This Week in The Journal

Brain Stimulation Restores Error Responses in Schizophrenia

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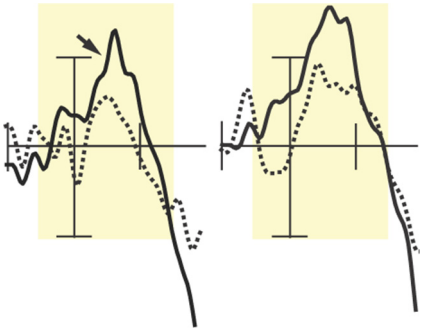
(see pages 12232–12240)

Schizophrenia is characterized by both positive symptoms (i.e., hallucinations and delusions) and negative symptoms (e.g., loss of motivation). Abnormal reinforcement learning, particularly a failure of prediction errors to modify beliefs or behaviors, has been hypothesized to contribute to both symptom types. For example, inadequate prediction-error generation may hypothetically allow delusional beliefs to persist despite contrary evidence, and an inability to use prediction errors to determine which actions lead to rewards might diminish one's motivation to seek such rewards.

Prediction errors alter the firing rate of dopaminergic neurons in the midbrain, leading to changes in dopamine release in target areas, such as the medial frontal cortex. Decreased dopamine release in the medial frontal cortex is thought to underlie the error-related negativity (ERN) that appears in electroencephalographic recordings when a person makes a mistake. Several studies have found that the ERN is reduced in people with schizophrenia, consistent with the hypothesis that prediction error signaling is dysfunctional in these patients.

Reinhart et al. confirmed that ERN amplitudes were lower in schizophrenic patients than in controls, and they found that this was accompanied by slower learning of a stimulus–response association. Moreover, patients with the most severe negative symptoms—particularly anhedonia and flattened affect—had the smallest change in ERN amplitude during learning. Remarkably, anodal transcranial direct-current stimulation (tDCS) of the medial frontal cortex increased the ERN amplitude and the rate of learning in both patients and controls. Indeed, after anodal tDCS, ERN amplitude and learning rate of schizophrenic patients were not significantly different from those of unstimulated controls. However, the effectiveness of tDCS was inversely related to symptom severity: those with the lowest delusion scores showed the most benefit of tDCS.

These results support the hypothesis that people with schizophrenia are impaired at learning from mistakes, perhaps as a result of blunted prediction-error responses. The correlation between the magnitude of ERN deficits and the severity of negative symptoms supports the hypothesis that these symptoms stem from faulty error prediction. Perhaps most importantly, the results raise the possibility that tDCS could relieve some symptoms of schizophrenia without producing the undesirable side effects associated with pharmacological treatment.



Under sham stimulation (left), the ERN (arrow) elicited by mistakes is smaller in schizophrenic patients (dashed lines) than in controls (solid lines). tDCS (right) increased ERN amplitude in both groups, such that the amplitude in patients was not significantly different from controls in the sham condition. See Reinhart et al. for details.

Ion Transporters Bring Water into Dendrites, Causing Beading

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(see pages 12172–12187)

Despite constant movement of ions across the neuronal plasma membrane, transmembrane ionic gradients are maintained by the continuous activity of ATP-dependent ion pumps, such as the Na^+/K^+-ATPase. Under some circumstances, however, the ionic gradient collapses, leading to waves of mass depolarization that sweep across the brain. Such waves, called spreading depolarization (SD), occur after stroke and traumatic brain injury. They also can occur at the onset of migraines and are thought to underlie migraine auras. SD waves can be triggered by excessive neuronal depolarization or reduced activity of the Na^+/K^+-ATPase, but the molecular mechanisms leading to their initiation and propagation are poorly understood.

During SD, extracellular K^+ concentrations and intracellular Na^+ and Ca^{2+} concentrations greatly increase, while extracellular Cl^- levels drop. These ionic changes lead to influx of water into cells, resulting in swelling of neuronal somata, focal swelling (beading) of dendrites, and loss of dendritic spines. How water enters dendrites has remained a puzzle, however, because dendrites don't express water channels (aquaporins). One hypothesis is that dendritic beading results from unregulated actin polymerization or destabilization of microtubules. Alternatively, beading may result from cotransport of water into dendrites by ion transporters.

To investigate the mechanisms of SD-associated dendritic beading, Steffensen et al. triggered SD waves in mouse brain slices with KCl. First, they confirmed that dendritic beading is not likely to result simply from osmosis, by demonstrating that a hypo-osmotic challenge did not cause beading in the absence of SD. They also found that inhibiting actin polymerization and stabilizing microtubules had no effect on SD-associated dendritic beading, indicating that disruption of the cytoskeleton is unnecessary. In contrast, although SD of normal amplitudes could be induced when extracellular Cl^- concentrations were reduced, SD-associated dendritic beading was significantly diminished. Beading was also reduced by inhibiting cation–Cl^- cotransporters and/or a HCO_3^-–Cl^- exchanger, even though SDs persisted under these conditions.

These results support the hypothesis that water transported along with Cl^- during SD contributes to dendritic beading. They further indicate that dendritic beading is not a necessary consequence of SD. This is important because dendritic beading can lead to irreversible neuronal damage, and reducing beading may reduce functional loss after stroke or traumatic brain injury.

This Week in The Journal is written by Teresa Esch, Ph.D.