Autoimmune Encephalitis Can Disrupt Executive Function

Have you ever been tempted to make an impulse purchase at the grocery store? If you’ve successfully put the ice cream back on the shelf in order to save money and avoid a sugar binge, you have used a process called executive function. Broadly, executive function refers to a set of cognitive processes that includes the regulation of impulses and emotions, direction of attention, and working memory. Executive function helps us to make choices that are smart and purposeful, taking into account conscious goals and long-term interests in addition to emotional urges.

Measuring Executive Function

You might have heard of a famous experiment called the Marshmallow Test. In this test, experimenters place a marshmallow in front of a child and give them a simple instruction: if they don’t eat the marshmallow for a certain period of time, they can get two marshmallows instead of one. While this might seem like an easy task, a lot of children can’t resist eating the first marshmallow\(^1\). Executive function typically improves with maturity, so young children have not yet fully developed these skills and therefore eat the tempting treat in front of them rather than holding out for a bigger treat\(^2\). In this case, executive function can help people resist their immediate impulses in order to get a bigger or better reward in the future.

Another aspect of executive function is conscious direction of attention. For example, drivers use this skill when they choose to focus on the road instead of on their cell phone screens. Researchers often measure this attentional component of executive function with something called a Stroop task\(^3\). In one common version of this task, participants are shown a series of words that spell out colors, like red, blue, and green. However, the goal of the task is to say out loud the color the word is printed in, rather than reading the word itself. It’s an automatic process to read words we see, so executive function is required to direct attention away from the written word and toward the color. Take a look at the picture below and try it yourself, saying only the color of the ink-- how fast can you go?

![Stroop task example](image)

Figure 1. An example of the Stroop task, a tool for researchers to study attentional aspects of executive function. The goal of the task is to say out loud the color the word is printed in (in this case, purple, red, blue, etc), ignoring the written word.

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Executive Function in the Brain

Scientists have studied how the structure and functions of the brain enable executive function. In brief, some parts of the brain serve in an “executive” position to keep other parts of the brain in check. The regions responsible for representing information about goals, a necessary component of executive function, tend to be toward the front of the brain, in a region called the prefrontal cortex. For example, the middle frontal gyrus, part of the prefrontal cortex, was active while participants completed a variant of the Stroop attention task described above\(^3\).

Using functional neuroimaging to measure brain activation patterns while people complete tasks that require different cognitive processes related to executive function, scientists have found a group of brain regions, called the executive control network (ECN), that are engaged during executive function\(^4\). Long projections called axons allow neurons in one brain region to send signals to other regions, forming structural connections between different parts of the brain. The electrical signals that are sent through the axons, allowing communication between brain regions, are called functional connections. The strength of both structural and functional connectivity between regions of the ECN corresponds to increased executive function capabilities. Therefore, executive function seems to depend on different parts of the brain being able to communicate and coordinate in order to help us achieve our goals.

Executive Function in AE

Many things can disrupt executive function, both temporarily and in the longer term, including stress, loneliness, and sleep deprivation\(^2\). A wide variety of medical and psychiatric conditions can also lead to executive dysfunction\(^5\).

Disruption of executive function is a common symptom of autoimmune encephalitis (AE), both during the illness and sometimes even following recovery. Memory problems are also common in AE and can be related to impaired executive function, though not always. With some subtypes of AE, particularly anti-NMDAR encephalitis, disrupted executive function is often present during the acute phase of the illness\(^6\).

The pathology of antibody action that produces many symptoms of AE also explains some of the associated disruptions to executive function. For example, anti-NMDAR encephalitis is caused in part due to production of Immunoglobulin G (IgG) antibodies that target NMDA receptors\(^6\). When these antibodies attack the NMDA receptors, one effect is that receptors are internalized into the cell, or made unavailable to help with sending signals between cells. Typically, NMDA receptors mediate signaling of glutamate, a neurotransmitter. As a result, when NMDA receptors are internalized due to an antibody attack in AE, glutamate signaling and communication between cells become dysregulated.

Since NMDA receptors are most prevalent in the hippocampus, a brain region involved in memory, and the frontal cortex, a hub for executive function, processes that rely on these regions are most affected by anti-NMDAR encephalitis\(^6\). Patients with anti-NMDAR encephalitis also have reduced structural and functional connectivity between brain regions, including the hippocampus\(^6,8\). Since executive function requires communication within a wide network of brain regions, disruption of this connectivity resulting from AE may lead to impairment of this process.

As with most symptoms of AE, the best way to restore executive function is to diagnose and treat AE quickly using appropriate immunotherapy treatments\(^6\). For some

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patients, however, executive function impairment persists even after treatment. In these cases, cognitive remediation therapies can be used to help patients practice executive function. For example, in one study of patients with limbic encephalitis, cognitive remediation therapies that directly targeted executive functioning skills helped patients to rebuild these skills following recovery. Fortunately, as researchers learn more about AE, doctors are able to diagnose and treat AE more effectively. These diagnostic and therapeutic improvements will hopefully lead to better cognitive outcomes for all patients with AE.

References: