

PART 2

PHYSIOLOGY AND CLINICAL STUDIES  
OF EYE MOVEMENTS

Edited by

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*Chapter 5*

**USING EYE MOVEMENTS TO PROBE DEVELOPMENT  
AND DYSFUNCTION**

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*Eye Movements: A Window on Mind and Brain*

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**Abstract**

Recording of saccadic eye movements has proved to be a valuable tool for investigation of brain function and dysfunction. Recent neurophysiological studies have revealed that the time from target appearance to saccade initiation can be modeled as an accumulator function in which both baseline and rate of rise of saccade-related activity contribute toward achieving threshold for movement initiation. In this chapter, we review recent saccadic eye-movement studies designed to track abilities across development and in disorders of frontal cortex and basal ganglia. Studies can be designed to probe the ability to initiate automatic vs voluntary saccades or to suppress saccades. The accumulator model can be used to explain normal developmental changes in voluntary saccade control that are present in normal development as well as in attention deficit hyperactivity disorder (ADHD), Parkinson's disease (PD), and Tourette syndrome (TS).

## 1. Introduction

One of the most important functions of the central nervous system is the generation of movement in response to sensory stimulation. The visual guidance of saccadic eye movements represents one form of sensory-to-motor transformation that has provided significant insight into our understanding of motor control and sensorimotor processing. The eyes have a simple and well-defined repertoire of movements, and the neural circuitry regulating the production of saccadic eye movements is now understood at a level that is sufficient to now link activation in cortical and subcortical areas with behavior and dysfunction. As a result, deficits in eye-movement control of various patient groups can now provide greater insight into the neural substrate underlying the pathophysiology. To properly interpret these insights one must have an understanding of the entire visuomotor loop involved in saccade control, from the visual input on the eye, through the many cortical and subcortical regions of the brain, to the motor output of the brain stem on the muscles that move the eyes, creating behaviors we can measure.

The primate retina has a specialized region in its center, the fovea, which serves the central 1° of the visual field and provides the greatest visual acuity (Perry and Cowey, 1985). In most visual areas of the primate brain, the fovea has the greatest representation, emphasizing the importance of foveal vision in many aspects of visual processing and visually guided behavior (Dow, Snyder, Vautin, & Bauer, 1981; Van Essen, Newsome, & Maunsell, 1984). To maximize the efficiency of foveal vision, we must have the ability to align the fovea rapidly upon objects in the visual world and then keep the fovea aligned upon these objects for a sufficient period of time for the visual system to perform a detailed analysis of the image. Saccadic eye movements are used to redirect the fovea from one point of interest to another and a fixation mechanism is used to keep the fovea aligned on the target during subsequent image analysis. This alternating behavior of saccade–fixation is repeated several hundred thousand times a day and is critical for complex acts such as reading or driving an automobile.

Saccades can be triggered by the appearance of a visual stimulus in the periphery (e.g., the sudden appearance or motion of a novel visual stimulus), or initiated voluntarily, in the absence of any overt sensory stimuli, motivated by the goals of the individual. They can also be suppressed during periods of visual fixation. In special situations where visually guided saccade plans and internally motivated saccade plans compete, the brain must inhibit the automatic response and instead promote the internally motivated saccade in order to perform the desired behavior. Several experimental paradigms have been devised to investigate the control of saccades in these different behavioral situations (see below).

Our understanding of the neural circuitry controlling saccades has increased dramatically in the past 30 years as a result of human behavioral, imaging, and clinical studies as well as animal behavioral, physiological, anatomical, and pharmacological studies. Figure 1 highlights some of the important brain areas that have been identified. Critical nodes in the network include regions of the parietal and frontal cortices, basal ganglia, thalamus, superior colliculus (SC), cerebellum, and brainstem reticular formation (see Hikosaka, Nakamura, & Nakahara, 2000; Leigh and Zee, 1999; Moschovakis,

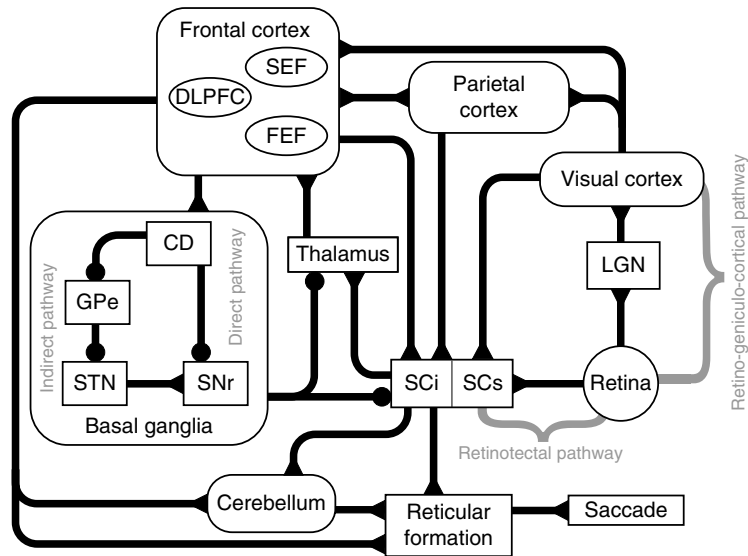


Figure 1. Schematic of brain areas involved in the control of visual fixation and saccadic eye movements. See text for details. See Appendix 1 for the list of abbreviations.

Scudder, & Highstein, 1996; Munoz, Dorris, Paré, & Everling, 2000; Munoz & Everling, 2004; Munoz & Fecteau, 2002; Munoz & Schall, 2003; Schall and Thompson, 1999; Scudder, Kaneko, & Fuchs, 2002; Sparks, 2002; Wurtz and Goldberg, 1989 for detailed review of aspects of the circuitry). Because these brain areas span much of the central nervous system, neurological immaturity, degeneration, or malfunction may influence the ability of a subject to maintain visual fixation and generate fast and accurate saccades. Consequently, many neurological and psychiatric disorders are accompanied by disturbances in eye movements and visual fixation which can now be used in the identification of the affected brain regions.

## 2. Overview of brain areas involved in saccade control

Eye movements are controlled by the synergistic action of the six extraocular muscles. The extraocular muscle motoneurons (MN) discharge a burst of action potentials to move the eyes and a tonic discharge to keep the eyes at a fixed position (see Leigh & Zee, 1999 for review). The burst discharge of the MN is generated by the brainstem premotor circuitry located in the mesencephalic, pontine, and medullary regions of the brainstem reticular formation (see Moschovakis et al., 1996; Scudder et al., 2002; Sparks, 2002 for detailed reviews). Excitatory and inhibitory burst neurons (EBN and IBN), which innervate the MN directly, are silent during fixation and discharge bursts of action potentials for

saccades in a specific direction. Other neurons located in the brainstem reticular formation control the discharge of EBN and IBN. Long-lead burst neurons (LLBN) discharge a high-frequency burst of action potentials for saccades and they also have a low-frequency buildup of activity before the burst. It is believed that LLBN project to the EBN and IBN to provide the burst input. The EBN and IBN are subject to potent inhibition from omnipause neurons (OPN) which discharge tonically during all periods of fixation and pause for saccades in any direction. Thus, in order to generate a saccade, the OPN must be silenced and then the LLBN activate the appropriate pools of EBN and IBN to produce the saccade command that is sent to the MN. Following completion of the saccade, the OPN reactivate and inhibit the EBN and IBN, thus preventing the eyes from moving any further. The tonic activity of the OPN ensures that any early, presaccadic activity among other premotor elements cannot lead to spurious activity among EBN and IBN, which would disrupt fixation.

