Executive Functions: Eye movements and Neuropsychiatric Disorders

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SYNOPSIS
Executive functions are cognitive processes that critically involve the frontal lobes and enable us to accomplish goals and make decisions in every day life. The brain regions responsible for some executive functions (spatial attention and memory) overlap with brain regions necessary for eye movements. Eye movements can be more reflexive (automatic) or more voluntary (willful). Voluntary eye movements, especially, have become a great tool with which to measure different aspects of executive functions in many human disorders. They also have been critical in differentiating subtypes and evaluating medication or treatment efficacy in clinical populations.
What are Executive Functions?

Executive functions are complex, higher order processes moderated primarily by the frontal lobe, specifically the prefrontal cortex. Attention, working memory, and strategy development are important executive functions. These abilities enable a person to accomplish future goals. The complexity of executive function has made a universally-accepted definition elusive, but three specific mechanisms are generally included. The first is planning or programming a future action. The second is maintaining a plan and program in mind until executed. The third is inhibition and resistance to distraction. The sequence of executive behavior includes anticipating and establishing a goal, forming a plan, executing the plan in the proper order, and evaluating the resulting behavior as it occurs. Executive functions are utilized when someone establishes the commonplace goal of going to the grocery store, formulates a plan to get there, executes the plan, and evaluates the progress in getting there, with changes, for instance, if road construction is encountered. Proper executive functioning requires the ability to maintain a plan in mind until it is necessary to complete a specific action. Executive functions surface in novel situations, when new information is presented or old information is interpreted in a new way, whereas established behaviors (e.g., writing one’s signature) require only subcortical (non-executive) monitoring. Executive functions define human behavior and are critical for everyday life. They influence social, emotional, intellectual, and organizational aspects of one’s life. Life can be devastated when executive functions are disrupted. Unfortunately, these disruptions are the defining feature of many human disorders.

Eye Movements and Executive Functions

Eye movements are any shift of position of the eye in its orbit. There are many different kinds of eye movements, which will be defined in the following section. Eye movements define what information reaches our retina, visual cortex, and, most importantly, higher cortical centers. Hence, eye movements are critically important for vision, attention and memory; they determine what we see, attend to, and remember about our surroundings. They are thus central to executive functions. Much scientific work also suggests that certain executive function brain circuitry, such as that for spatial attention and spatial working memory, overlap parts of the eye movement brain circuitry. For these reasons, better understanding of eye movements may serve as a valuable window into executive functions.

Classes of Eye Movements

There are several classes of eye movements, for the most part with distinct neural circuitry. Eye movements serve to stabilize images on the retina and keep objects of interest on the fovea, the retinal area that has the greatest visual acuity and the greatest representation in visual cortices. Without compensatory eye movements during self-motion (locomotion) or head movement, images of the visual world would blur and slip across the retina with each movement. Two classes of eye movements, vestibulo-ocular and optokinetic reflexes, evolved to stabilize images on the retina during such head and body perturbations. For example, with head motion to the right, vestibular sensors in the inner ear are triggered and signal nuclei in the horizontal and vertical gaze centers of the
brainstem to create an equal and opposite eye velocity signal. The result is the vestibulo-ocular reflex, initiated within about 15 ms, a rapid eye movement to the left to compensate for the head movement and keep the retina stable with respect to the world. The second mechanism, the optokinetic reflex, complements the first by using full-field visual information about self-movement to compensate for the perturbation of the visual world on the retina. That is, as a result of self-motion to the right, the visual image will move across the retina in a leftward direction. The speed of the image drift on the retina triggers nuclei in the brainstem to create an equal leftward eye velocity signal. The result is the optokinetic reflex, an eye movement in the same direction as the retinal slip to keep the retina stable with respect to the world.

