

Chapter 18

Eye Movements as Biomarkers to Evaluate Pharmacological Effects on Brain Systems



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Abstract Eye movements lend themselves to the study of pharmacological influences on sensorimotor and cognitive processes. In this chapter, we provide an introduction to the study of pharmacological influences on eye movements. We will first

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introduce key concepts and methods in pharmacological research before providing a selective but representative overview of studies that have evaluated pharmacological effects on oculomotor control. We will focus on benzodiazepines and other sedative compounds, antipsychotics, anticonvulsants, mood stabilizers, ketamine, nicotine, methylphenidate, and dextroamphetamine in healthy individuals, and we will survey treatment effects of antipsychotics in schizophrenia, stimulants in ADHD, and stimulants in Parkinson's disease. We will introduce the concept of pharmacological model systems and will explain how eye movements may be used in such designs.

18.1 Introduction and Learning Objectives

Eye movement paradigms have been widely used to probe the functional cortical and subcortical systems involved in sensorimotor and cognitive processes that are selectively intact or disturbed in various clinical conditions. Increasingly, these paradigms have been used as potential biomarkers to evaluate pharmacological effects on these functional brain systems. A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a drug.

There are several reasons why eye movement paradigms are particularly useful tools for examining pharmacological effects on sensorimotor and cognitive systems. First, the neurophysiologic and neurochemical basis of oculomotor control has been well characterized both from single unit recording studies of non-human primates and functional imaging studies in humans. Second, advances in behavioral pharmacology have clarified effects of certain drugs on specific brain regions that are important for subserving oculomotor control. Third, oculomotor performance can be reliably measured and quantified, and paradigms can be experimentally manipulated to better understand underlying differences in performance changes. Fourth, eye movement tasks are relatively easy to perform with limited burden placed on patients and can be used across a range of ages and clinical severity levels. Finally, these paradigms may be used to examine dose dependent effects or to evaluate acute versus chronic exposure in clinical samples.

The focus of this chapter will be on the applied use of eye movements in clinical research settings as biomarkers for: (1) side effect profiles of drugs in healthy individuals; (2) identifying treatment targets in model systems of disease; (3) evaluating potential cognitive enhancement effects of drugs in healthy individuals; and (4) effects of pharmacological treatments on sensorimotor and cognitive systems in psychiatric conditions and neurologic conditions. We begin with an overview of methods and approaches in pharmacology to provide a context for the introduction to the literature examining pharmacological effects on eye movements in subsequent sections of the chapter.

A major learning objective of this chapter is to learn about fundamental methods in psychopharmacological research, both generally and specifically with regards to eye movements. Having read this chapter you should be able to design a pharma-

ological study of eye movements by making use of key recommendations for the conduct of such studies. You will also have acquired an overview of the effects of psychopharmacological compounds on eye movement control, both in healthy individuals and in psychiatric and neurological patients. On the basis of this introduction, you will be able to understand and critically evaluate current empirical studies in the field.

18.2 Historical Annotations

The study of pharmacological treatments on eye movements began as early as the 1940s. Initially, studies focused on the examination of agents or drugs on basic aspects of visual tracking, such as nystagmus (rapid involuntary eye movements) induced by chronic alcohol use (Bender & Brown, 1948) or barbiturate (Rashbass, 1959) or decreased vergence with barbiturate use (Westheimer & Rashbass, 1961). These findings were typically derived from single case studies or conducted using small samples of healthy individuals. Further, there was a movement in the field toward quantifying the sedating effects of drugs, such as alcohol, barbiturates, and anticonvulsants using eye movements in contrast to more subjective means such as an individual's rating of drowsiness. One of the earliest eye movement studies to evaluate the sedative effects of medication on eye movements was conducted by Aschoff (1968), in which reduced saccade velocity and increased reaction time was observed in response to intravenously administered diazepam. Several other studies demonstrated the effects of alcohol use on eye movements, including reduced velocity (Wilkinson, Kine, & Purnell, 1974), reduced amplitude, and overall decreased quality of saccade waveforms (Guedry, Gilson, Schroeder, & Collins, 1974).

In more recent years, research has focused on evaluation of pharmacological treatments on aspects of cognition in both healthy individuals and clinical populations, including pharmacogenetic effects, and use of eye movement measures as biomarkers for the evaluation of potential cognitive enhancers or and the identification of treatment targets in model systems of disease. These studies will be described in further detail in Sects. 18.4 and 18.5.

18.3 Methods and Approaches in Pharmacology

In this section, special emphasis is placed on methodological issues for designing, planning, and conducting a pharmacological study or clinical trial. Considerations for optimizing eye movement paradigms for pharmacological studies are presented.

18.3.1 *What Is Pharmacology? What Is Psychopharmacology?*

Initially, it is important to define some key terms. *Pharmacology* is the study of how therapeutic or non-therapeutic chemical agents (i.e., drugs) influence biological systems (at the cellular, physiologic, organ, and organism levels), and the mechanisms by which they do so. Pharmacology often divides a drug's interactions with the body into their pharmacokinetic and pharmacodynamics aspects (Tambour & Crabbe, 2010). *Pharmacokinetics*, sometimes described as what the body does to a drug, incorporates drug absorption, distribution, metabolism, and excretion. *Pharmacodynamics*, described as what a drug does to the body, involves receptor binding, post-receptor effects, and chemical interactions. A drug's pharmacokinetics and pharmacodynamics are both genetically and environmentally influenced (Tambour & Crabbe, 2010).

Psychopharmacology is the scientific field that utilizes drugs or other chemical agents to understand neural function, to prevent and treat mental illness and drug abuse, and to understand how nontherapeutic psychoactive drugs and natural substances alter human mood, cognition, motor activity, endocrine, and other centrally mediated functions (Stolerman, 2010). When using psychopharmacology as a tool, especially for psychologists and cognitive neuroscientists, it is of interest to understand how drugs influence cognition, perception, mood, and behavior through their actions on cellular receptors.

As mentioned above, pharmacokinetics and pharmacodynamics are both at least in part influenced by genetics. The field of *pharmacogenetics* studies how genetic variation influences the response to a drug. More specifically, it is the study of how polymorphisms in genes that encode transporters, metabolizing enzymes, receptors, and other drug targets are related with variations in responses to drugs, including toxic and therapeutic effects (Tambour & Crabbe, 2010). The terms *pharmacogenetics* and *pharmacogenomics* are often used interchangeably, however, we prefer to make the following distinction: while pharmacogenetics focus on single gene variants (i.e., single gene-drug interactions), pharmacogenomics refer to several gene variants across the whole genome (i.e., multiple gene-drug interactions).

Genes contain information that determines the structure of proteins. Any variations in the DNA sequence (mutations) may alter the expression or the structure of proteins. DNA mutations that occur at a frequency of 1% or greater are termed polymorphisms (Tambour & Crabbe, 2010). Polymorphisms in genes coding for a protein that carries a drug to its target cells or tissues may cripple the enzyme that activates a drug or aid its removal from the body, and thus may induce pharmacokinetic or pharmacodynamic variations leading to individual differences in the response to the drug. Examples of genetic variations that affect the response to pharmacological agents are single nucleotide polymorphisms (SNPs), repetitive sequences, deleted DNA sequences, and alterations in chromosome structure (Reilly, Lencer, Bishop, Keedy, & Sweeney, 2008). Common sources of genetic variation examined in pharmacogenetic studies include SNPs that are located in genes coding for sites

of drug action (e.g. receptors or transporters), and drug metabolizing enzymes (e.g. cytochrome P450 enzyme variants) (Reilly et al., 2008) (see Box 1).

Box 1: Drug Metabolizing Enzymes

Cytochromes P450 are a good example of how drug metabolizing enzymes influence the response to a drug. Cytochromes P450 (CYPs) belong to a large superfamily of metabolizing enzymes. Within the CYP2 family, polymorphic CYP2D6 was one of the first and most important drug-metabolizing enzymes to be characterized at the genetic level (Tambour & Crabbe, 2010). It is estimated that CYP2D6 is responsible for the metabolism and elimination of approximately 25% of clinically used drugs (Wang et al. 2009). CYP2D6 is primarily expressed in the liver and there is substantial variation among people in the amount and the efficiency of CYP2D6 enzyme produced: four phenotypes have been described: “poor metabolizers”, “Intermediate metabolizers”, “rapid metabolizers”, and “ultrarapid metabolizers”. Ultrarapid metabolizers have multiple copies of the CYP2D6 gene expressed and greater-than-normal CYP2D6 activity. Therefore, ultrarapid metabolizers may not achieve therapeutic levels of a certain drug with usual doses and may require several doses to show a response. On the other hand, poor metabolizers are at increased risk of toxicity from CYP2D6 substrate drugs (Tambour & Crabbe, 2010).

What do these and other pharmacogenetic phenomena mean for psychologists, psychiatrists and cognitive neuroscientists? First, it is important to be aware that such phenomena as genetic differences in drug metabolizing exist. Cognitive effects of drugs in a sample of individuals may be blurred or may not be found at all due to the existence of inter-individual differences in genetic variation. Second, it might also be the case that “poor” and “good” responders to the drug under study may occur within the same sample—this might be due at least in part to differences in genetic make-up.

Accordingly, some researchers also take blood or saliva samples from their participants in order to perform DNA analyses to determine whether associations between gene variants and drug outcomes exist (see Fig. 18.1). Two scenarios are possible in this context: First, participants of a drug study may be genotyped after the study was conducted – this would be an a posteriori analysis strategy to find whether genetic polymorphisms influence drug outcome. Second, other researchers opt for an a priori strategy—that is having a specific hypothesis on the consequences of a genetic polymorphism beforehand.

An example of the latter approach is the evaluation of the relationship between working memory, variants in the gene coding for the enzyme COMT (the *COMT* gene) and the pharmacological substance tolcapone (a COMT inhibitor). COMT (catechol-*O*-methyltransferase) is an enzyme that breaks down catecholamines such as dopamine, epinephrine, and norepinephrine—all of which are neurotransmitters important for working memory and associated cognitive abilities. One already

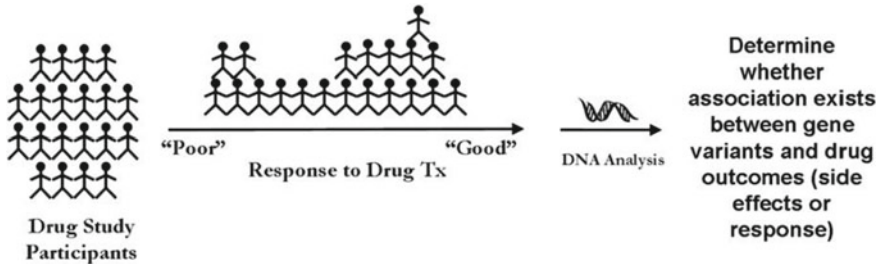


Fig. 18.1 Genetic variation may account for “poor” and “good” responders to a drug. Reprinted from Reilly et al. (2008), Copyright (2008), with permission from Elsevier

known and well-studied polymorphism in the *COMT* gene is the so-called Val158Met (rs4680) polymorphism. This is a functional SNP resulting in a valine (Val) to methionine (Met) substitute thereby altering the activity of the enzyme. The Met-allele is the low-activity allele; being homozygous (that is having two copies of the Met-allele) leads to a 3–4-fold reduction in enzymatic activity compared to being homozygous for the Val-allele (Lachman et al., 1996). As a consequence, carriers of the Met-allele degrade dopamine slower and thus are known to have higher tonic levels of dopamine in the frontal cortex (Bilder, Volavka, Lachman, & Grace, 2004).

Higher tonic levels of dopamine in prefrontal and frontal areas have been associated with better working memory performance (Bilder et al. 2004). A recent study by Farrell and colleagues (Farrell, Tunbridge, Braeutigam, & Harrison, 2012) found that males who are homozygous for the Met-allele outperformed those men who are homozygous for the Val-allele in the N-back task, a task measuring working memory performance. Furthermore, the *COMT* inhibitor tolcapone reversed these differences between the two genotype groups: it worsened N-back performance in MetMet participants but enhanced it in ValVal participants (Farrell et al., 2012).

18.3.2 *Methodological Issues in Pharmacological Studies of Eye Movements*

The following section addresses various topics on study design such as sample size, method of drug delivery, and the “window of opportunity” for evaluating drug effects. Furthermore, the use of eye movements to evaluate effects of acute versus long-term exposure to drugs as well as the reliability and sensitivity of eye movement measures is discussed.

Box 2: Is My Study a Clinical Trial?

Before conducting your research, you will need to check with the appropriate authorities in your country whether your study will be considered a clinical trial. For example, in the United States this is the Food and Drug Administration (FDA) which is responsible for drug approval, in the United Kingdom the Medicines and Healthcare Products Regulatory Agency (MHRA), and in Germany the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM).

In medical research, a clinical trial refers to a study which provides measures of efficacy for new interventions, drugs, or devices (Van Spall, Toren, Kiss, & Fowler, 2007). Clinical trials are an essential part of the development and licensing of medicinal products. They are intended to prove the efficacy of new medicinal products and to demonstrate their safety. Clinical trials are performed before the product concerned is placed on the market and after licensing, for instance to provide important findings on long-term effects of treatment or to test whether the drug also works in other patient groups. An overview of the phases of clinical research is depicted in Table 18.1. It might be the case that the authority in your country will decide that your study might be a phase-IV clinical trial. In that case, it is advisable to check whether your university or research unit offers support for conducting a clinical trial. Some universities have specialized clinical trial units which offer support and guidance for the procedures relating to clinical trials such as registration and monitoring.

It is also helpful to familiarize oneself with the guidelines made by the International Conference on Harmonization (ICH). The ICH guidelines provide helpful documents on topics such as Good Clinical Practice (GCP) and the content of clinical study reports. Finally, for publication in most scientific journals it is often necessary to register your study with an eligible database such as <http://www.clinicaltrials.gov>. Another helpful link on the web is the checklist by the CONSORT (Consolidated Standards of Reporting Trials) group which gives recommendations for reporting clinical trials: <http://www.consort-statement.org/consort-statement/>.

18.3.2.1 How Do I Determine the Right Sample Size?

During the planning process of your study, you will need to generate an estimate of your sample size. This is important for several reasons. First, you will need a certain number of participants in order to be able to find a statistical effect of a certain size. Second, you will need to make a project schedule and get an idea of how long it will take to test all participants. Third, you also need the number of participants to calculate the costs of the study, e.g. for the reimbursement of the participants and for study personnel who will be in charge of running the study.

Table 18.1 Phases of clinical research

Phase	Question	Method/subjects
Pre-clinical	Is it worth testing?	In vitro: test tube or cell culture In vivo: animals
I	Dose ranging and safety—Is it safe?	Healthy humans
II	Efficacy—Does it work?	Patients (small sample)
III	Comparison—Does it work better?	Patients (large, multi-center samples)
IV	Comparison—What more can we learn?	After approval and marketing, e.g. other patient groups

See also <https://www.nlm.nih.gov/services/ctphases.html> or <http://www.fda.gov/ForPatients/Approvals/Drugs/default.htm> for further information

How do you determine the minimum number of participants for your pharmacological study? This is best done by performing an a priori power analysis. The power of a statistical test is the probability that its null hypothesis (H_0) will be rejected given that it is in fact false. Obviously, significance tests that lack statistical power are of limited use because they cannot reliably discriminate between H_0 and the alternative hypothesis (H_1) of interest (Faul, Erdfelder, Lang, & Buchner, 2007).

In a priori power analyses, sample size N is computed as a function of the required power level ($1 - \beta$), the pre-specified significance level α , and the population effect size to be detected with probability ($1 - \beta$). For clarification, β is the so-called type II error (i.e. a “false negative”) when you reject H_1 although in fact H_1 is true. The type I error (i.e. α , the “false positive”) is the error you make when you reject H_0 and decide that H_1 is true when in fact H_0 is true. Typically, your α error (i.e. your level of significance) is set at the 5% level ($p = 0.05$). It is often recommended that the power of your statistical test greater or equal to 80% ($p \geq 0.80$) (Faul et al., 2007). Sample size N and statistical power can be calculated for many different statistical tests such as t tests, F tests, χ^2 tests, z tests and some exact tests (e.g. using G*Power (Faul et al., 2007).

18.3.2.2 Study Population

One of the first considerations in choosing the study population should be whether you want to test male participants only or both males and females. Many pharmacological studies only include males in order to avoid possible confounding effects from fluctuations in hormone levels due to menstrual cycle. A disadvantage of the “males only” design is that you can only make generalizations about half of the population and you cannot analyze your data concerning any possible sex differences. Indeed, at least some cognitive functions vary during the phases of the menstrual cycle such as memory performance (Farage, Osborn, & MacLean, 2008; Sherwin, 2012). However, this issue has not been studied extensively.

If you test both males and females, it will be useful to document for females the first day of the last menstruation to be able to infer in which phase of the cycle (follicular or luteal) the cognitive testing took place. You might want to keep the menstrual phase constant for all female participants if you do not want additional variance in your data, or you might test females both in the follicular and in the luteal phase if you wish to distinguish between those and analyze your data accordingly. At the minimum, menstrual cycle should be well documented for your study to be able to account for this factor in data analysis.

Another issue concerns the decision to test healthy individuals only or to include a sample of patients. If you plan a pharmacological study that includes patients, then be aware that patients greatly vary intra- and inter-individually regarding psychopathology and medication history, even within a single diagnostic category. This means that drug effects cannot be studied without the confounding effects of psychopathology and medication. A good example of this issue is schizophrenia, an illness that is highly heterogeneous with significant variation in amount and kind of medication between patients. Again, it is crucial to document all medications the patients take and for some classes of medications there are conversions to standard units which make the different medications and doses of medications comparable between patients (e.g. a standard in schizophrenia research is to convert different antipsychotics to chlorpromazine equivalents). If you are interested in treatment efficacy of a substance and you test healthy individuals only, then treatment efficacy is difficult to assess: deficit correction cannot be determined in healthy participants unless deficits are first induced.

18.3.2.3 Study Design: Between- or Within-Subjects?

In a between-subjects design, different groups of participants are tested in parallel (sometimes called a parallel group design), with each group receiving a different substance (see Fig. 18.2). Note that in a between subjects design, each participant is only tested once.

In contrast, in a within-subjects design, all participants undergo each treatment condition, that is, each participant receives all substances (see Fig. 18.2) in what is referred to as a cross-over design. Note that in a within-subjects design, each participant is tested several times. In this instance randomization of treatment conditions across participants is crucial.

Importantly, it should be pointed out that randomization cannot be implemented in every study. Clinical studies of treatment effects in patients in particular are often limited in study planning, e.g. by self-assignment of patients rather than randomization (see Sect. 18.4 below).

What are the advantages and disadvantages of between- and within-subjects designs? In between-subjects designs, a large number of participants per group is required in order to have enough statistical power to detect treatment effects. By contrast, within-subjects designs offer higher statistical power and a smaller sample size is sufficient. The different treatment groups in a between-subjects design have to be

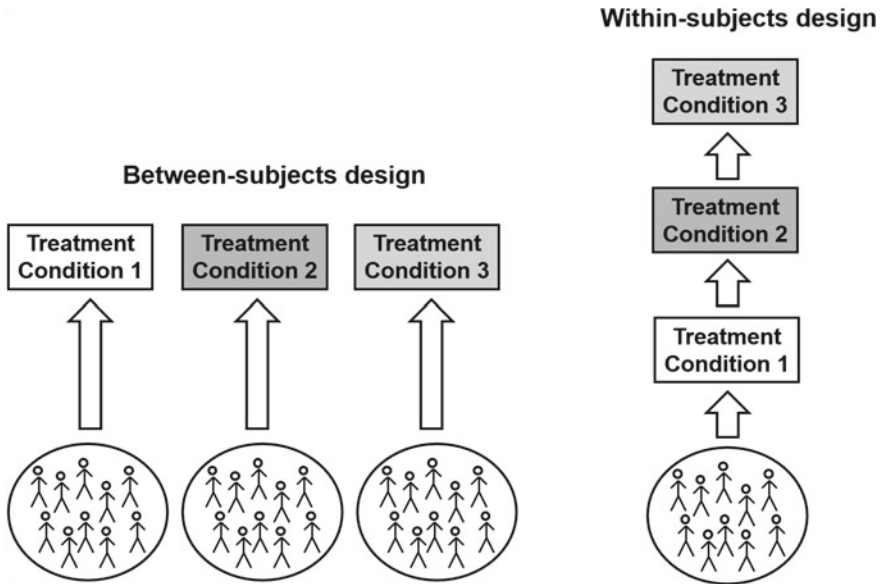


Fig. 18.2 Pharmacological studies can be divided in between-subjects design (i.e., group design) and within-subjects design (i.e., repeated-measures design)

carefully matched regarding demographic variables (and other possible confounding variables) such as level of education, age, and sex—otherwise the variance between the different treatment conditions is too high due to individual differences which arise from the participants. In within-subjects designs, variability between treatment conditions is generally low, as each participant undergoes all treatment conditions and by doing so serving as his/her own control (i.e. error variance associated with individual differences is low).

Despite the advantages of within-subjects designs, an important issue to consider in such studies concerns drug washout. The washout period refers to the time that is required for the administered compound to be eliminated from the body. Whilst this period varies between drugs, in experimental psychopharmacological studies with within-subjects designs, assessments often take place at one-week intervals. This is done not only to allow sufficient time for drug washout but also to control potential influences on behavior or performance that may vary throughout the week.

Another potential limitation of the sensitive within-subjects design concerns effects on performance of repeated exposure to the tasks under investigation (see also Sect. 18.3.3.2 below). Whilst oculomotor tasks tend to be trait-like and stable over time (Meyhöfer, Bertsch, Esser, & Ettinger, 2015), performance improvements have been observed following task repetition, likely reflecting effects of learning (e.g. Dyckman & McDowell 2005; Ettinger et al., 2003a). Such improvements may be problematic in within-subjects pharmacological studies as they may overlay or

Table 18.2 Latin square design for randomizing the order of treatment conditions in a within-subjects design (A = substance 1, B = substance 2, C = substance 3)

	Time 1	Time 2	Time 3
Group 1	A	B	C
Group 2	B	C	A
Group 3	C	A	B

counteract genuine drug effects (e.g. Ettinger et al. 2003b; Green, King, & Trimble, 2000).

As mentioned above, randomization is crucial in study design. When opting for a between-subjects design, you need to ensure that participants are randomly allocated to the different treatment groups. At the same time, you have to monitor the recruitment of participants so that all groups will be closely matched regarding individual variables of the participants. If you decide on a within-subjects design, you need to randomize the order of the treatment conditions across the participants. There are several ways of randomizing conditions; one established method is the Latin square method. A Latin square design is a blocking design with two orthogonal variables: the 2 blocking variables are divided into a tabular grid with the property that each row and each column receives each treatment exactly once. In a pharmacological study, these two blocking variables would be group of participants and time. If there are three different substances, then a Latin square design will lead to nine squares (3 points in time \times 3 substances), see Table 18.2.

In summary, a pharmacological study should follow the “gold standard” – that is a randomized, controlled trial (RCT): randomized meaning randomization to treatments (see above) and controlled referring to comparison to a placebo condition. Furthermore, a pharmacological study should ideally be double-blind: both the participant and the experimenter (including individuals collecting, scoring, and analyzing data) are unaware which substance is administered in the respective treatment condition. This design controls for expectancy effects on the part of both parties.

18.3.2.4 The Window of Opportunity Is Crucial in Evaluating Drug Effects

Section 18.3.1 already introduced the concepts of pharmacokinetics and pharmacodynamics. Indeed, if you plan a pharmacological study, you need to familiarize yourself with some of the facts concerning your study drug, e.g. how quickly it is absorbed, when peak plasma concentrations are reached, how stable plasma concentrations are and how fast the drug is metabolized. Acquiring this information is important as you will only have a certain “window of opportunity” when plasma concentrations of your drug have reached a stable plateau in which you need to run your paradigms to be able to detect drug effects. Usually, you will find information on pharmacokinetics and pharmacodynamics in the summary of product characteristics (SPC) and in papers in pharmacology journals.

An important point to consider in this context is the route of administration for your drug. The route of administration will influence how fast the drug is absorbed and metabolized and this in turn will influence your window of opportunity for testing. An example is nicotine, which can be administered in several different ways, for instance via subcutaneous injection, a chewing gum or a lozenge, with a nasal spray or as a patch. While subcutaneous injection, chewing gum, lozenge and nasal spray deliver nicotine quickly (i.e. within minutes), nicotine from a patch is absorbed more slowly (a stable plateau is reached after approximately 2–4 h). However, the plasma nicotine concentrations will be more stable and longer lasting with a patch, thereby increasing the window of opportunity for testing.

With different routes of administration, different undesirable effects (side effects) arise. Thus, you will need to balance the way of administration against the severity of the side effects. For instance, it might seem appealing to deliver nicotine via nasal spray because it is quick, however the tingling sensations in the nose and a high incidence for nausea might be unfavorable. In contrast, nicotine delivery via patch might be time-consuming, but the side effects will be milder as nicotine is absorbed less rapidly.

18.3.2.5 Eye Movements Can Be Studied to Evaluate Both Acute and Long-Term Drug Effects

While most researchers opt for testing the acute effects of a certain drug on the sensorimotor and cognitive processes that underlie oculomotor behavior, eye movement paradigms also have the potential to provide information on the long-term effects of drugs on these processes.

A good example for the usefulness of eye movements in evaluating the long-term effects of medication is a study about the effects of two different benzodiazepines. As discussed below, benzodiazepines amplify the effect of the neurotransmitter gamma-aminobutyric acid (GABA), and thereby exerting sedative, sleep-inducing, and anxiolytic effects, and thus are often prescribed for sleep and anxiety disorders. Benzodiazepines are highly effective, but the risk of becoming addicted is also high. Therefore, they are usually only prescribed for a limited time period. However, there are a considerable number of patients who become chronic users. In a study by van Steveninck and colleagues (van Steveninck et al., 1997), the effects of the chronic use of the two benzodiazepines temazepam and lorazepam were evaluated. Chronic users of these medications (length of use was 1–20 years) were compared with control participants regarding plasma benzodiazepine concentrations, saccadic performance, visual analog scales, and other measures after having received a single dose of temazepam or lorazepam. Saccade performance was studied because the maximal velocity of saccadic eye movements is a highly sensitive parameter for sedative benzodiazepine effects (Hommer et al., 1986; van Steveninck et al., 1992), i.e. the sedative effect of benzodiazepines can be shown with saccadic slowing. Results showed that for temazepam, there were no significant differences between chronic users and controls regarding plasma concentration and saccadic velocity; both groups

showed comparable saccadic slowing. However, for lorazepam, the chronic users showed reduced sensitivity to the effects of the drug as they exhibited less saccadic slowing than the controls. This effect on saccades demonstrates the reduced drug sensitivity in the chronic users. Nevertheless, despite this indication for tolerance in the chronic lorazepam users, a single dose of lorazepam still caused significant slowing effects on saccadic eye movements (van Steveninck et al., 1997).

This example shows that eye movement measures are sensitive not only to reveal acute drug effects, but also the effects of long-term exposure to drugs as discussed in Sects. 18.1 and 18.2 below.

18.3.3 Recommendations Towards Optimizing Eye Movement Paradigms for Pharmacological Studies

The following section provides some guidelines and considerations for optimizing eye movement paradigms for pharmacological studies. Topics include methods of standardization and addressing practice effects that occur with repeated testing (e.g., before and after treatment). Finally, we present some recommendations for task parameters in oculomotor paradigms.

18.3.4 Standardization: General Recommendations

Standardization of methods is crucial in order to be able to provide a safe environment for your participants and to obtain repeatable results. This section will focus on some general recommendations for the execution phase of a pharmacological study.

Prior to starting a research study, it is helpful to establish and document Standard Operating Procedures (SOPs). According to the ICH Guideline for Good Clinical Practice E6(R1), SOPs are *detailed, written instructions to achieve uniformity of the performance of a specific function*. More precisely, SOPs should include all the necessary steps the study personnel has to perform at each testing session. These steps may include, amongst others, how to administer the study drug, how to give the instructions to the participants, how to calibrate the eye tracker and how to run the eye movement paradigm with the respective computer software. It is important that SOPs are sufficiently detailed and easy to understand. It is also useful to have a time table for each testing session in which all the events of a testing session are documented, that means the experimenter has a list with each step that has to be performed (e.g. check vitals, hand out questionnaire, administer drug, etc.) and writes down when each step was performed. That way, timeliness is granted and no step is forgotten during the course of events.

Special emphasis should be given to the instructions for the participants. Written instructions are preferred; however, the experimenter should always ensure that

the participant understands the task—a good way for doing this is to let the participant explain the task in her/his own words after she/he has read the text. When explanation of instructions is needed, it is important to use exactly the same words (and ideally stress the same syllables) because the way information is presented might influence the performance of the participant. For example, in an antisaccade task it may well make a difference whether participants are instructed “to look in the opposite direction” or “to look at the mirror image location” of the peripheral stimulus—the demands on the processes involved in the vector transformation are considerably greater in the latter instance (Hutton & Ettinger, 2006; Mosimann, Felblinger, Colloby, & Muri, 2004).

SOPs are also critical for data processing and analysis. Usually, physiological data such as eye movement data require visual inspection aside from automatic processing steps with computer software. Therefore, criteria should be defined for data analysis to which all raters adhere. Examples for such criteria include criteria for excluding artifacts in data and when trials need to be excluded. Moreover, it is important that the raters of the data are blind to experimental conditions, that is, they must not know whether it is data from the placebo or verum group conducting analyses—this will help to minimize expectancy effects.

18.3.5 Repeated Testing and Practice Effects

The section provides recommendations and considerations for addressing repeated testing and practice effects that arise in the context of a within subject design (see Sect. 18.3.2.3). A standard way of accounting for practice effects is to counterbalance experimental sessions (i.e. drug conditions) (see Sect. 18.3.2.3).

In addition to counterbalancing drug conditions, some researchers also introduce a so-called “baseline session” to their study design. A baseline session includes all procedures as the drug conditions (i.e. eye movement paradigms, questionnaires, visual analog scales, etc.) but without the substances (verum or placebo). Data from the baseline session can be taken into account when analyzing your data for drug effects: findings are interpreted relative to baseline performance and test whether there is improvement compared to baseline. Moreover, a baseline session has the advantage that participants will already be familiar with all the experimental procedures when they start with the randomized sessions. Practice effects from baseline to the first drug session (i.e. practice effects between first session and second session) might be the strongest but these practice effects might already decrease between the first and the second drug session (i.e. session two and three).

Another issue with repeated testing is that eye movement paradigms should exhibit high test-retest reliability (Ettinger et al., 2003a). Ideally, you consult published data on reliability or conduct your own reliability study before your pharmacological project to test whether performance on your eye movement paradigms stays stable over several sessions in the absence of pharmacological influences.

Finally, when statistically analyzing your repeated-measures data, it is advisable to include order of administration as a factor as it might play a role. It is thorough to look at effects of order in your data, however, most papers do not report on this issue when the “gold standard” of counterbalancing was used.

18.3.6 Recommendations for Designing an Eye Movement Paradigm

As aforementioned, one problem with eye movement research is the lack of standardization of task parameters across different research groups and studies. Therefore, it is difficult to compare results across studies. However, recently, researchers have made an effort to establish guidelines for particular parameters in eye movement paradigms, e.g. recommendations for stimulus size and trial length. These guidelines have been mainly designed for research in psychiatry and neurology; but these recommendations are transferable to the field of pharmacology. So far, recommendations for standardization have been addressed extensively by Smyrnis (2008) and Antoniadou and colleagues (Antoniadou et al., 2013). Although these recommendations might still be tentative, they provide a good starting point for working out the many details of a final synthesis of recommendations in an effort to achieve the standardization of oculomotor function test procedures and outcome measurements (Smyrnis, 2008). While the paper by Smyrnis gives advice on smooth pursuit and saccadic eye movement tasks, the paper by Antoniadou and coworkers aimed at establishing an internationally standardized antisaccade protocol. For additional information on eye movement task recommendations, you can refer to the original publications.

18.4 Findings from Pharmacological Effects on Eye Movements in Healthy Individuals

In the following section, the main applications for studying the pharmacological effects on eye movements in healthy individuals are considered, specifically (1) studies designed to monitor side effects of drugs, (2) the use eye of movement tasks as treatment targets in model systems of disease, and (3) examination of eye movements as biomarkers for the study of cognitive enhancement.

18.4.1 Eye Movement Tasks Can Be Used to Monitor Side Effects of Drugs

Eye movement measures have been used as biomarkers to monitor sedative and other side effects across a range of drugs on sensorimotor and cognitive processes.

18.4.1.1 Benzodiazepines and Other Sedatives

Benzodiazepines are commonly used for the treatment of symptoms of anxiety. Benzodiazepines increase the effects of the neurotransmitter gamma-aminobutyric acid (GABA) and are mediated through agonism of GABA-benzodiazepine chloride receptor complex, such as GABA_A 2 and GABA_A 3 receptors (Reilly et al., 2008). The mechanism of this class of drugs results in anxiolytic, hypnotic, anti-convulsants, and muscle relaxant effects (Möhler, Fritschy, & Rudolph, 2002). The influence of benzodiazepines on eye movements is well established. Studies with nonhuman primates have shown that GABA-ergic projections from the substantia nigra pars reticulata to the superior colliculus are involved in the generation of saccades (Hikosaka & Wurtz, 1983; Reilly et al., 2008). A local injection of a GABA agonist into the superior colliculus reduces saccadic amplitude and increases latency of saccades (Hikosaka & Wurtz, 1985a, 1985b). Similarly, prolonged latency and fixation deficits following an injection of a GABA agonist into the frontal eye fields have been demonstrated (Dias, Kiesau, & Segraves, 1995).

In healthy control subjects, numerous studies have indicated a dose-dependent slowing of saccade peak velocity subsequent to benzodiazepines exposure, including diazepam, lorazepam, midazolam, and tenazepam (Ball et al., 1991; Rothenberg & Selkoe, 1981a). Additionally, there is evidence for log-linear correlations between peak saccadic velocity and serum benzodiazepine concentrations after exposure to temazepam, diazepam, and nitrazepam (Bittencourt, Wade, Smith, & Richens, 1981), as well as correlations between diazepam-induced changes in saccadic eye velocity and increasing plasma diazepam concentrations (Hommer et al., 1986). The most consistently reported effect of benzodiazepines, and one that has been shown to be more sensitive to the sedative effects of these medications than traditional neuropsychological measures, is decreased saccade velocity (Blom, Bartel, de Sommers, van der Meyden, & Becker, 1986; de Visser et al., 2003; Salonen, Aaltonen, Aantaa, & Kanto, 1986).

Benzodiazepines administered to healthy individuals can also influence other saccade parameters, including decreasing saccade acceleration and deceleration, and potentially increased saccade error (Ball et al., 1991). Masson and colleagues (2000) conducted a placebo-controlled double-blind study examining the effects of low dose lorazepam on prosaccade latency using a gap and overlap paradigm. This paradigm varies the temporal interval between central fixation offset and the peripheral target appearance. A gap condition refers to the temporal gap between the offset of the fixation target and peripheral target, while the overlap condition refers to the persistence

of the fixation target after the appearance of the peripheral target (see Pierce et al., this volume). These manipulations result in a shortening of saccade latency in gap trials due to a release of the visual fixation system, or lengthening of latency in overlap trials due to persistent engagement of the fixation system after the peripheral target appearance. Compared to placebo, lorazepam significantly increased the latency of prosaccades under both conditions, though did not modify the gap/overlap effect; this finding suggests a generalized slowing of response time, without modification of the fixation release system. Notably, this effect on prosaccade latency may be drug specific, as it has not been observed by midazolam (Ball et al., 1991).

Similar to findings from saccade tasks, benzodiazepines have been shown to decrease smooth pursuit velocity (Padoan, Korttila, Magnusson, Pyykko, & Schalen, 1992). Further, reduced smooth pursuit velocity has also been shown to correlate with serum concentrations of benzodiazepines, such as temazepam and diazepam (Bitencourt, Wade, Smith, & Richens, 1983). In addition to effects on pursuit velocity, a placebo-controlled double blind study revealed that lorazepam resulted in increased smooth pursuit latency, reduced pursuit gain, and increased catch-up saccade activity to correct for reduced velocity (Masson et al., 2000), particularly at higher doses. Other studies have also observed dose-dependent reductions in smooth pursuit gain in healthy participants following diazepam exposure (Rothenberg & Selkoe, 1981b).

To conclude, the effects of benzodiazepines on eye movements have most consistently shown a dose-dependent slowing of peak saccade and smooth pursuit velocity. These findings have been shown to be more sensitive markers of the sedative effects of benzodiazepines compared to other measures of psychomotor speed and attention (Reilly et al., 2008). Furthermore, the association between serum concentrations of benzodiazepines and effects on velocity of saccadic and pursuit eye movements suggest that this is a sensitive and reliable measure of this class of drug's pharmacokinetics and pharmacodynamics.

18.4.1.2 Antipsychotics

Antipsychotic medications render their effectiveness, in part, through their ability to block central dopamine receptors, particularly D2 receptors. In addition to D2 antagonism, this class of medications also renders their benefit through 5HT-2 antagonism. Antipsychotics have been associated with the emergence of extrapyramidal side effects, such as involuntary movements. First-generation (or typical) antipsychotics refer to medications developed in the 1950s and were first used to treat psychosis, often at doses that resulted in sedation or adverse extrapyramidal effects (Reilly et al., 2008). Conversely, second-generation (or atypical) antipsychotics emerged in the 1990s, and are effective at typically lower doses and with less adverse side effects. First-generation antipsychotics block D2 receptors, while second-generation antipsychotics moderately block D2 receptors, but also block serotonin and other receptors.

As with benzodiazepines, the most consistent finding of the effects of first and second-generation antipsychotic medications is slowed saccadic peak velocity. In a

study conducted by Lynch, King, Green, Byth, and Wilson-Davis (1997), healthy participants completed prosaccade (or visually guided saccade) and pursuit eye movement tasks before and 2, 4, and 6 h after administration of single doses of lorazepam (2.5 mg) or the first-generation antipsychotic haloperidol (2, 4, or 6 mg). Findings from this study indicated that similar to lorazepam, haloperidol exposure resulted in a dose-dependent decrease in peak saccade velocity on the visually guided saccade task at the higher doses (i.e., 4 and 6 mg). Further, there was no effect of haloperidol on saccade latency, and no effect of haloperidol on pursuit position error, velocity, or saccadic intrusions during the smooth pursuit task. These results parallel prior studies indicating that first-generation antipsychotics result in slowed peak saccade velocity, though do not adversely affect smooth pursuit (Holzman, Levy, Uhlenhuth, Proctor, & Freedman, 1975; King et al., 1995; Reilly et al., 2008).

Several studies have examined the effects of antipsychotics on cognitive or attentional control. In a randomized cross-over study completed by Green and King (1998) healthy subjects performed visual fixation (i.e., no saccade), prosaccade, and antisaccade tasks after receiving single doses of the benzodiazepine lorazepam (2 mg), the first-generation antipsychotic chlorpromazine (50, 75, and 100 mg), and placebo. The prosaccade task consisted of target displacements at 30 and 40°. The no-saccade task required the subject to fixate on a central location, and when the appearance of a peripheral target occurred, they were instructed to not look to the target, but remain fixated at the central location. The antisaccade paradigm, a measure of inhibitory behavioral control, requires a subject to fixate centrally to a target, and when a peripheral target appears, they are instructed to generate a saccade and to its mirrored location in the opposite direction. The results of the study indicated a dose-dependent decrease in peak saccade velocity in the antisaccade and prosaccade tasks after exposure to chlorpromazine. However, chlorpromazine exposure did not affect antisaccade latency or error rate (the percentage of trials where a saccade was incorrectly made to the target) on the antisaccade or no-saccade tasks. Chlorpromazine slowed prosaccade latency at the highest doses, while lorazepam increased both antisaccade latency, as well as errors during the antisaccade and no-saccade tasks.