Inputs to the brainstem premotor circuitry arise from several structures including the frontal cortex, SC, and cerebellum. Although our understanding of how these inputs are coordinated to control the actions of the brainstem premotor circuit precisely are incomplete, significant progress has been made in recent years.

The SC plays a critical role in the control of visual fixation and saccadic eye movements. The superficial layers of the SC (SCs) contain neurons that receive direct retinal inputs as well as inputs from other visual areas (Robinson & McClurkin, 1989). These visual neurons are organized into a visual map of the contralateral visual hemifield.

The intermediate layers of the SC (SCi) contain neurons whose discharges are modulated by saccadic eye movements and visual fixation (see Munoz et al., 2000; Munoz & Fecteau, 2002 for review). These neurons are organized into a retinotopically coded motor map specifying saccades into the contralateral visual field. Neurons that increase their discharge before and during saccades, referred to as saccade neurons, are distributed throughout the SCi. Neurons that are tonically active during visual fixation and pause during saccades, referred to as fixation neurons, are located in the rostralateral pole of the SC where the fovea is represented. These saccade and fixation neurons in the SC project directly to the brainstem premotor circuitry in the reticular formation to influence behavior.

The (SCi) receives inputs from posterior parietal cortices, frontal cortices, and basal ganglia which all play a role in the voluntary selection of potential saccadic targets to ultimately influence behavior. Visual inputs that are crucial for maintaining visual fixation or generating saccades are directed from visual cortex, through the parietal lobe, to the (SCi). One area in particular that lies at the sensory-motor interface is the lateral intraparietal area (LIP). Projections from LIP to the (SCi) are involved in sensory-motor transformations and attentional processing (see Andersen et al., 1997; Colby & Goldberg, 1999; Glimcher, 2001 for detailed reviews).

The frontal cortex receives direct projections from the visual cortex but areas like the frontal eye fields (FEF) are strongly interconnected with parietal visual areas (see Schall, 1997; Schall & Thompson, 1999 for reviews). This is a vital point as FEF may act as a central hub connecting several frontal areas such as supplementary eye fields (SEF), and the dorsolateral prefrontal cortex (DLPFC) with the parietal cortex, the (SCi) and also the

basal ganglia. The SEF and the DLPFC are known to play a role in working memory and decision making. The numerous connections between FEF, parietal lobe, and SCi makes this an excellent system to combine stimulus-driven saccade signals and internally driven voluntary saccade signals. Indeed, it is not uncommon to find neurons with similar firing patterns in all three areas (Munoz & Schall, 2003; Paré & Wurtz, 2001; Wurtz, Sommer, Paré, & Ferraina, 2001). This is not to say that all information must go through the FEF, because the FEF, SEF, and DLPFC all project to the SCi. In addition FEF and SEF also project to the cerebellum and brainstem reticular formation directly.

The frontal cortex also connects through the basal ganglia (see Figure 1) to participate in presaccadic processing (for detailed review, see Hikosaka et al., 2000, 2006). These pathways through the basal ganglia allow for the integration of motivation and reward information with saccade planning. There is a *direct pathway* in which the frontal areas project to the caudate nucleus (CD) to excite GABAergic neurons which in turn project directly to the substantia nigra pars reticulata (SNr). The neurons in the SNr form the major output of the basal ganglia. They are GABAergic and they project to the SCi and the thalamus. The thalamus then projects back to frontal and parietal cortices. Via this direct pathway through the basal ganglia, activation of cortical inputs will lead to disinhibition of the SC and thalamus because the signals pass through two inhibitory synapses.

There is also an *indirect pathway* through the basal ganglia in which a separate set of GABAergic neurons in the CD project to the external segment of the globus pallidus (Gpe). Neurons in the Gpe are GABAergic and project to the subthalamic nucleus (STN). Neurons in the STN then send excitatory projections to the SNr, which in turn projects to the SCi and thalamus. Thus, the indirect pathway travels through three inhibitory synapses and activation of cortical input will serve to inhibit the SCi and thalamus.

### 3. Saccadic eye-movement tasks

Figure 2 illustrates some of the saccadic eye-movement tasks used to probe brain function and dysfunction. The pro-saccade task (Figure 2a) is used to probe the ability of subjects to initiate automatic visually triggered saccades. The anti-saccade task (Figure 2b) is used to probe the ability of subjects to suppress the automatic visually triggered saccade and instead initiate a voluntary response in the opposite direction. It is believed that these tasks probe very different mechanisms. Visually triggered saccades can be triggered by visual inputs to the saccade-generating circuit, while anti-saccades require both saccadic suppression and voluntary saccade execution (see Munoz and Everling, 2004 for review).

The pro- and anti-saccade tasks can be used in combination with a variety of additional conditions. For example, fixation state can be manipulated by the presence or absence of the fixation point at the time of target appearance. There are both exogenous and endogenous components of fixation control (Paré and Munoz, 1996; Reuter-Lorenz, Oonk, Barnes, & Hughes, 1995). The endogenous component of fixation is required to maintain steady fixation independent of whether there is a visual stimulus on the fovea, while the exogenous component is mediated by the presence of a visible stimulus on the fovea.



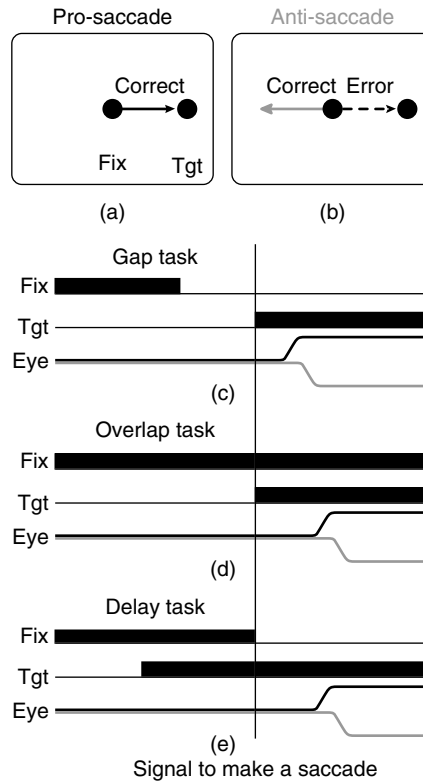


Figure 2. Some of the paradigms used to investigate saccadic function and dysfunction. (a) In the pro-saccade task, the participant is instructed to look (solid black arrow) from the center position (Fix) to the peripheral target (Tgt). (b) In the anti-saccade task, the subject is instructed to suppress the automatic pro-saccade (dotted black arrow) and instead generate a voluntary saccade in the opposite direction (solid gray arrow). Direction errors are defined as saccades triggered toward the target. (c) In the gap condition, the central fixation point disappears 200 ms prior to target appearance. (d) In the overlap condition, the fixation point remains illuminated during target presentation. (e) In the delayed saccade task, the participant is instructed to maintain fixation upon the central fixation point until it disappears.

