This Week in The Journal

Neurexin-3α Point Mutation Promotes Transmitter Release

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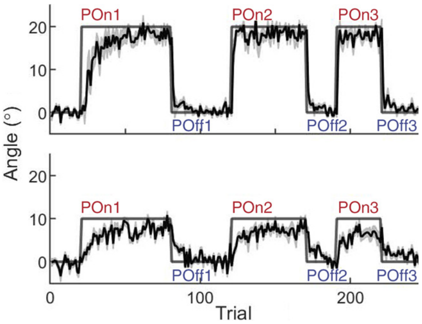
(see pages 9065–9082)

Synapse formation and maintenance are regulated by transsynaptic interactions between presynaptic neurexins and their postsynaptic ligands. Neurexins are encoded by three genes, each of which produces α and β isoforms. Alternative splicing at six extracellular sites in α-neurexins increases structural diversity, enabling neurexins to interact with several postsynaptic partners. Such diversity may underlie differences in neurexin function across neuron types, but this has complicated efforts to study neurexin function and discern how genetic variation in these proteins contributes to risk of neurological and psychiatric disorders.

Because knockout of neurexins—the most common tool for investigating function—can obscure cell type- and isoform-specific effects, Restrepo et al. took a different approach. They compared the effects of Nrxn3α knockdown to the effects of knockdown plus replacement with one of the following four transcripts: wild-type Nrxn3α with the alternative exon at splice site 4 (SS4); wild-type Nrxn3α lacking SS4; or a mutant form of Nrxn3α (A687T) that has been linked to intellectual disability and epilepsy in a human patient, again with or without the SS4 exon.

Consistent with previous results, knocking down Nrxn3α did not affect excitatory or inhibitory transmission in cultured mouse hippocampal neurons. Furthermore, three of the four replacement transcripts had no effect on synaptic phenotypes. But replacement of endogenous Nrxn3α with SS4-lacking Nrxn3α^{A687T} increased the frequency of miniature EPSCs, the amplitude of evoked EPSCs, the size of presynaptic clusters of vesicular glutamate transporters, and the size of the readily releasable pool of synaptic vesicles, and it decreased the paired-pulse ratio at excitatory synapses. Similarly, replacing endogenous Nrxn3α with SS4-lacking Nrxn3α^{A687T} *in vivo* reduced the paired-pulse ratio at synapses between CA1 axons and regular- and burst-spiking neurons in the subiculum. Most remarkably, the change in paired-pulse ratio occluded long-term potentiation at CA1 synapses with burst-spiking neurons, which was previously shown to involve increased release probability, but it did not affect potentiation at synapses with regular-spiking neurons, which involves postsynaptic changes.

These results suggest that the Nrxn3α A687T mutation increases release probability in hippocampal excitatory, but not inhibitory neurons and has synapse-specific effects on plasticity. Importantly, the effect is seen only with some alternatively spliced isoforms, highlighting the diverse roles and effects produced by neurexins and their mutations.



When a perturbation is introduced (POn) during a cursor-moving task, subjects gradually adapt to the perturbation during the first learning block. When the perturbation is large (top), subjects may create a new internal model, so they can adapt quickly when the perturbation is turned off (POff) and back on again. When the perturbation is small (bottom) subjects appear to update a baseline model, and must readapt each time the perturbation is removed or reintroduced. See Oh and Schweighofer for details.

Error Size Dictates When to Update Old or Create New Models

Youngmin Oh and Nicolas Schweighofer

(see pages 9237–9250)

Motor learning is thought to involve the creation of internal models that predict the effects of motor commands. If a command fails to produce the expected result, existing models are updated or new models are created. Updating existing models requires less neural capital than creating new models and is likely to be the best option when conditions change slowly. In contrast, creating new models allows one to switch rapidly between new and previously learned models, which is advantageous when conditions fluctuate repeatedly.

Based on such reasoning, Oh and Schweighofer created a computational model incorporating several rules. First, people maintain multiple motor models: one that predicts the effects of motor commands under baseline conditions; one or more "expert" models that predict motor effects when previously encountered perturbations reoccur; and a "novice" model with unspecific predictions. Each model includes some uncertainty about the expected effect of the motor command. When a command is issued and its effects are determined, the model with the smallest prediction error, weighted by its uncertainty, is engaged and used to guide subsequent actions. If neither baseline nor expert models explain the effect of the motor command, the novice model is modified to create a new expert model.

This computational model made several predictions about how movements will be affected in a visuomotor task in which a cursor must be moved in the presence or absence of external perturbation. With small perturbations, the baseline model will be updated over several trials. After such updating, removal of the perturbation will require readaptation to the baseline condition, which will again take several trials. If the perturbation is then reintroduced, gradual readaptation will be required. In contrast, if the perturbation is large, a new model will be created. In this case, people will be able to switch quickly back to the baseline condition when the perturbation is removed, and then switch quickly back to the adapted condition when the perturbation is reintroduced.

This model accurately predicted the movements of human volunteers, supporting the hypothesis that people update existing models when prediction errors are small and create new models when prediction errors are large. Future work must determine where these models are stored and how they are updated.

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