In a parallel group placebo-controlled study comparing the effects of acute doses of the second-generation antipsychotics amisulpride (300 mg) and risperidone (3 mg), and the first-generation antipsychotic chlorpromazine (100 mg), healthy control subjects performed prosaccade and antisaccade eye movement tasks before and 3 h after drug exposure (Barrett, Bell, Watson, & King, 2004). Although amisulpride did not affect eye movement parameters, both risperidone and chlorpromazine resulted in a slowing of peak saccadic velocity and increased error rates on the antisaccade task. None of the antipsychotic medications had an effect on prosaccade or antisaccade latencies.

To summarize this section, antipsychotic medications have similar sedating effects to those reported in benzodiazepine use, particularly at higher doses, as both may result in a slowing of peak saccade velocity. However, the dose-dependent slowing of peak velocity has only been reported with use of first-generation antipsychotics, which may be suggestive of D2 antagonism. However, unlike benzodiazepines, antipsychotic medications do not result in significant changes in prosaccade or anti-

saccade latencies in healthy individuals, and first-generation antipsychotics do not seem to adversely affect pursuit velocity among healthy individuals (Reilly et al., 2008).

18.4.1.3 Anticonvulsants and Mood Stabilizers

Anticonvulsant and mood stabilizing medications are used for treatment of seizure disorders and as acute and maintenance treatments for bipolar disorder. These drugs have several mechanisms of action, with glutamatergic antagonism as a common mechanism among many of them.

Newer anticonvulsant medications, such as gabapentin, are associated with less serious side effects than those reported with use of older medications, such as carbamazepine. Noachtar, von Maydell, Fuhry, and Buttner (1998) compared the effects of gabapentin (600 mg) to carbamazepine (400 mg) and placebo in healthy individuals. Participants performed prosaccade and smooth pursuit tasks 2, 5, and 7 h after drug administration. Compared to placebo, both gabapentin and carbamazepine resulted in a reduction of peak saccade velocity; however, the effects of gabapentin on saccade velocity were present only at 2 h, whereas carbamazepine's effect was observed at 7 h after administration. Additionally, the duration of saccades was significantly longer with carbamazepine both at 2 and 7 h after intake, effects which were not observed with gabapentin. These findings illustrate the utility of eye movements for illustrating different pharmacokinetic properties of drugs, as it appears that the gabapentin may be cleared more readily than carbamazepine and with fewer adverse effects.

Another anticonvulsant that is commonly used as mood stabilizer in the treatment of affective disorders is lamotrigine, which is a glutamatergic antagonist and 5-HT agonist. In a double blind, crossover study conducted by Cohen and colleagues (1985), healthy volunteers completed prosaccade and smooth pursuit tasks after receiving 120 and 240 mg of lamotrigine, 10 mg of diazepam (a benzodiazepine known to cause sedation), 0.5 and 1.0 g of phenytoin (an anticonvulsant medication), and placebo. Diazepam resulted in a reduction in saccade peak velocity, which lasted 8 h after administration. Further, diazepam exposure increased saccade duration but not latency. These effects were not seen in lamotrigine or phenytoin. Lastly, both phenytoin and diazepam reduced smooth pursuit performance, while lamotrigine did not have this effect. The findings of this study are consistent with other studies that have shown no adverse effects on smooth pursuit tracking after lamotrigine administration (Peck, 1991), and which suggest that lamotrigine may have a more favorable side effect profile compared to other anticonvulsant medications.

Lithium is a mood stabilizing medication that is often used in the treatment of bipolar disorder, and early studies with this clinical population have suggested that adverse effects on smooth pursuit maybe associated with lithium exposure (Holzman, O'Brian, & Waternaux, 1991; Levy et al., 1985). To examine this hypothesis, Flechtner and colleagues (1992) examined smooth pursuit performance in healthy individuals after receiving either lithium carbonate injection or placebo. Subjects completed a smooth pursuit task at baseline and after 2 weeks of receiving treatment

under randomized double blind conditions. No differences in the quality of smooth pursuit eye movements between the placebo and lithium groups were observed, suggesting that smooth pursuit impairment may be attributable to disease rather than lithium exposure effects in clinical populations.

18.4.2 Eye Movement Measures Are Studied as Treatment Targets in Model Systems of Disease

The following section will consider research that uses eye movements as surrogate treatment targets in pharmacological model systems of psychiatric and neurological diseases. A *pharmacological model system* refers to the administration of a drug with known effects (agonist/antagonist) on neurotransmitter systems to healthy humans or animals, resulting in changes that mimic symptom characteristics of a particular disease.

An example of such a model is administration of ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist that induces transient psychotomimetic effects in healthy individuals as well as temporary cognitive impairments similar to those observed in schizophrenia (Krystal et al., 2003). Individuals with schizophrenia demonstrate impairment in saccadic and pursuit eye movements (see chapter by Smyrnis et al. in this volume), leading Radant, Bowdle, Cowley, Kharasch, and Roy-Byrne (1998) to examine the effects of ketamine on eye movements in healthy individuals as a pharmacological model for this illness. Healthy individuals received either a placebo or ketamine infusion in a randomized single blind placebo controlled design with oculomotor performance measured using prosaccade, antisaccade, and smooth pursuit tasks. Subjects received progressively higher doses of ketamine with plasma concentrations of 50, 100, 150, and 200 ng/ml over a 2-h period, with oculomotor tasks administered after each infusion step. Compared to placebo ketamine induced a dose-dependent decrease in peak velocity prosaccade, increase in prosaccade latency, decrease in smooth pursuit gain, and increase in catch-up saccade frequency and amplitude during pursuit. Interestingly, ketamine did not adversely impact antisaccade performance. A recent study replicated the adverse effect of ketamine on smooth pursuit performance and additionally showed that these drug-induced impairments are accompanied by reductions in blood oxygen level dependent (BOLD) signal in a task-related network of primary visual cortex, area V5 and the right frontal eye field (FEF) (Steffens et al., 2016). Overall, these findings provide partial support for the effects of ketamine in inducing eye movement abnormalities observed in individuals with schizophrenia, such as impaired smooth pursuit, and illustrate the potential of NMDA receptor antagonism as a pharmacological model for schizophrenia (Radant et al., 1998).

Another application of a pharmacological model system is to evaluate the effects of antipsychotic medications among healthy individuals under the transient effects of ketamine and observe whether such medications can prevent or ameliorate any

temporarily induced behavioral deficits. A recent study by Schmechtig et al. (2013) adopted this approach using a double-blind, randomized, placebo-control, parallel groups design in which healthy individuals performed prosaccade, antisaccade, and smooth pursuit tasks under one of four conditions: (1) placebo capsule and saline infusion, (2) placebo capsule and ketamine infusion, (3) risperidone capsule (2 mg) and saline infusion, or (4) risperidone capsule (2 mg) and ketamine infusion. As previously observed (Radant et al., 1998), ketamine was associated with impairment in smooth pursuit, reflected by increased saccadic frequency and decreased velocity gain, but was not observed to impact prosaccade or antisaccade performance. Risperidone administration resulted in a decreased gain and slower peak velocities in both the prosaccade and antisaccade tasks, and risperidone did not reverse any of the ketamine-induced oculomotor changes. These findings suggest that risperidone lacks cognitive enhancing effects on oculomotor biomarkers in the ketamine model system of schizophrenia (Schmechtig et al., 2013).