The presence or absence of the exogenous component influences performance in pro- and anti-saccade tasks (Fischer & Weber, 1992; Munoz, Broughton, Goldring, & Armstrong, 1998). In the gap saccade task (Figure 2c), the initial fixation point disappears and the subject is in complete darkness for some period of time prior to target appearance. The prior disappearance of the fixation point removes exogenous fixation at the time of target appearance and only endogenous fixation signals remain to suppress saccade initiation. In this condition, reaction times (RTs) are reduced and the frequency of express saccades is facilitated (Fischer & Boch, 1983; Fischer & Weber, 1993; Paré & Munoz, 1996). In the anti-saccade task, the insertion of the gap period prior to target appearance leads to

increases in the percentage of direction errors (Fischer & Weber, 1992; Munoz et al., 1998). In the overlap condition (Figure 2d), the fixation point remains illuminated at the time of target appearance leading to increased saccadic reaction time (SRT) and reduced error rates.

Saccades are triggered via parallel descending pathways from the cerebral cortex to the (SCi) and brainstem reticular formation. Visually triggered saccades are initiated by the sudden appearance of a visual stimulus and are mediated by the (SCi), with important inputs from the visual and posterior parietal cortices (Guitton, Buchtel, & Douglas, 1985; Hanes & Wurtz, 2001; Schiller, Sandell, & Maunsell, 1987). Lesions of posterior parietal cortex increase RT of visually guided saccades (Heide & Kompf, 1998).

Volitional saccades, generated by internal goals, sometimes in the absence of any overt triggering stimulus, rely upon circuitry that includes higher brain centers such as the frontal cortex and the basal ganglia (Dias & Segraves, 1999; Gaymard, Ploner, Rivaud-Pechoix, & Pierrot-Deseilligny, 1998; Hikosaka et al., 2000; Pierrot-Deseilligny, Israel, Berthoz, Rivaud, & Gaymard, 1991). Lesions of the FEF have only a modest effect on visually guided saccades, but they produce significant impairment in the generation of voluntary or memory-guided saccades (Dias & Segraves, 1999; Gaymard et al., 1998; Gaymard, Ploner, Rivaud, Vermersch, & Pierrot-Deseilligny, 1999). These movements have increased RTs and reduced saccadic velocities. Lesions of the DLPFC reduce the ability of subjects to suppress reflexive pro-saccades in the anti-saccade task (Guitton et al., 1985; Pierrot-Deseilligny et al., 1991; Pierrot-Deseilligny et al., 2003; Ploner, Gaymard, Rivaud-Pechoux, & Pierrot-Deseilligny, 2005). Thus, a critical function of the DLPFC may be the voluntary suppression of unwanted or visually triggered saccades.

Single-cell recording in non-human primates has identified the neurophysiological correlates of saccadic suppression, preparation, and execution that are used to interpret behavioral performance. Fixation neurons in the (SCi) and FEF are tonically active during visual fixation and pause for saccades, while saccade neurons are silent during visual fixation and burst during saccade production (see Munoz & Schall, 2003; Munoz & Everling, 2004 for review). The drop in fixation activity that occurs during the gap period in the gap saccade task correlates with reduced SRT and represents the neural correlate of the gap effect and fixation disengagement (Dorris & Munoz, 1995; Dorris, Paré, & Munoz, 1997). This drop in fixation activity leads to disinhibition of the saccadic system and a reciprocal increase in low-frequency pre-target activity among subsets of saccade neurons in the brainstem reticular formation (i.e., LLBN), SCi, and FEF (Everling & Munoz, 2000; Dorris et al., 1997; Munoz et al., 2000). This increase in activity prior to target appearance (i.e., pre-target activity) represents the neural correlate for saccadic preparation because its intensity is correlated negatively to SRT (Everling & Munoz, 2000; Dorris et al., 1997; Dorris & Munoz, 1998; Munoz et al., 2000).

Correct performance on anti-saccade trials (i.e., successful suppression of visually triggered pro-saccades) requires that saccade neurons in the FEF and (SCi) be inhibited before target appearance (see Munoz & Everling, 2004 for review). Fixation neurons in the FEF and SC appear to carry this saccadic suppression signal because they discharge at a higher frequency during this instructed fixation period on correct anti-saccade trials.

This task-dependent modulation of neuronal excitability in the FEF and (SCi) is adaptive and essential for successful performance. On anti-saccade trials, target appearance elicits a phasic visual response among saccade neurons in the (SCi) and FEF contralateral to the stimulus that could serve to trigger a direction error. This activity must be suppressed and saccade neurons in the opposite (SCi) and FEF activated to generate the correct anti-saccade. We have hypothesized that DLPFC and/or SNr provide the essential saccadic suppression signals on anti-saccade trials that are required to inhibit the saccade neurons prior to target appearance (Munoz & Everling, 2004). Immaturity or dysfunction of prefrontal cortex and/or basal ganglia will influence the ability to selectively recruit these saccadic suppression signals making it harder to inhibit unwanted or reflexive saccades.

#### 4. Accumulator models describe reaction times

Models have been developed to explain the stochastic variability of RT (Luce, 1986). The accumulator model has been particularly useful at interpreting neurophysiological and behavioral data related to the initiation of saccadic eye movements. This type of model supposes that in response to a stimulus, a signal grows until it reaches a threshold thereby triggering a movement in response to the stimulus (Figure 3). Models of this sort include three sources for the stochastic variability evident in RTs: variable baseline (e.g., Trappenberg, Dorris, Munoz, & Klein, 2001); variable threshold (e.g., Grice, Nullmeyer, & Spiker, 1982; Nazir & Jacobs, 1991); and variable rate of rise from baseline to threshold (e.g., Carpenter, 1988; Ratcliff, 1978). How are aspects of these models instantiated at the level of the single cell, a single brain area, and the entire saccadic generating circuitry? The pattern of movement-related activity recorded from saccade neurons in the FEF and SC of monkeys performing various saccade tasks has been analyzed to evaluate these alternative models of RT (Dorris et al., 1997; Dorris & Munoz, 1998; Everling et al., 1998; Everling & Munoz, 2000; Hanes & Schall, 1996; Paré & Hanes, 2003). Both pre-target (i.e., variable baseline) and post-target (i.e., rate of rise) information processing can contribute to the accumulation of activity toward the threshold.

Figure 3 illustrates how an accumulator model can be implemented to describe the behavior of subjects performing pro- and anti-saccade tasks. In the pro-saccade task (Figure 3a), many saccade neurons (i.e., visuomotor neurons) in the (SCi) and FEF contralateral to the target will discharge both a phasic visual response following the appearance of the visual target (boxed in area in Figure 3a) and a motor-related burst that is time-locked to the saccade. If the level of pre-target activity is high, then the visual response will add to it thus exceeding the saccadic threshold and an express saccade will be triggered (solid thick lines in Figure 3a). If pre-target activity is low, then the visual response will not reach threshold and the system will have to wait for the subsequent accumulation of activity to threshold to trigger a regular latency saccade. In the gap condition, the early disappearance of the fixation point leads to disinhibition of saccade neurons in the (SCi) and FEF which elevates pre-target activity, making it easier to trigger express saccades.

