apoE3. This latter finding nicely explains the ε4 allele dose-dependent reduction of AD age of onset.

Consisting of distended axons and dendrites filled with vesicles, autophagic intermediates, mitochondria, and other organelles, dystrophic neurites are major AD lesions thought to contribute to pathophysiology and dysfunction in AD brain (Dickson, 1997). An interesting finding of both studies is that the formation of dystrophic neurites is significantly affected by apoE4, the mechanism of which is unclear. The results suggest that apoE4 intensifies the toxicity of the amyloid plaque toward axons and dendrites in contact with the deposit. An intriguing observation of Huynh et al. (2017) was that ASO treatment of APP/PS1-21/ε4 at 6 weeks increased plaque size and frequency as shown by Aβ immunostaining, although X-34 dye staining that labels the β sheet fibrillar core of the plaque showed no such increase. Since overall amyloid load was unchanged, these results imply that the increased ASO-associated plaque size and frequency derived from deposition of non-fibrillar, and thus perhaps less toxic, Aβ. Understanding how apoE4 alters Aβ toxicity is an important goal of future studies.

Finally, the therapeutic implications of these studies are profound, namely that apoE-targeted therapies, in particular for *APOE4* carriers, need to be administered very early in the disease process to affect Aβ-related pathogenic mechanisms, preferably for prevention before the occurrence of significant Aβ seeding. This strategy may reduce the risk of failure for future AD clinical trials, provided low-amyloid presymptomatic patient populations most likely to benefit from an apoE-targeted therapy are recruited. Their findings also highlight potential benefits of segregating patients into different treatment groups according to their *APOE* genotype status. Of note, a recent study shows that apoE also influences tau-mediated neurodegeneration (Shi et al., 2017). If this bears out, one might be able to still target apoE somewhat later in the process of AD pathogenesis and still have beneficial effects of apoE lowering. Increasing the success of AD clinical trials is a critical goal given the poor AD trial track record of the past decade (Cummings, 2017). The combined results of Liu et al. (2017) and Huynh et al. (2017) provide deep mechanistic insights into how *APOE4* is the strongest genetic risk factor for AD and add very crucial voices to the growing chorus of early intervention for prevention of AD.

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Homeostatic Scaling of AMPA Receptors by Semaphorin

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Regulation of AMPA receptors mediates homeostatic scaling. In this issue of *Neuron*, Wang et al. (2017) identify a new role of secreted semaphorin 3F and elucidate how it triggers synaptic downscaling of AMPA receptors through regulation of the binding of Sema3F holoreceptor complex to AMPA receptors.

Neuronal circuits maintain structural and functional plasticity to enable information storage during learning and memory and in response to environmental challenges. Nonetheless, neurons possess an adaptive compensatory mechanism to prevent runaway hyper-excitation or over-inhibition to maintain neuronal and network stability. This form of plasticity, named homeostatic plasticity, can be achieved by adjusting neuronal excitability, synaptic scaling, or the balance between excitation

and inhibition in response to altered network activity (Turrigiano, 2012). These homeostatic changes can occur globally at all synapses of a single neuron or at individual synapses.

The best-characterized homeostatic regulatory mechanism is synaptic scaling, in which neurons restore stable firing in response to the perturbation of the network activity by generating compensatory changes in synaptic strength. The regulation involves the change of surface α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors on postsynaptic neurons, namely changes in the composition and abundance of synaptic AMPA receptors. For example, increased neuronal activity by chronic pharmacological administration of bicuculline induces the downscaling of surface AMPA receptors, whereas long-term activity blockade by tetrodotoxin (TTX) administration causes AMPA receptor upscaling. Nonetheless, how the neurons sense and respond to activity perturbation remains unclear. Furthermore, the change in the surface AMPA receptors during synaptic scaling can be achieved by regulating exocyctic and endocytic membrane traffic of the receptors, trafficking of the receptors between synaptic and extrasynaptic compartments, and interaction of the receptor subunits with scaffolding and signaling proteins such as transmembrane AMPA receptor regulatory proteins (reviewed in Pozo and Goda, 2010; Turrigiano, 2008). Nonetheless, the signaling pathways and the molecular interaction mechanisms underlying the AMPA receptor trafficking and expression need further investigation. Therefore, it is critical to identify the molecular controls that regulate synaptic scaling.

