches, they linked the memory-promoting effects of transient dopamine release during the experience to a persistent change in neuronal network activity. During sleep after the novel experience, hippocampal neuronal activity patterns from the experience continued to be frequently reactivated and memory for the experience became enhanced.

In rodents, memory is often studied in the context of spatial memory. Principal neurons in the hippocampus exhibit robust spatial tuning, such that they are only active when an animal is at particular positions in an environment. These neurons are referred to as place cells[5]. For a given environment, the activity of hippocampal place cells is thought to provide the neural substrate for a road map and for knowing where one is on the map. In this scheme, the quality and stability of the map would be directly correlated with the quality and stability of the spatial component of memory. Think back to traveling to a new place; do memories of where you went stand out? What makes hippocampal spatial codes for novel experiences stable and the experiences memorable? It was previously suspected that hippocampal place codes for novel environments were stabilized by dopamine[6], but how does dopamine support the long-lasting stabilization process?

To understand how dopamine improves spatial stability, and eventually memory, McNamara *et al.*[4] first showed that neurons in the ventral tegmental area (VTA) fired in bursts in the novel environment, which is known to result in dopamine release in its target areas, including the hippocampus.

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