A third class of eye movements serves to rapidly shift gaze (up to 900 degrees per second) to bring a new object of interest to the fovea. These so-called saccades are often further subdivided into two general subclasses: reflexive and voluntary. Reflexive saccades include those saccadic eye movements that are elicited in response to a sudden movement, flash, or change in the environment. The latency of a reflexive saccade after onset of a visual target is typically about 200-250 ms, but it can be as short as 70-80 ms. Voluntary saccades are more complex, involve executive functions, are thought to critically involve frontal cortex, and have latencies as long as 400 ms. In real life, for instance, the same environment can result in different voluntarily controlled saccadic eye movements, depending on what information is sought or needs to be remembered. This was elegantly demonstrated by Yarbus in 1967 when he presented the same picture to subjects several times while tracking their eyes, but each time asked a different question. Depending on the question, the subjects scanned the picture with a strikingly different set of voluntary saccades as they acquired the pertinent information. Figure 1 illustrates an example of the scanpaths of one naïve subject. The first panel illustrates the scanpath when the picture was preceded with the question, “What are they doing?”. The subject made saccades that followed the gaze of the two women in the picture and then dwelled on the hands, the table, and the objects on the table. The second panel illustrates the scanpath when the same picture was preceded with the question, “How old are they?”. In this context, the subject almost exclusively dwelled on the women’s faces.

In the research lab or clinic, a prosaccade task is frequently used to elicit reflexive saccades (see Figure 2). Typically, in this paradigm, as the subject fixates a center spot, a visual target will appear and the subject is instructed to look at the target. Voluntary saccades can be elicited by many different eye movement paradigms (see also Figure 2). In an antisaccade task, a peripheral target is presented (as in the prosaccade task), but the correct response is to look to the opposite side of the screen, away from the target. The antisaccade task requires a person to (1) inhibit the reflexive inclination to look at the target and (2) generate a voluntary saccade to the opposite part of the screen. Abnormal responses in the antisaccade task include increased latency and directional errors (looking to the target). A delayed saccade task also requires a voluntary saccade. This task is similar to a prosaccade task in that the person is required to make an eye movement to the target. However, the person is also instructed to wait until a go signal is given (a tone or change in fixation cue). Therefore, the person must inhibit the reflexive tendency to look at the target immediately and generate a voluntary saccade when a somewhat arbitrary cue is presented. A third commonly used voluntary saccade paradigm is a memory saccade task. This task is identical to the delayed saccade task,
except that the target is removed from the screen during the delay period. Now, the person must inhibit the eye movement until the go signal and also remember where the target was presented. Hence, this task also demands working memory.

**Smooth pursuit eye movements** (SPEMs) function to keep a small moving stimulus on the fovea and are typically much slower than saccades, with a maximum velocity of about 100 °/s. Smooth pursuit is a voluntary task requiring both motivation and attention. Hence, if you choose to track a mosquito, when the mosquito takes off, your eye would initiate smooth pursuit 100-150 ms later, a latency that is generally shorter than that for a saccade. Thus, your eyes would lag a bit behind the mosquito. After about another 100 ms, this would be remedied by a “catch-up saccade” during pursuit so that your eyes were directly upon the mosquito. SPEMs are the result of a complex transformation from visual motion signals at the fovea to an oculomotor signal. Cortical input to the smooth eye movement generation centers in the brainstem is required to enable a smooth tracking motion. At the same time, however, there must be suppression of the optokinetic reflex and (if the eye movement is accompanied by head tracking) the vestibulo-ocular reflex. SPEM paradigms are used frequently to measure executive function in clinical populations. One measure of accuracy in SPEM paradigms is pursuit gain (the ratio between eye velocity and target velocity) such that gain below 1.0 indicates that the pursuit system cannot match the velocity of the target. Errors in gain can be amended with catch-up saccades (when smooth pursuit lags behind the target) and back-up saccades (when tracking gets ahead of the target). Further, there can be intrusive saccades (jerky motions that interrupt ideal smooth pursuit tracking) that are indicative of abnormal processing.

**Vergence** is the only disconjugate eye movement, that is, where the eyes move simultaneously in opposite directions. Vergence movements occur reflexively in order to focus and reduce disparity between the locations of an image on the retina of each eye.

**Eye movements in Human Disorders**

Voluntary eye movements, as a general class, can be used to tease out specific deficits of different aspects of executive function in various clinical populations. More specific identification of deficits can be critical to clinical assessment of the patient. By careful comparisons of performance on voluntary eye movement tasks, a “deficit in executive function” (as generally classified, for example, by a neuropsychiatric test) can be broken down into separable aspects of executive function, including the voluntary planning, generation and accuracy of a response, the ability to inhibit or control impulsivity, and working memory. Voluntary eye movements have further been linked to different anatomical circuitry, and their use has also illustrated subtypes within some patient populations. Eye movements, especially as measured in voluntary saccade paradigms, have proven to be useful, sensitive, and reliable tools in defining the executive function deficits seen in a spectrum of clinical populations, including neurological, developmental, and psychiatric disorders.