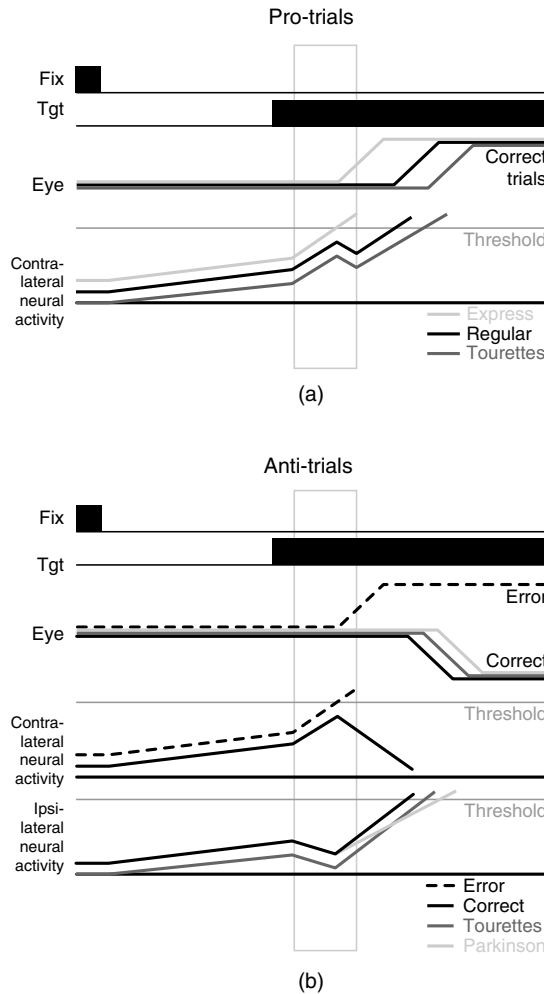


Figure 3. Race model to describe behavior. Activity among saccade neurons in the SC and FEF accumulates toward threshold to initiate a saccade. (a) In the pro-saccade task, pre-target and post-target factors contribute to accumulation of activity. Immediately following target appearance, many saccade neurons discharge a phasic visual response (boxed in area). With sufficient pre-target activity, the phasic visual response can lead to the immediate threshold crossing, triggering an express saccade (light gray trace), whereas reduced pre-target activity can lead to increased RTs (dark gray trace). (b) In the anti-saccade task, pre-target and post-target factors contribute to threshold crossing. The phasic visual response (boxed in area) is registered on the contralateral side of the brain, however, to initiate a correct anti-saccade, activity must cross threshold on the ipsilateral side of the brain. If pre-target activity is too high, the phasic visual response will exceed saccade threshold and a direction error will be triggered (dashed trace).

In the anti-saccade task (Figure 3b), there are two processes racing toward threshold: a process initiated on the contralateral side of the brain by the appearance of the target which serves to initiate the automatic prepotent response; and another process initiated on the ipsilateral side of the brain by the inversion of the stimulus vector to initiate a voluntary anti-saccade. To perform the task correctly, the process related to the initiation of the automatic pro-saccade (i.e., direction error) must be cancelled or suppressed, to allow time for the voluntary response (i.e., correct saccade) to grow toward threshold. Neurophysiological studies have revealed that a critical step in the completion of the anti-saccade task is the reduction of excitability of saccade neurons in the Sc<sub>i</sub> and FEF before the target appears (Everling et al., 1998, 1999; Everling & Munoz, 2000). If pre-target activity is too high, then the visual response will sum with the elevated pre-target activity to trigger a direction error (dashed line in Figure 3b). If pre-target activity is suppressed, then the visual response will not exceed threshold and instead activity can accumulate on the side ipsilateral to the target so that a correct anti-saccade can be triggered (solid traces in Figure 3b).

## 5. Normal Development

Performance on saccadic eye-movement tasks varies dramatically across the life span (Abel, Troost, & Dell'Osso, 1983; Biscaldi, Fischer, & Stuhr, 1996; Bono et al., 1996; Fischer, Biscaldi, & Gezeck, 1997; Moschner & Baloh, 1994; Munoz et al., 1998; Olincy, Ross, Young, & Freedman, 1997; Pratt, Abrams, & Chasteen, 1997; Sharpe & Zackon, 1987; Spooner, Sakala, & Baloh, 1980; Warabi, Kase, & Kato, 1984; Wilson, Glue, Ball, & Nutt, 1993). We have now investigated saccadic eye-movement performance in over 300 normal participants between the ages of 4 and 85 years (Munoz et al., 1998, 2003). All of these participants performed separate blocks of pro- and anti-saccade trials in which target location (left or right) and fixation condition (gap or overlap) were randomly interleaved within each block. Figures 4a and b illustrates the systematic variations in SRT that occur between the ages of 4 and 85 years in the pro- and anti-saccade tasks, respectively. The "U-shaped" pattern is present in both pro- and anti-saccade tasks across both gap and overlap conditions. Mean SRTs tend to be greatest for the youngest and oldest subjects and are at a minimum for subjects around 20 years of age. Note that the gap effect, the difference between gap and overlap conditions, was constant across subject age.

The amount of intra-subject variability in SRT, expressed as the coefficient of variation (CV) (standard deviation/mean \* 100), also varied systematically across subject age (Figures 4c, d). CV was greatest for the youngest and oldest subjects in our sample and was minimal for adult subjects between the ages of about 20–70 years.

Express saccades are the shortest latency visually triggered saccades (Fischer & Ramsberger, 1984; Fischer et al., 1993; Paré & Munoz, 1996) that humans can make and, in our lab (Munoz et al., 1998, 2003), they are initiated between 90 and 140 ms after target appearance. Figure 4e shows the percentage of express saccades elicited in the pro-saccade task with gap and overlap conditions. Express saccades were most prevalent

