Executive Functions: Eye Movements and Neuropsychiatric Disorders

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What Are Executive Functions?

Executive functions are complex, higher order processes moderated primarily by the frontal lobe, specifically the prefrontal cortex. The complexity of executive function has made a universally accepted definition elusive, but attention (focusing on relevant information and ignoring distractors), working memory (maintaining information until execution), and motor planning (goal-directed motor planning and programming) are generally considered key executive functions. Executive functions influence social, emotional, intellectual, and organizational aspects of one's life. Life can be devastated when executive functions are disrupted. Unfortunately, such disruptions occur in 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 are defined in the next section titled 'Classes of eye movements.' Eye movements determine what information reaches our retina, visual cortex, and most important, 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 the brain circuitry subserving certain executive functions, such as that for spatial attention and spatial working memory, overlaps parts of the brain circuitry subserving control of eye movements. Thus, better understanding of eye movements provides a valuable window into executive functions.

Classes of Eye Movements

There are several classes of eye movements, with, for the most part, distinct neural circuitry. Eye movements serve to stabilize images on the retina and to 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. In the case of the vestibulo-ocular reflex, when the head moves 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 that the vestibulo-ocular reflex initiates a rapid eye movement to the left (within about 15 ms) to compensate for the head movement, keeping 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 entire 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 $900^\circ s^{-1}$) to bring a new object of interest to the fovea. These saccades are often further subdivided into two general subclasses: reflexive and voluntary. Reflexive saccades are elicited in response to a sudden movement, flash, or change in the environment. The latency (onset of movement) of a reflexive saccade to 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 participants several times but each time asked a different question. Depending on the question, the participants scanned the picture with a strikingly different set of voluntary saccades to acquire the pertinent information. In a similar fashion, Figure 1 illustrates an example of the scanpaths of a naïve participant viewing a Vermeer painting.
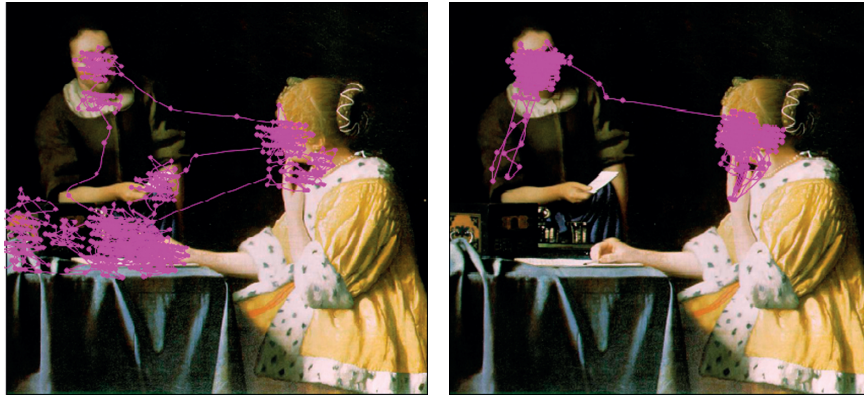
Figure 1 Scanpaths of a naïve individual viewing Vermeer's *Mistress and Maid*. This person was told that two pictures would be presented sequentially for 5 s each and that before each picture, a question would be asked. The person was told to look at the picture for the answer and reply after the viewing finished. (Left) The first question asked was, "What are they doing?" The picture was then presented, and the person's scanpath was recorded for 5 s. The individual then replied, "delivering and receiving a letter." (Right) The second question asked was, "How old are they?" The same picture was presented again and the scanpath recorded for 5 s. The person then replied "35." The scanpaths for the same picture were very different based simply on the context of what the individual was asked.

The first panel illustrates the scanpath when the picture was preceded with the question, "What are they doing?" The participant 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 participant looked almost exclusively at the women's faces.