*Neurological* – **Tourette’s syndrome** and **Parkinson’s disease** are both movement disorders involving the basal ganglia. Both disorders show deficits in executive function with evidence of disrupted prefrontal-basal ganglia circuits. Voluntary eye movement deficits are consistent with these documented impaired executive functions. Both groups show increased antisaccade latency and antisaccade
errors. The effect of medication on voluntary eye movements in Tourette’s syndrome is
not clearly known. On the other hand, dopaminergic medications, routinely given to treat
Parkinson’s disease, do improve the patients’ voluntary eye movement performance.
Further, there is evidence that voluntary saccade performance does differentiate subtypes
of Parkinson’s disease patients so that akinetic-rigid Parkinson’s disease patients have
more difficulty on voluntary eye movement tasks than tremor-dominant patients.

Developmental – Autism is a developmental behavioral disorder marked by
abnormal language and social communication resulting from deficits in the limbic and
cortical structures. There have been numerous studies investigating voluntary eye
movement performance in children and adults with autism as a means of understanding
the etiology and social implications of this disorder. For instance, voluntary eye
movements (saccade and SPEM) have been used to show that executive function abilities
are delayed in autistic patients; their voluntary abilities seem to mature at a lower level
and at a slower rate. Likewise, results from voluntary saccade tasks have suggested that
deficits in autistic individuals critically involve the prefrontal cortex.

Psychiatric – Schizophrenia is the psychiatric disorder that has been studied the
most extensively with eye movements, and it will be discussed in detail in the next
section. Attention-deficit / hyperactivity disorder (ADHD) is characterized by
symptoms (sometimes beginning before age 7) of inattention, hyperactivity, or
impulsivity that cause impairment at school, home, or work. ADHD patients have been
shown to be impaired on a countermanding task (similar to a delayed saccade task, but a
stop signal may be presented on some trials indicating the response should be withheld),
which suggests that their impairment mainly consists of increased impulsivity. In
addition, voluntary eye movement deficits have shown subtype differences within the
ADHD population such that patients classified as ADHD-Inattentive have better motor
planning and less impulsivity than ADHD-Combined patients with both inattentive and
impulsive characteristics. Interestingly, methylphenidate improves the voluntary eye
movement performance of both ADHD subtypes. Bipolar disorder is a mood disorder
marked by cycling periods of mania and depression. Tested in voluntary eye movement
paradigms, bipolar patients have been shown to have an inhibition problem with no
deficit in working memory. Patients in the manic phase tend to have better performance
on voluntary smooth pursuit eye movement.

Eye Movement Deficits in Schizophrenia
What is Schizophrenia?
Schizophrenia is a psychiatric disorder that is usually characterized by
hallucinations, delusions, and negative symptoms such as blunted affect, alogia, and
avolition. It is also characterized by a multitude of cognitive dysfunctions in areas such
as executive control, working memory, and attention. These disrupted executive
functions are more persistent than psychotic symptoms and correlate with the more
negative aspect of the disorder. Schizophrenia is the most prevalent mental illness in the
world, occurring in about 1% of the population. It is also considered the most costly and
debilitating mental disorder and is among the top causes of disability in developing
countries. In 2002, it cost the United States approximately 65 billion dollars, and this
estimate only accounted for patient hospitalizations, loss of work, and cost of disability.
More robust measures of cognitive deficits are crucial for schizophrenia given that there
is a strong positive correlation between improved cognitive functioning, medication adherence, and long-term prognosis. Classically, neuropsychological tests have been used to investigate cognitive dysfunctions in schizophrenia, but recently, eye movement tasks have been shown to be a more sensitive and reliable measure of these deficits. Eye movements are also more easily mapped to specific neural structures and, hence, may be a more specific biological marker to differentiate subtypes. For these reasons, the study of eye movements is an important research tool that may shed some much needed light on both executive functions and debilitating human disorders such as schizophrenia, topics that have evaded researchers for decades.