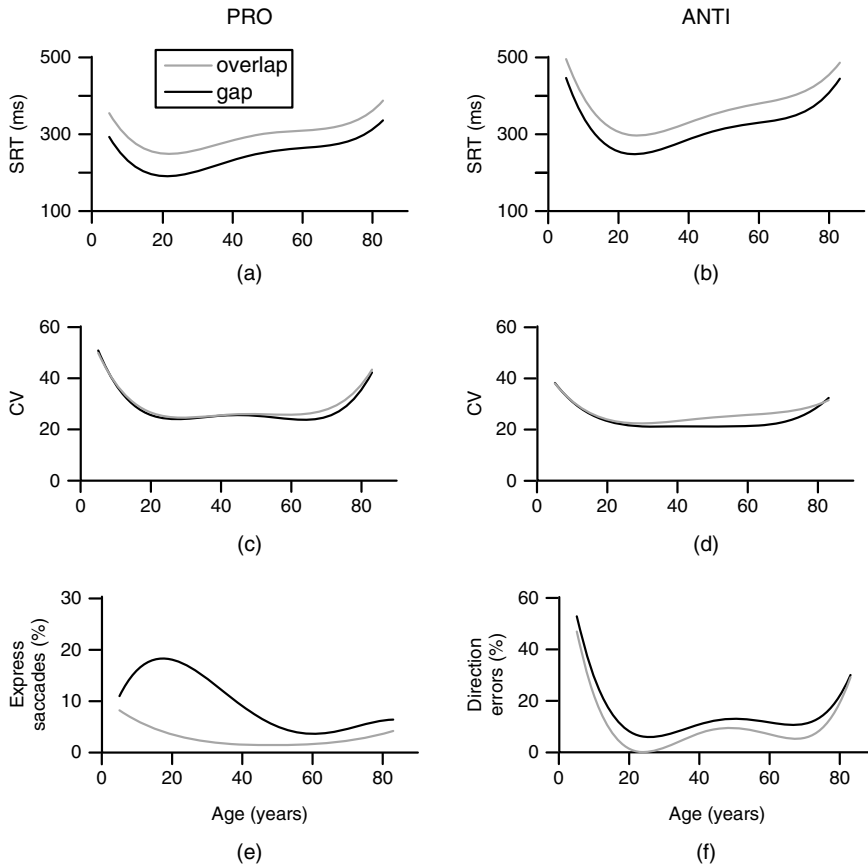


Figure 4. Behavioral performance from 300 control subjects ranging in age from 4–85 years performing the immediate pro-saccade (a, c, e) and anti-saccade tasks (b, d, f) in the gap (gray lines) and overlap (black lines) conditions. (a, b): Mean saccadic reaction time; (c, d): Intra-subject variability in RT expressed as the coefficient of variation (CV = standard deviation/mean \* 100); (e): Percent of express saccades elicited in the pro-saccade task; (f): % of direction errors (automatic saccades made to the target) in the anti-saccade task. Subjects aged 4–15 years are represented in bin widths of one year, subjects aged 16–30 years are represented in bins of three years and subjects older than 30 years are represented in bin widths of five years width. The mean of each bin was plotted (centered on the bin) and a 4th-degree polynomial was fit to the data.

in the gap condition. More importantly, the percentage of express saccades diminished with subject age and reached a minimum among the elderly.

Figure 4f shows the percentage of direction errors triggered in the anti-saccade task. The curve is U-shaped. There is a rapid improvement in saccadic suppression attained throughout 5–20 years. Then, saccadic suppression abilities begin to falter among subjects greater than 70 years.

The normative data illustrated in Figure 4 can be accounted for with the race model (see Figure 3). We hypothesize that young children lack strong voluntary control over saccade-generating circuits because they have more variable RTs, initiate more express saccades in the pro-overlap condition, and generate a greater percentage of direction errors in the anti-saccade task. As a consequence, pre-target activity among (SCi) and FEF saccade neurons presumably varies considerably from trial to trial (i.e., variable baseline). The result is more variability in RTs, including higher percentages of automatic express saccades, and increased percentage of direction errors in the anti-saccade task. The time course of the improvement in saccade control between the ages of 5–20 is consistent with several changes in frontal lobe function and connectivity (see Paus, 2005 for review). Such maturation of frontal functional connectivity could produce the changes in performance in the saccadic tasks.

## 6. Eye-Movement Abnormalities in clinical studies

There are multitudes of studies investigating eye-movement dysfunction in a variety of neurological and psychiatric disorders (*Attention Deficit/Hyperactivity Disorder*: Feifel et al., 2004; Huang-Pollock, & Nigg, 2003; Klein, Raschke, & Brandenbusch, 2003; Munoz et al., 2003; *Tourette syndrome*: Farber, Swerdlow, & Clementz, 1999; LeVasseur, Flanagan, Riopelle, & Munoz, 2001; *Autism*: Goldberg et al., 2002; Minshew, Luna, & Sweeney, 1999; van der Geest, Kemner, Camfferman, Verbaten, & van Engeland, 2001; *Huntington's Disease*: Blekher et al., 2004; Fawcett, Moro, Lang, Lozano, & Hutchison, 2005; Winograd-Gurvich et al., 2003; *Parkinson's Disease*: Chan, Armstrong, Pari, Riopelle, & Munoz, 2005; Crawford, Henderson, & Kennard, 1989; Kimmig, Haussmann Mergner, & Lucking, 2002; Vidailhet et al., 1994; *Schizophrenia*: Avila, Hong, & Thaker, 2002; Broerse, Crawford, & den Boer, 2001; Clementz, 1996; Obayashi, Matsushima, Ando, H., Ando, K., & Kojima, 2003; see also Everling & Fischer, 1998; Sweeney, Takarae, Macmillan, Luna, & Minshew, 2004 for reviews) and the normative data illustrated in Figure 4 can be used as the backdrop for comparison. Here, we focus on the eye-movement abnormalities identified in three specific disorders – ADHD, PD, and TS. This comparison illustrates how eye-movement recording can be used to gain insight into pathophysiology.

## 7. Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD), a neurobehavioral disorder estimated to affect approximately 5% of children is characterized by the symptoms of impulsiveness, hyperactivity, and inattention that often persist into adulthood (Barkley, 1997). Response inhibition may be an important component of the disability because ADHD subjects have difficulty suppressing inappropriate behavioral responses (Mostofsky et al., 2001; Shue & Douglas, 1992). At present, the etiology of ADHD remains poorly defined.

Several observations support a hypothesis of a frontostriatal deficit, possibly involving dysfunction in dopamine transmission, which may produce the symptoms of ADHD (Castellanos et al., 2002; Feifel, Farber, Clementz, Perry, & Anllo-Vento, 2004; Kates et al., 2002; Seidman, Valera, & Bush, 2004; Willis & Weiler, 2005; see Castellanos, 2001; Castellanos & Tannock 2002 for reviews).

We hypothesized that children and adults diagnosed with ADHD may have specific difficulties in oculomotor tasks requiring the suppression of automatic or unwanted saccadic eye movements. To test this hypothesis, we compared the performance of 114 ADHD and 180 control participants ranging in age from 6 to 59 years (Munoz et al., 2003). In the pro-saccade task, mean SRT was elevated modestly but significantly in ADHD, relative to age-matched controls (Figure 5a). This increase was present in both the gap and the overlap conditions. Perhaps more dramatically, intra-subject variability was also increased significantly in ADHD (Figure 5c). In other words, response latencies among ADHD subjects were more variable. Although ADHD subjects tended to generate more express saccades than control subjects, this difference did not reach significance (Figure 5e).