Secreted molecules can shape homeostatic regulation globally or locally at individual synapses. Known examples include brain-derived neurotrophic factor, tumor necrosis factor-α, and retinoic acid (Pozo and Goda, 2010). However, it is unclear how these factors sense changes in neural activity to mediate synaptic scaling. Semaphorin proteins, which are well-known neuronal guidance cues during neural development, mediate signals through the activation of holoreceptors, which comprise ligand-binding subunits, neuropilins (Npns), and signal-transducing subunits, plexins (Kumanogoh and Kikutani, 2013). Specifically, semaphorin 3F (Sema3F) exerts a repulsive signal through the activation of the Npn-2/plexinA3 (PlexA3) holoreceptor. Sema3F signaling is also involved in later stages of neuronal development, such as dendritic morphogenesis, and in synapse development and functioning (Tran et al., 2009). In particular, the localization of Npn-2 in postsynaptic density fractions in the adult mouse brain suggests that Sema3F/Npn-2 signaling may function in mature synapses.

In this study, Wang et al. show that Sema3F functions at excitatory synapses and plays a key role in homeostatic synaptic plasticity (Wang et al., 2017). Similar to the regulation of its receptor Npn-2, Sema3F is highly expressed in the mouse embryonic and early postnatal neocortex, subsequently decreasing upon development. Sema3F is mainly expressed in the excitatory neurons of the cerebral cortex. Chronic elevation of activity in cortical neurons by bicuculline administration enhances secretion of Sema3F, whereas activity blockade by TTX does not exert a similar effect. This raises the possibility that secreted Sema3F may mediate homeostatic scaling. Indeed, while prolonged treatment of cortical neurons with bicuculline induces downscaling of AMPA receptors, as indicated by the decreased surface expression of AMPA receptor subunit GluA1, Sema3F deletion abolishes this reduction. The role of Sema3F appears to be specific to the homeostatic downscaling of AMPA receptors, but not their upscaling. Interestingly, similar to bicuculline treatment, Sema3F treatment alone is sufficient to reduce surface GluA1 expression in cortical neurons. Thus, Sema3F may mediate the downscaling of AMPA receptors in neurons in response to chronic elevated activity.

Moreover, the enrichment of Npn-2 in the postsynaptic density suggests that Sema3F may mediate its action during homeostatic plasticity by interacting with its holoreceptor at postsynaptic sites. Interestingly, Npn-2 expression is concentrated at the dendritic spines of cortical neurons, where excitatory synapses reside, and is co-localized with GluA1 puncta. The decrease of surface GluA1 induced by bicuculline administration is abolished in Npn-2$^{-/-}$ cortical neurons, suggesting that Sema3F/Npn-2 signaling is required for the neuronal activity-induced downscaling of AMPA receptors. The attenuation of the activity-induced decrease in the amplitude of miniature excitatory postsynaptic currents in Npn-2 knockout neurons corroborates the notion that Npn-2 is critical for mediating the neuronal activity-induced reduction of synaptic strength.

Several CUB (complement C1r/C1s, Uegf, Bmp1) domain-containing transmembrane proteins such as Neto1 bind to glutamate receptors to regulate their functions (Wang et al., 2012). The localization of CUB domains containing Npn-2 to the excitatory synapses prompted the investigation into whether Npn-2 interacts with AMPA receptors. Indeed, *in vitro* interaction reveals that Npn-2 specifically interacts with GluA1 through the Npn-2 CUB domains, and this specific interaction can be confirmed in the adult mouse brain. Although the other subunit of the Sema3F holoreceptor, PlexA3, does not directly interact with GluA1, the existence of Npn-2 facilitates the formation of the Npn-2/PlexA3/GluA1 receptor complex. Because the downscaling of AMPA receptors caused by chronic elevated activity occurs in a Sema3F-dependent manner, it is critical to examine whether Sema3F modulates the binding of Npn-2 and GluA1 in the Npn-2/PlexA3/GluA1 receptor complex. Indeed, Sema3F treatment disrupts the association between Npn-2 and GluA1. While mutating the semaphorin-binding sites of Npn-2 does not affect the *in vitro* interaction between Npn-2 and GluA1 or PlexA3, the Sema3F-dependent decreased association of Npn-2 and GluA1 is abolished. Therefore, the Sema3F-dependent dissociation of Npn-2 and GluA1 is likely dependent on the specific interaction between Sema3F and Npn-2.