In the research lab or clinic, a prosaccade task is frequently used to elicit reflexive saccades (see Figure 2). In this paradigm, the participant fixates a center spot, a visual target appears to the left or right of center, and the participant 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 correct location opposite the target. 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 the go signal is presented. A third commonly used voluntary saccade paradigm is a memory-guided 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 $100\,°\mathrm{s}^{-1}$. Smooth pursuit is a voluntary task requiring both motivation and attention. Hence, if one chooses to track a mosquito, when the mosquito takes off, one's eyes would initiate smooth pursuit 100–150 ms later, an onset of movement that is generally shorter than that for a saccade. Thus, the eyes would first begin to pursue but lag a bit behind the mosquito. After about another 100 ms, this is remedied by a 'catch-up saccade' that repositions the moving eyes directly on 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 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). Gain values below 1.0 indicate that the pursuit system is not matching the velocity of the target. Errors in gain can be amended with catch-up saccades (when
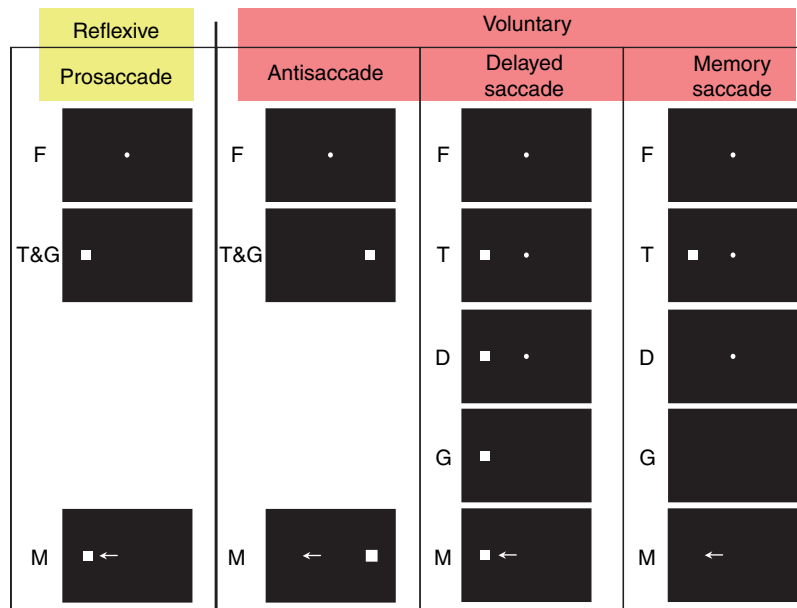
Figure 2 Examples of four saccade tasks. All tasks are presented sequentially from top to bottom, and the arrows indicate the direction of the correct eye movement. Prosaccade: This is a reflexive task in which an individual begins by fixating the center point (F). Once fixation is maintained, a target light appears, and the person makes an eye movement to the light (T&G). Antisaccade: An individual begins by fixating the center point (F). The target light then appears (T&G), and the person is to make an eye movement to the equal and opposite position of the target. Delayed Saccade: The individual begins by fixating the center point (F). Next, the target light appears (T), followed by a delay period (D), during which the person must continue fixating the center point. At some variable time, the fixation light disappears, which serves as a go signal (G) for the person to begin an eye movement to the target. Memory Saccade: The individual fixates the center point (F). The target light then flashes on the screen (T), followed by a delay period (D), during which the individual must continue fixating the center point. At some variable time, the fixation light disappears, which serves as the go signal (G) for the person to begin an eye movement to the remembered location where the target had previously flashed. F, fixation screen; T, target onset; G, go signal to begin an eye movement; D, delay period, when the participant must wait for the go signal; M, eye movement.

smooth pursuit lags behind the target) and backup saccades (when tracking gets ahead of the target). Further, there can be intrusive saccades, which interrupt smooth pursuit tracking and are indicative of inhibitory failures or inappropriate activations.

Vergence is the only disconjugate eye movement; that is, 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 in different aspects of executive function in clinical populations. By careful comparison 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 impulse responding,

and working memory. Voluntary eye movements have been linked to different anatomical circuitry and can be used to characterize subtypes within some patient populations.

Neurological

Tourette's syndrome and Parkinson's disease are 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 voluntary eye movement performance. Further, voluntary saccade performance differentiates between subtypes of Parkinson's disease patients such that akinetic-rigid Parkinson's disease patients have more difficulty on voluntary eye movement tasks than do tremor-dominant patients.

Developmental

Autism is a developmental behavioral disorder marked by abnormal language and social communication resulting from deficits in limbic and cortical structures. Numerous studies have investigated 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 (saccades and SPEMs) have been used to show that executive function abilities are delayed in autistic patients; their voluntary abilities seem to mature to a lower level and at a slower rate. Likewise, results from voluntary saccade tasks suggest that deficits in autistic individuals critically involve the prefrontal cortex.

Psychiatric

Eye movements have been studied most extensively in schizophrenia, as is discussed 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 to indicate 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. Specifically, patients classified as ADHD-Inattentive have better motor planning and are less impulsive than ADHD patients with both inattentive and impulsive characteristics. Interestingly, methylphenidate improves the voluntary eye movement performance of both ADHD subtypes. Bipolar disorder is a disturbance in mood marked by cycling periods of mania and/or depression. Bipolar patients have been shown to have an inhibition problem but to date no deficit in working memory on voluntary eye movement paradigms. Bipolar patients, as well as lithium-withdrawn manic patients, have been shown to perform more poorly than normal controls on a SPEM task.

Eye Movement Deficits in Schizophrenia

What Is Schizophrenia?