In the anti-saccade task, mean SRT (Figure 5b) and CV (Figure 5d) were also elevated for children and adults with ADHD. Most importantly, ADHD subjects also initiated many more direction errors in the anti-saccade task (Figure 5f). Thus, ADHD participants had considerable difficulty exerting voluntary control over saccade generation. These findings are consistent with fronto-striatal pathophysiology. We hypothesize that this pathophysiology results in poor voluntary control over the saccade-generating circuitry. This can be modeled with the race model (see Figure 3). Figure 3a shows how variable levels of pre-target activity among saccade neurons in the (SCi) and FEF can lead to saccades with variable RTs. Poor control over pre-target activity will lead to increased variability in RTs and, on anti-saccade trials, when pre-target activity is too high, the phasic visual response registered on saccade neurons contralateral to the stimulus will trigger anti-saccade errors (see Figure 3b). Thus, we conclude that pathophysiology in ADHD specifically leads to poor control of excitability of saccade neurons prior to target appearance.

## 8. Parkinson's disease

The motor impairments of Parkinson's disease (PD), including muscle rigidity and slowness of movement (Taylor, Saint-Cyr, & Lang, 1986; Owen et al., 1993; Berry, Nicoloson, Foster, Behrmann & Sagar, 1999; Lezak, 1995), result from degeneration of dopaminergic neurons in the substantia nigra pars compacta (Leenders & Oertel, 2001; Bergman & Deuschl, 2002). In addition to their slowed movements, individuals with PD are often impaired in their ability to suppress automatic behavioral responses (Henik, Dronkers, Knight, & Osimani, 1993; Owen et al., 1993).

We investigated saccade control in 18 PD patients and compared their performance to age- and sex-matched control participants (Chan et al., 2005). In the pro-saccade task,



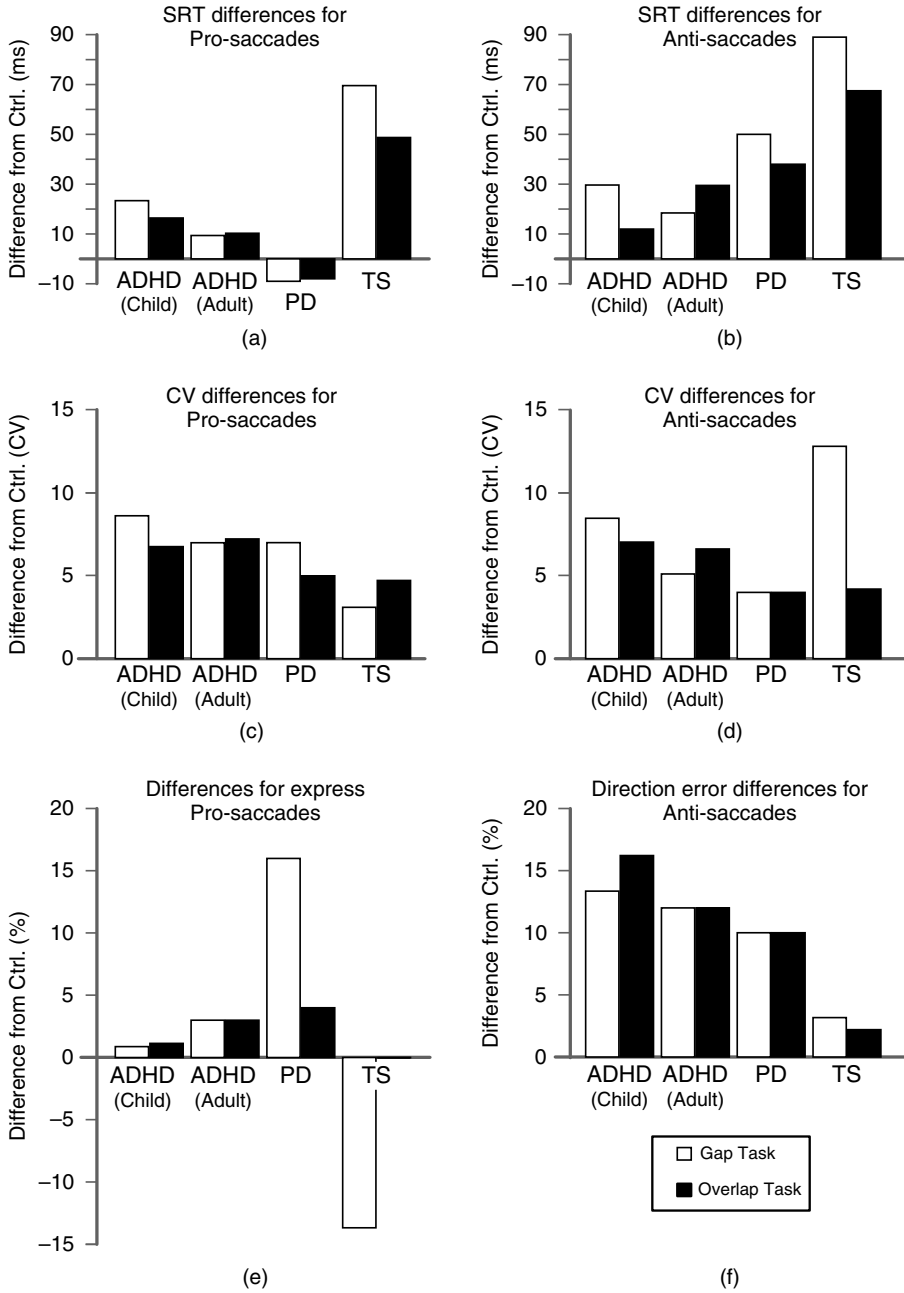


Figure 5. Behavioral performance of ADHD (Child and Adult), PD, and TS patients contrasted to age- and sex-matched control subjects in the pro-saccade (a, c, e) and anti-saccade (b, d, f) tasks. Values on ordinate are expressed as differences from control values (see Figure 4).

PD patients had shorter mean SRT that just failed to reach significance (see Figure 5a). Recall that among normal elderly, mean SRT was increased, compared to young adults (Figure 4a). Thus, the PD patients were performing like younger adults in the pro-saccade task. They had faster SRTs (although non-significantly different from control) in both gap and overlap conditions (see Figure 5a), and they generated significantly more express saccades (Figure 5e). This latter finding was particularly surprising because elderly individuals tend not to make express saccades. However, unlike young controls, PD patients had more variable SRT, expressed as an increase in CV (see Figure 5c).

A very different picture of impairment emerged among the PD patients in the anti-saccade task. SRTs for correct anti-saccades were significantly slower (see Figure 5b) and more variable (see Figure 5d), compared to age-matched controls. In addition, PD patients generated a significantly greater proportion of direction errors in both the gap and overlap conditions (see Figure 5f).

The deficit in automatic saccade suppression and increased variability in SRT that we observed among PD patients is consistent with a disorder of the prefrontal-basal ganglia circuit. Impairment of this pathway may lead to disinhibition or release of the automatic saccade system from top-down inhibition and produce deficits in volitional saccade control. In the race model (see Figure 3), this manifests as an increase in pre-target activity among saccade neurons in the (SCi) and FEF in PD. As a consequence, more express saccades will be triggered in the pro-saccade task (light gray line in Figure 3a) and more direction errors will be triggered in the anti-saccade task (dashed lines in Figure 3b). When PD patients are able to suppress the automatic pro-saccade on anti-saccade trials, then their SRTs are exaggerated (Figure 5b). Thus, we hypothesize that the rise to threshold that takes place among saccade neurons in the (SCi) and FEF ipsilateral to the stimulus is slowed or abnormal (light gray traces in Figure 3b).