Chronic elevation of neuronal activity reduces the interaction between Npn-2 and GluA1 in cortical neurons in a Sema3F-dependent manner. Specifically, expressing the Npn-2 mutants that do not interact with Sema3F or with GluA1 in Npn-2-deficient neurons shows that the interaction of Npn-2 and Sema3F as well as with GluA1 at postsynaptic sites is crucial for mediating the AMPA receptor downscaling. Thus, these findings

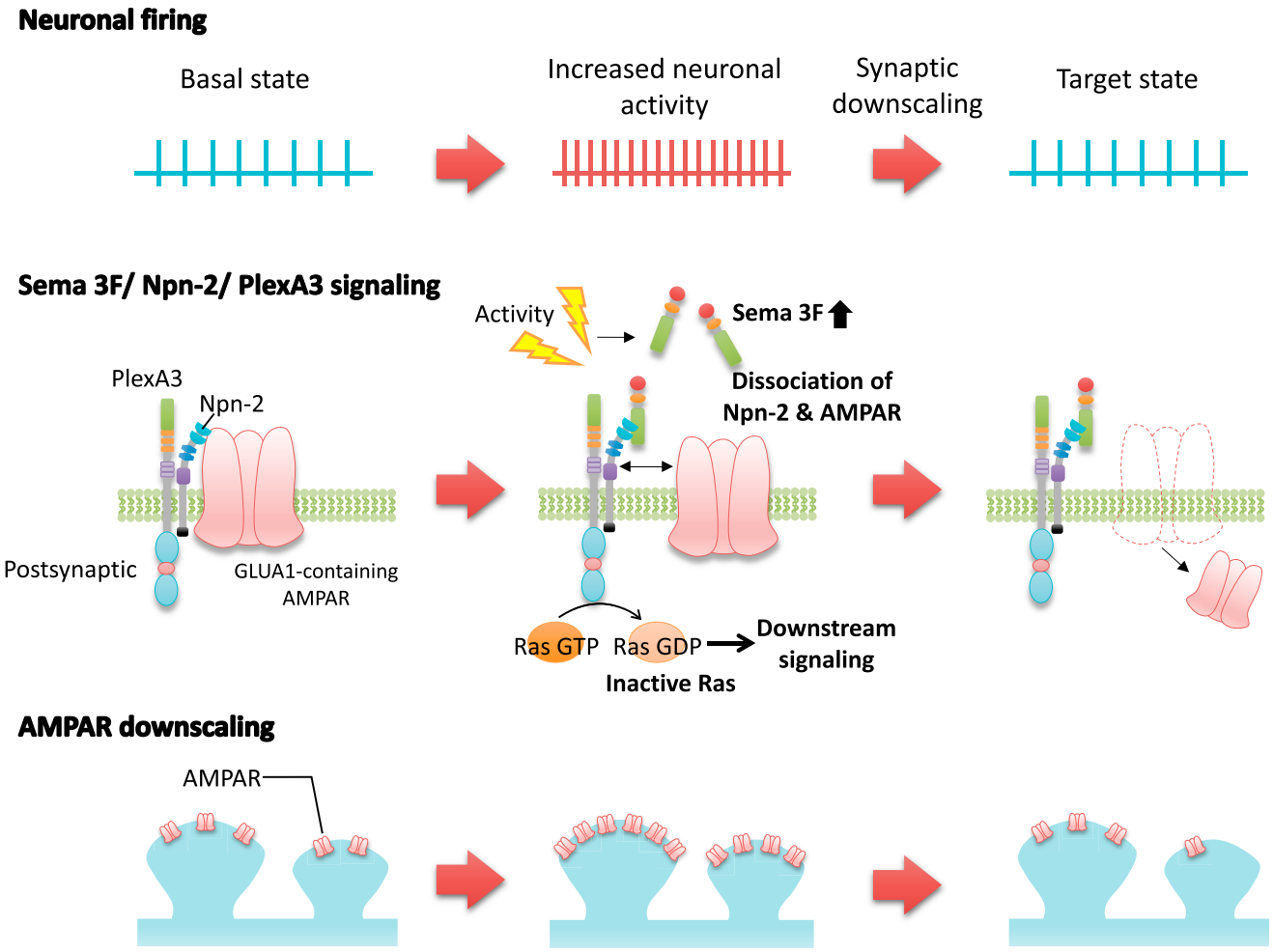

Figure 1. Sema3F-Dependent PlexA3/Npn-2 Holoreceptor Signaling Mediates Downscaling of AMPA Receptors in Synaptic Scaling
Chronic elevated neuronal activity increases Sema3F secretion. Both the Sema3F-dependent regulation of the molecular interaction between Npn-2 and AMPA receptors and PlexA3-dependent inactivation of Ras are required for the reduction of surface AMPA receptors.

suggest that the elevation of neuronal activity downscales AMPA receptors through the Sema3F-dependent modulation of Npn-2/GluA1 interaction. The other signal-transducing subunit of the Sema3F holoreceptor, PlexA3, is also required for synaptic downscaling upon chronic activity elevation. Specifically, the Ras GTPase-activating activity of PlexA3 is critical for the Sema3F-mediated dissociation of GluA1 and Npn-2 from the Npn-2/PlexA3/GluA1 receptor complex and the AMPA receptor downscaling.