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 65×10^9, and this estimate accounted only for patient hospitalizations, loss of work, and cost of disability. Schizophrenia is a psychiatric disorder that is usually characterized by hallucinations, delusions, blunted affect, alogia (i.e., poverty of speech), and avolition. Numerous cognitive functions in areas such as executive control, working memory, and attention are disturbed. These disrupted executive functions are more persistent than psychotic symptoms. More robust measures of cognitive deficits are crucial, given that there is a strong positive correlation between improved cognitive functioning 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 for differentiating subtypes. For these reasons, the study of eye movements is an important research tool that will shed light on both executive functions and debilitating human disorders such as schizophrenia.

Eye Movement Deficits

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

There seem to be two basic deficits in the SPEMs 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 observed in schizophrenia are saccadic intrusions. These eye movements are not compensatory and are thus inappropriate. Common examples of saccadic intrusions are square-wave jerks and anticipatory saccades. A square-wave jerk is a small pair of saccades whose initial direction takes the eyes off the target. After a 100–250 ms intersaccadic interval, during which pursuit continues, a second saccade returns the eyes to the target. Anticipatory saccades overshoot the location of the target. These saccades have

larger amplitudes than those of square-wave jerks and longer intersaccadic intervals, and they do not maintain continuous pursuit during the intersaccadic period. Both these types of intrusive saccadic eye movements are rarely found in young controls (although they are sometimes found in older people) and indicate inappropriate activation or lack of inhibition of the saccadic system during smooth pursuit.

In addition to smoothpursuit deficits, 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 participants typically are slower to generate a saccade to the correct location and make more errors (i.e., eye movements to the target) compared with normal controls. In contrast, many studies have demonstrated that schizophrenic participants perform normally or in some cases faster than controls on a prosaccade task. This pattern of saccade task performance has in some studies been related to the participant's performance on SPEMs. That is, schizophrenic patients with smooth pursuit deficits make significantly more errors on the antisaccade task than schizophrenic patients without eye tracking deficits.

Biological Basis of Eye Movement Deficits

Schizophrenic patients with SPEM deficits do not show abnormal slow phases of vestibulo-ocular and optokinetic responses. This dissociation suggests that the smooth pursuit abnormalities in schizophrenia are due to cortical deficits rather than deficits in common brainstem motor output pathways. Evidence for a prefrontal cortex dysfunction model of schizophrenia has also gained support. One key piece of evidence for such a model came from the similarity between symptoms of blunted affect, avolition, and inattention seen in schizophrenic patients and symptoms exhibited by neurological patients with a loss of frontal lobe function. A further piece of evidence in support of frontal lobe dysfunction in schizophrenia came from eye movement research. It was already well established that frontal regions, especially the frontal eye fields, play a role in saccades. Further research also demonstrated that lesions in the frontal eye fields disrupt SPEMs. Hence, frontal dysfunction could account for both pursuit deficits and saccadic deficits.

It is interesting to note that between 50% and 85% of individuals with schizophrenia exhibit SPEM dysfunction, in contrast to only about 8% of normal controls. Similarly, about 60% of individuals 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 nonimpaired patients (for either pursuit gain or voluntary saccade performance) may prove to be more useful than the classic clinical subtypes in characterizing homogeneous subgroups of patients.

Genetics of Eye Movement Deficits

In the late 1970s and early 1980s, a series of studies 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 monozygotic twins than dizygotic twins exhibited abnormal smooth pursuit eye tracking. Moreover, about half of clinically well first-degree relatives of schizophrenic patients exhibit SPEM deficits, a prevalence much greater than recurrence risk for schizophrenia in first-degree relatives, which is about 6.5%. In addition, some recent reports suggest that 25–50% of nonsymptomatic first-degree relatives of schizophrenic patients exhibit antisaccade deficits. Within the last several years, linkage has been reported for both smooth pursuit deficits and anti-saccade deficits in genetic studies of schizophrenia. Endophenotypes such as eye movement dysfunctions may be a more penetrant expression of a schizophrenia susceptibility gene than schizophrenia.

Importance of Subtypes and Genetics for Outcome

Eye movement monitoring is an important research tool because it affords the opportunity to use a quick, easy, and noninvasive 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 patients will show a greater benefit from a specific medication. Such a finding has been reported with nicotine and schizophrenia: patients impaired on an antisaccade task showed a greater benefit from nicotine than did nonimpaired 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 provide an efficient, noninvasive way to study the role of abnormal brain processes in a variety of human disorders. Their study may afford the development of more effective and efficient treatments of executive dysfunction.

See also: Attention Deficit Hyperactivity Disorder; Attention and Eye Movements; Attention: Models; Autism; Brainstem Control of Eye Movements; Cognitive Deficits in Schizophrenia; Cortical Control of Eye Movements; Eye Tracking and Mental Illness; Eye and Head Movements; Eye Movement Disorders; Frontal Eye Fields; Prefrontal Cortex: Structure and Anatomy; Psychophysics of Attention; Saccades and Visual Search; Saccadic Eye Movements; Schizophrenia: Epidemiology, Clinical Features, Course and Outcome; Visual Attention.

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