Previous investigations on motor and cognitive control in PD have identified similar deficits to what we have described. Cognitive processes, such as attention control, are also impaired in PD (Brown & Marsden, 1990). Individuals with PD were faster than controls on a reflexive visual-orienting task (Briand, Hening, Poizner, & Sereno, 2001) and showed impairment in suppression of visuomotor activation (Praagstra & Plat, 2001). In the Stroop task, participants are presented with color or neutral words in various colors and asked to ignore the word and name its color. Individuals with PD demonstrate greater difficulty in inhibiting the reflexive response to read the word (Henik et al., 1993). These parallel findings across various cognitive and oculomotor tasks suggest a common mechanism underlying a general deficit in automatic response suppression in PD.

It has long been known that the slow, hypokinetic movements of PD can be improved through the provision of external cues (Cunnington et al., 1995; Jahanshahi et al., 1995; Morris, Iansek, Matyas, & Summers, 1996). For example, stride length can be increased with external visual cues (Morris et al., 1996) and reaching movement speeds can be improved during visually cued conditions (Majsak, Kaminski, Gentile, & Flanagan, 1998); thus, automatic motor actions (i.e., movements to an external visual cue) appear to be spared in PD, unlike movements which are volitional. Even more intriguing is the observation that long-latency reflexes are also altered in PD. Tatton and colleagues (Tatton & Lee, 1975; Tatton,

Eastman, Bedingham, Verrier, & Bruce, 1984) demonstrated that long-loop reflexes, which are presumed to include transcortical pathways, are exaggerated in PD (see also Mortimer & Webster, 1979; Rothwell, Obeso, Traub, & Marsden, 1983). These exaggerated “M2” responses in PD have been attributed to reduced inhibition onto cortical motor output neurons. Thus, it appears that PD patients are hyper excitable to sensory stimuli, and automatic responses to external stimuli are enhanced or exaggerated.

## 9. Tourette Syndrome

Tourette Syndrome (TS) is an inherited condition characterized by the presence of motor and phonic tics which can be worsened by anxiety or fatigue (Singer, 1997) and improved by concentration (Jankovic, 1997). Although the physiological basis for tics and TS remains unknown, a substantial amount of evidence suggests a disorder of frontal-striatal circuits (Kates et al., 2002; Singer, 1997). It has been suggested that TS may result from overactivity of the direct pathway through the basal ganglia (Hallet, 1993). TS patients may therefore experience abnormal control of voluntary saccadic eye movements.

Previous studies examining saccades in TS patients have reported conflicting results. Pro-saccade RTs in TS patients have been reported as normal or only slightly elevated (Farber et al., 1999; Straube, Mennicken, Reidel, Eggert, & Muller, 1997), but saccade durations may be reduced (Farber et al., 1999). Anti-saccades have greater RT (Farber et al., 1999; Straube et al., 1997), and peak velocities may be reduced (Straube et al., 1997). The frequency of direction errors among TS subjects performing the anti-saccade task has been reported as normal (Straube et al., 1997) or abnormally high (Farber et al., 1999; Narita, Shawkat, Lask, Taylor, & Harris, 1997).

We initially hypothesized that because of overactivity in the direct pathway, TS subjects would have faster RTs, more express saccades in the pro-saccade task and more direction errors in the anti-saccade task. To test these hypotheses, we investigated saccade control in 10 TS patients and compared performance to age-matched control participants (LeVasseur et al., 2001).

Contrary to our initial hypothesis, TS patients were significantly *slower* than control subjects in saccade initiation (Figures 5a–b). In addition, TS patients did not initiate more direction errors in the anti-saccade task (Figure 5f). These results suggest that the ability to inhibit automatic visually triggered saccades was not impaired in TS. Instead, it suggests that pre-target activity in TS was below that of control subjects leading to prolonged mean SRT (dark gray lines in Figures 3a and b).

## 10. Delayed saccade task

We were initially surprised when TS patients did not initiate more direction errors in the anti-saccade task. However, a previous study (Flanagan, Jakobson, & Munhall, 1999) noted that TS patients initiated tics most frequently in a task with a long and variable

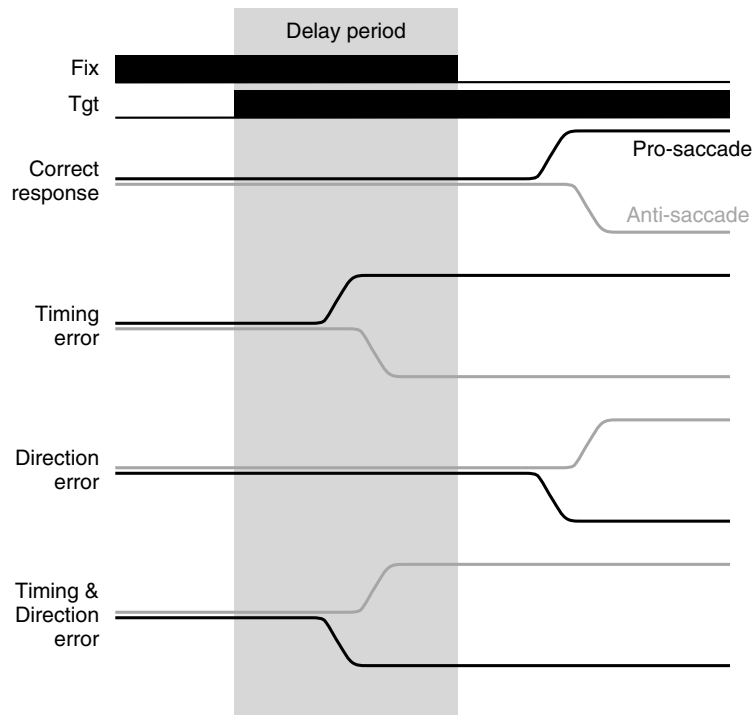


Figure 6. Schematic representation of types of responses possible in the interleaved pro-saccade (black traces)/ anti-saccade(gray traces) saccade delay task. See text for details.

delay period. Therefore we also measured eye movements in the delayed saccade task with a random delay period interleaving pro- and anti-saccade trials randomly (Figure 6). Subjects could therefore initiate several types of errors: (1) timing errors, correct saccade direction but initiated during the variable delay period; (2) direction errors, incorrect saccade direction initiated at the correct time, after the delay period; and (3) combined timing and direction errors.