Hence, the findings of this study collectively demonstrate that increased neuronal activity triggers the downscaling of AMPA receptors by enhancing the secretion of Sema3F, which functions through its holoreceptor, Npn-2/PlexA3 (Figure 1). The homeostatic scaling is achieved through a tightly coordinated Sema3F- and PlexA3-dependent regulation of the association between Npn-2 and GluA1. The secreted Sema3F acts as a cellular sensor for activity perturbation, linking the change in network activity to the downstream signaling pathways. Characterizing the cellular source of Sema3F will shed light on the detailed cellular feedback mechanism in synaptic scaling. The Sema3F-dependent modulation of Npn-2/PlexA3 holoreceptor exerts dual functions, with Npn-2 serving as a core component of the trafficking machinery regulating the expression of AMPA receptors while PlexA3 promotes a signaling cascade following Ras inactivation. Further dissection of the molecular machinery will provide insights into understanding the mechanisms that regulate synaptic scaling. For example, how does dissociation of Npn-2 and AMPA receptors regulate the fate of AMPA receptors? Uncovering whether AMPA receptors undergo endocytosis or degradation and what downstream pathways are regulated upon the inactivation of Ras signaling will help connect this synaptic function of PlexA3 with other pathways that regulate synaptic homeostasis.

Indeed, as altered homeostatic plasticity stability is associated with neurodevelopmental diseases, a better understanding of the molecular mechanisms that mediate synaptic scaling is critical. To date, the molecules that mediate synaptic scaling only associate with a distinct

molecular process in the downscaling of AMPA receptors, e.g., either as a component to regulate the molecular interaction with AMPA receptors or as a part of signaling pathways. Wang and colleagues lay out a comprehensive and clear picture on how Sema3F mediates the synaptic scaling through modulating the interaction of its holoreceptor complex with and downscaling of AMPA receptors.

Homeostatic plasticity regulated by semaphorin/plexin signaling may also involve the functional coordination of presynaptic and postsynaptic sites. For example, it is well known that retrograde signals from muscle can regulate presynaptic homeostatic plasticity at the neuromuscular synapses in *Drosophila* (Davis and Müller, 2015). Specifically, perturbing muscle activity by attenuating the functions of postsynaptic glutamate receptors leads to presynaptic homeostatic plasticity (i.e., increased neurotransmitter release), which offsets the decreased postsynaptic efficacy and thus restores normal muscle excitation. A recent study published in *Nature* shows that another semaphorin member, Sema2b, which is secreted from muscle, enhances neurotransmitter release from presynaptic motor neurons to maintain normal muscle excitation (Orr et al., 2017). Sema2b is specifically released from muscle and acts on PlexB in motor neurons. The specific action of Sema2b/PlexB is mediated via the potentiation of readily releasable pools of synaptic vesicles through actin dynamics and in turn increases the probability of neurotransmitter release. Thus, during homeostatic plasticity, elevation of activity stimulates the secretion of semaphorins as feedback mechanisms and triggers semaphorin-mediated signaling at synapses to control the pre- and postsynaptic strength through independent molecular mechanisms. The secretion of Sema2b and Sema3F exerts their distinct functions by regulating neurotransmitter release at the presynaptic nerve terminals and postsynaptic neurotransmitter receptors, respectively. The specificity of the semaphorin/plexin signaling in homeostatic plasticity is most likely mediated through the expression and the controlled secretion of specific ligands as well as the coupling of their co-receptors at the pre- and postsynaptic terminals. The characterization of the role of semaphorin/plexin signaling in two different homeostatic plasticity paradigms highlights that the precise control of semaphorin/plexin signaling is critical for maintaining the stability of synaptic transmission and network activity during neural development.

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A Sing-Song Way of Vocalizing: Generalization and Specificity in Language and Birdsong

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Spoken languages such as German are extremely discrete, whereas others such as Portuguese are melodic or "sing-song" wherein identifying a word relies on what comes before and after. Perhaps surprisingly, birdsong also exhibits specificity and generalization as articulated by Tian and Brainard (2017).

Efficient performance of motor skills, including ones of vocal nature, relies on the precise control of movements to (1) generate individual motor gestures and (2) rapidly organize them into sequences. Multiple occurrences of the same motor gesture can exhibit substantial variability, adding complexity to their identification by a potential receiver and their articulation by the sender. One source of variability stems from the influence of sequential context, as when gestures present modifications depending on their interaction with other gestures composing a motor sequence. Co-