**Eye Movement Deficits in Schizophrenia**

Nearly a hundred years ago, using a photographic technique, Diefendorf and Dodge were the first to report in 1908 that smooth pursuit eye movements were impaired in schizophrenia. They found that these types of eye movements were commonly interrupted by saccades. With the advent of new techniques for measuring eye movements as well as renewed interest, much is now known about smooth pursuit eye movement deficits in schizophrenia.

There seem to be two basic deficits in the smooth pursuit eye movements of people with schizophrenia: (1) reduced gain of smooth pursuit, and (2) increased saccadic events. Pursuit gain is a measure of the accuracy of the smooth eye movement, and people with schizophrenia show reduced gain, that is, their eyes do not keep up with the target and they often fall behind. As a result, schizophrenic patients often exhibit increased saccadic activity (catch-up saccades) during smooth pursuit. These saccades are automatic and compensatory in nature and serve to quickly refoveate the target on the retina. Other increased saccadic events often observed in schizophrenia are saccadic intrusions. These eye movements are not compensatory in nature and are thus inappropriate and disruptive. Common examples of saccadic intrusions are square-wave jerks and anticipatory saccades. A square-wave jerk is defined as a small pair of saccades whose initial direction is independent of the target being tracked with a 100-250 ms intersaccadic interval, during which pursuit continues. Anticipatory saccades are defined as saccades that overshoot the location of the target. These saccades have larger amplitudes than square-wave jerks, longer intersaccadic intervals, and do not maintain continuous pursuit during the intersaccadic period. Both of these types of intrusive saccadic eye movements are rarely found in young controls (although sometimes found in the elderly) and indicate inappropriate activation or lack of inhibition of the saccadic system during smooth pursuit.

In addition to smooth pursuit deficits, in the last decade or so a number of saccadic eye movement dysfunctions have been identified in schizophrenia. Numerous studies have shown deficits in various voluntary saccade tasks, including delayed, remembered, or predictive saccades. In an antisaccade task, schizophrenic subjects typically have difficulty generating the correct saccade to the opposite side of space with increased latency as well as increased errors (i.e., eye movements to the target) compared to normal control subjects. In contrast, many studies have demonstrated that schizophrenic subjects are normal or in some cases hyper-reflexive on a prosaccade task. This pattern of saccade task performance (abnormal voluntary and normal or hyper-active reflexive) has in some studies been related to the subject’s performance on smooth pursuit eye movements. That is, schizophrenic patients with smooth pursuit deficits
make significantly more errors on the antisaccade task than schizophrenic patients without tracking deficits.

**Biological Basis of Eye Movement Deficits**

In the 1970’s and 1980’s, a number of studies found no deficits in the smooth phase of vestibulo-ocular and optokinetic reflexes in schizophrenic patients with smooth pursuit eye movement deficits. These findings suggested that the smooth pursuit deficits in schizophrenia are due to cortical deficits, given a lack of deficits in the smooth phases of these other eye movements which share common brainstem motor output pathways. At this same time, evidence for a prefrontal cortex dysfunction model of schizophrenia was gaining support. One key piece of evidence for such a model came from schizophrenic patients whose negative symptoms were found to be strikingly similar to the symptoms exhibited by patients with a loss of frontal lobe function. These shared features included a lack of goal-oriented behavior, apathy, flat affect, asociality, and inattentiveness. A further piece of evidence in support of frontal lobe dysfunction in schizophrenia came from eye movement research. At this time in the late 1980’s, it was well established that frontal regions (especially the frontal eye fields) played a role in saccades. It was also determined that frontal eye field lesions disrupted smooth pursuit eye movements. Hence, both pursuit deficits and saccadic deficits could be accounted for by a frontal dysfunction.

It is interesting to note that between 50% and 85% of people with schizophrenia exhibit smooth pursuit eye movement deficits. These deficits are only found in about 8% of normal subjects. Similarly, about 60% of people with schizophrenia exhibit antisaccade eye movement deficits. People with schizophrenia are heterogeneous in terms of both smooth pursuit deficits and voluntary saccade deficits. This division of impaired and non-impaired patients (for either pursuit gain or voluntary saccade performance) may prove to be a more useful biological marker than the classic clinical subtypes that are commonly used to describe people with schizophrenia.