In this task, TS, PD, and ADHD subjects made more errors relative to age-matched control subjects (Figure 7). The distribution of the different types of errors varied between tasks and disorders. Here we focus on the distribution of only timing errors (Figure 7a) – those saccadic errors triggered in the correct direction but which occurred prematurely, during the variable delay epoch. ADHD, PD, and TS patients all generated more timing errors when compared to age-matched control subjects. However, the time when these errors were generated varied across the different patient groups. Among ADHD and PD patients, timing errors were initiated early in the delay epoch – the occurrence of timing errors did not increase for longer delay intervals (Figure 8). In sharp contrast, TS patients made few timing errors during short delay epochs and instead generated more timing errors later in the delay epoch. This is evident by the fact that the occurrence of

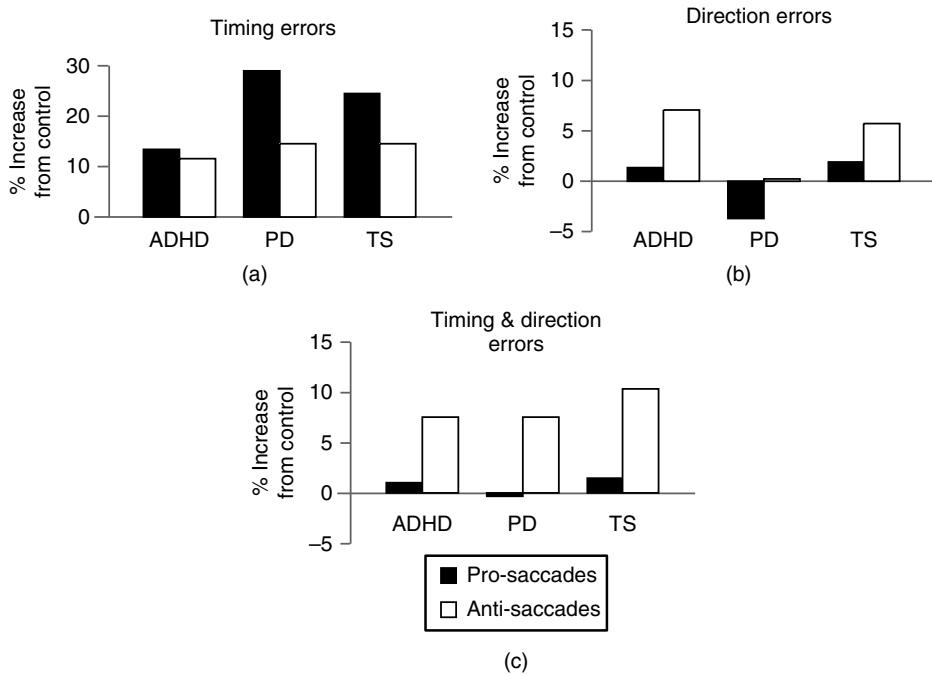


Figure 7. Performance of ADHD, PD, and TS subjects relative to age-matched controls in the delay saccade task.

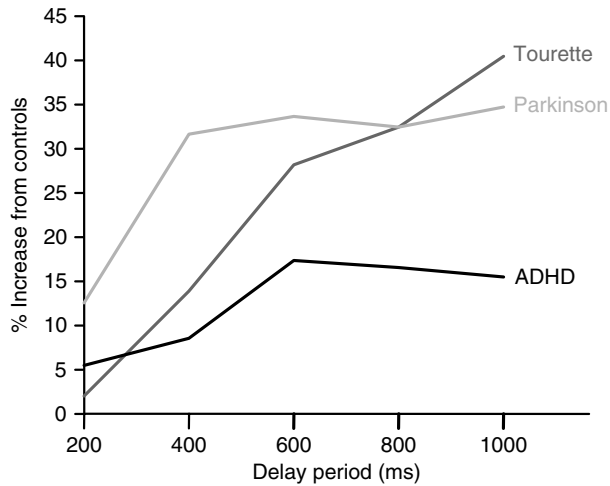


Figure 8. Timing errors as a function of delay duration in the delay saccade task. Data collapsed across pro- and anti-saccade tasks. Timing errors were constant for ADHD and PD across delay interval, whereas in TS, timing errors increased with increasing delay interval.

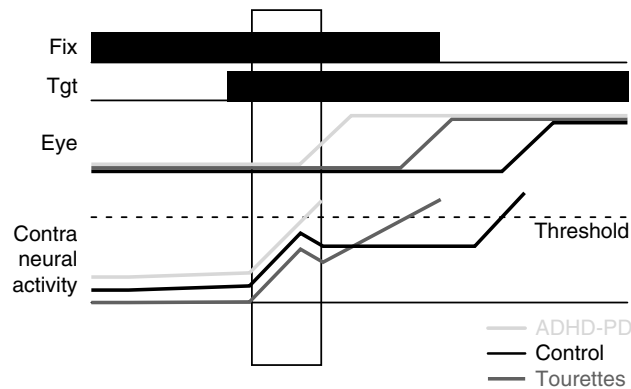


Figure 9. Race model predictions of performance in the delay saccade task. See text for details.

timing errors increased for longer and longer delay periods (see Figure 8), suggestive of disruption of a different type of saccadic suppression mechanism.

Figure 9 provides an explanation for the results we obtained in the delayed saccade task in ADHD, PD, and TS. As described above, we believe that in ADHD and PD, there is poor control over excitability in the saccadic generating circuitry. As a result, SRTs are variable and it is difficult for these subjects to suppress automatic visually triggered saccades (e.g., light gray lines in Figure 9). In the delayed saccade task this results in timing errors, saccades that are triggered shortly after target appearance. However, in TS, the timing errors occurred later in the delay period (see Figure 8). The prolonged SRT in the immediate pro- and anti-saccade tasks (see Figures 5a, b), suggests that in TS patients, saccade neurons in the (SCi) and FEF are at a lower level of excitability (i.e., reduced pre-target activity). However, during the delay epoch, pre-saccadic activity drifts toward threshold triggering premature responses later in the delay epoch (Figure 9).

## 11. Conclusions

Fixation and saccadic signals are distributed across a network of brain areas that extends from the parietal and frontal cortices, through the basal ganglia and thalamus, to the SC, cerebellum, and brainstem reticular formation. Evidence is accumulating to show that these competing signals may interact at multiple levels of the neuraxis. Thus, it is likely that specific functions are not localized to only one brain area. Rather, they may be distributed across multiple areas. Activity among saccade neurons in some of these areas (e.g., SCi and FEF) accumulates toward threshold to trigger saccadic eye movements. This chapter summarizes how knowledge of the circuit can be used to tease apart deficits in different patient groups. The race model can be used to interpret these deficits and make specific predictions about how brain pathology can influence excitability in the saccade-generating circuitry in the brain.

## Appendix A

### A.1. List of abbreviations

ADHD:	attention deficit hyperactivity disorder
CD:	caudate nucleus
CV:	coefficient of variation
DLPFC:	dorsolateral prefrontal cortex
EBN:	excitatory burst neuron
FEF:	frontal eye field
GABA:	$\gamma$ -amino-butyric acid
GPe:	external segment of the globus pallidus
IBN:	inhibitory burst neuron
LGN:	lateral geniculate nucleus
LIP:	lateral intraparietal area
LLBN:	long-lead burst neuron
MN:	motoneuron
OPN:	omnipause neuron
PD:	Parkinson's disease
RT:	reaction time
SC:	superior colliculus
SCi:	intermediate layers of the superior colliculus
SCs:	superficial layers of the superior colliculus
SEF:	supplementary eye field
SNr:	substantia nigra pars reticulata
SRT:	saccadic reaction time
STN:	subthalamic nucleus
TS:	tourette syndrome

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