**Genetics of Eye Movement Deficits**

In the late 1970’s and early 1980’s, there were a series of studies that investigated the genetics of smooth pursuit deficits in monozygotic and dizygotic twins who were discordant for schizophrenia. These studies found that a larger proportion of the monozygotic twins, compared to the dizygotic twins, exhibited smooth pursuit deficits. This early data on twins in combination with more recent research on non-affected first degree relatives – findings that as many as half of the relatives exhibit SPEM deficits – has given credence for the existence of an eye-tracking gene. Similar support has been found using the antisaccade task, where 25% to 50% of non-symptomatic first-degree relatives exhibit eye movement deficits. Within the last several years, markers on Chromosome 6p21 have been found to have a strong correlation to smooth pursuit dysfunction. And the occurrence of this smooth pursuit dysfunction is more prevalent than the manifestation of schizophrenia, as evidenced by the prevalence of the smooth pursuit dysfunction in symptom-free first-degree relatives. This suggests that smooth pursuit eye movement dysfunctions is more penetrant than schizophrenia itself, and it raises the possibility that the two manifestations may result from a single genetic trait. The exact expression of the trait may depend on any number of factors such as prenatal health and environmental stress.

**Importance of Subtypes and Genetics for Outcome**
Eye movement monitoring is an important research tool because it affords us the opportunity to use a quick, easy, and non-invasive technique to help identify behaviors that may indicate susceptibility for schizophrenia. Since it is possible that people with schizophrenia who exhibit eye movement deficits are genetically differentiable from those who do not, eye tracking may provide more reliable and robust criteria for the classification of different groups of people with schizophrenia. Such a biologically-based classification system may allow us to investigate particular antipsychotic medication effects across different subgroups of schizophrenic patients. For example, it is possible that task-impaired subjects will show a greater benefit from a specific medication. Such a finding has been reported with nicotine and schizophrenia, where patients impaired on an antisaccade task showed a greater benefit from nicotine than non-impaired patients and controls. A similar subtype-specific medication effect has also been demonstrated in Parkinson's disease. It was found that akinetic-rigid patients are poorer than tremor-dominant patients on voluntary eye movement tasks, such as the antisaccade task, and that only tremor-dominant patients were able to significantly improve their performance on this task after dopaminergic medications were administered. A better understanding of subtype-specific medication effects would be pivotal in assigning the most effective medication to the patients who would benefit the most.

In summary, eye movements provide invaluable information about executive functions, and their study may allow us to develop more effective and efficient treatments for a variety of human disorders.
Further Reading


**Relevant Websites**

Figure Captions

Figure 1: Scanpaths of a naïve subject. This subject was told that two pictures would be sequentially presented for five seconds each, and that before each picture a question would be asked. The subject was told to look at the picture for the answer and reply after the viewing finished. Left Panel - The first question asked was, “What are they doing?” The picture was then presented and the scanpath of the subject was recorded for five seconds. The subject then replied, “delivering and receiving a letter”. Right Panel - The second question asked was, “How old are they?” The same picture was presented again and the scanpath of the subject was recorded for five seconds. The subject then replied, “35”. The scanpaths for the same picture were very different based simply on the context of what the subject was asked.

Figure 2: Examples of four saccade tasks. All tasks are presented sequentially from top to bottom, and the arrows indicate the direction of the correct eye movement. Panel 1: Prosaccade – this is a reflexive task in which a subject begins by fixating the center point (F). Once fixation is maintained, a target light appears and the subject makes an eye movement to the light (T&G). Panel 2: Antisaccade – a subject begins by fixating the center point (F). The target light then appears (T&G), and the subject is to make an eye movement to the equal and opposite position of the target. Panel 3: Delayed Saccade – the subject begins by fixating the target (F). Next, the target light appears (T) followed by a delay period (D) during which the subject must continue fixating the center point. At some variable time point, the fixation light disappears, which serves as a go signal for the subject to begin an eye movement to the target (G). Panel 4: Memory Saccade – the subject fixates the center point (F). The target light then flashes on the screen (T) followed by a delay period (D) during which the subject must again continue fixating the center point. At some variable time, the fixation light disappears, which again serves as the go signal for the subject to begin an eye movement to the location where the target light had previously flashed (G). (F) fixation screen; (T) target onset; (G) go signal to begin an eye movement; (D) delay period when the subject must wait for the go signal.
What are they doing?

How old are they?
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<th>Voluntary</th>
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**Saccade Tasks**