18.4.3 Eye Movements Are Used as Biomarkers for the Study of Cognitive Enhancement

Several drugs, both therapeutic and those of abuse, may alleviate cognitive deficits among clinical populations or enhance normative cognitive functions among healthy individuals. The most widely studied drug class for such cognitive enhancing effects is stimulants, which render their effects through augmentation of synaptic action of norepinephrine and dopamine neurotransmitter systems (and to a lesser extent, serotonin).

18.4.3.1 Nicotine

Nicotine is a cholinergic agonist that binds to nicotinic acetylcholine receptors and has stimulant properties. These receptors facilitate the release of other neurotransmitters, including dopamine, acetylcholine, and glutamate and are involved in regulating multiple cognitive functions. At certain doses, nicotine's beneficial effects include increased psychomotor speed, improved sustained attention, and greater performance on tasks of cognitive control (Reilly et al., 2008). Cholinergic inputs to structures in the brainstem, including the superior colliculi, facilitate motor outputs for the initiation of saccades (Kobayashi & Isa, 2002). For example, in single unit recordings of animals who are administered nicotine, there is a greater firing of cells in the substantia nigra, which resulted in shorter saccade latencies subsequent to increased inhibitory input to the fixation zone of the superior colliculus (Clarke, Hommer, Pert, & Skirboll, 1985).

In a study examining the effects of nicotine on antisaccade performance, a group of healthy individuals who smoked 10–20 cigarettes a day completed baseline and

re-test antisaccade tasks on each of two test sessions separated between 2 and 7 days (Rycroft, Hutton, & Rusted, 2006). The antisaccade task employed in this study included a 200 and 500 ms gap condition in order to increase potential for observing the effects of nicotine on antisaccade performance. Sessions were counterbalanced, such that half of the participants smoked between baseline and retesting in their first session and did not smoke during the second session, and the other half of the sample did not smoke during the first session, but smoked between baseline and retesting in the second session. This study design enabled evaluation of whether acute nicotine exposure between baseline and retesting influence antisaccade performance. Results of the study indicated that nicotine exposure improved antisaccade performance reflected by a decrease in antisaccade error rate and antisaccade latency from baseline to retest. However, this effect was present only among subjects who smoked during the first session but not those who smoked during the second session. One explanation for these findings is that practice effects between session 1 and 2 were larger than the effect of nicotine. Thus, it is possible that the potential enhancing effects of nicotine are apparent when subjects have not been already exposed to the task. The findings of Rycroft et al., 2006 are consistent with other eye movements studies, which have demonstrated that nicotine administration results a reduction in antisaccade latencies and error rate (Depatie et al., 2002; Ettinger et al., 2009; Larrison, Briand, & Sereno, 2004; Powell, Dawkins, & Davis, 2002), possibly due to nicotine's contribution to improved attention and control in the inhibition of reflexive responses. Evidence from functional neuroimaging shows that antisaccade improvements with nicotine are accompanied by reduced, i.e. more efficient BOLD signal (Ettinger et al., 2009).

Less consistent findings of cognitive enhancing effects of nicotine on smooth pursuit performance have been reported (Kasparbauer et al., 2016). For example, in a study examining nicotine effects on smooth pursuit, Domino, Ni, and Zhang (1997) evaluated pursuit eye movements in healthy non-smokers and smokers before and after inhalation of a sham cigarette or a cigarette of their preferred choice. Smooth pursuit performance was measured at 5 min before and at 0, 3, 6, 10, 20, and 30 min after smoking a sham cigarette or tobacco cigarette. An increase in smooth pursuit velocity was observed when tracking a 15 degree per second velocity stimulus for both smokers and non-smokers, but not at slower tracking speeds (i.e., 6 degree per second velocity stimulus). Other studies, however, have reported contrasting findings of the effects of nicotine exposure on smooth pursuit performance. For example, Olincy, Ross, Young, Roath, and Freedman (1998) found that healthy smokers abstinent from cigarettes for several hours prior to testing did not show any change in pursuit gain 10–15 min after smoking.

There is therefore variable evidence for nicotine's potential enhancing effects on oculomotor measures, with perhaps some indication that it may improve antisaccade performance and smooth pursuit under certain conditions. The variability in findings may be influenced by methodological differences including subjects' familiarity with the task, baseline smoking status, and stimulus presentation conditions.

18.4.3.2 Methylphenidate

Methylphenidate is a commonly prescribed psychostimulant medication, most often to individuals with attention deficit hyperactivity disorder (ADHD), where its efficacy for treating clinical symptoms is well established and its beneficial effects on cognitive deficits in this clinical population is increasingly appreciated. Methylphenidate renders its clinical efficacy on ADHD symptoms and cognitive deficits through blockage of the dopamine transporter thereby increasing the availability of dopamine and noradrenaline. More recently, methylphenidate has been under consideration as a potential cognitive enhancer in healthy individual individuals, although there has been limited empirical support to support this use.

Allman, Ettinger, Jooper, and O'Driscoll (2012) evaluated the effects of a single 20 mg dose of methylphenidate on oculomotor performance among healthy male volunteers in a double-blind placebo-controlled crossover design study. Subjects performed no gap prosaccade and antisaccade tasks, a predictive saccade task and a smooth pursuit task. Eye movement testing occurred at a baseline visit and then again at two subsequent visits separated by 1 week visits where subjects were randomized to receive methylphenidate or placebo (with the opposite condition assignment at the third visit). As noted above (Sect. 18.3.3.2), the baseline visit prior to randomization reduces the likelihood of practice effects on the medication trial. Compared to the placebo condition, methylphenidate administration resulted in significantly reduced prosaccade latency, significantly increased peak velocity and frequency of predictive saccades (particularly in conditions with predictable timing), and increased gain and reduced saccades during pursuit tracking. Antisaccade performance (latency or error rate) was unaffected by methylphenidate treatment in these healthy individuals. These findings of speeded prosaccade latency and improved smooth pursuit are generally consistent with those observed in studies of ADHD patient groups treated with methylphenidate, and may reflect enhancing effects in timing related behavioral functions. However, a more recent study did not find improvements in SPEM performance, albeit with a larger dose of 40 mg (Kasparbauer et al., 2016).

18.4.3.3 D-Amphetamine

Dextroamphetamine (D-amphetamine), is another psychostimulant medication that is prescribed for the treatment of ADHD and that is also under investigation as a potential cognitive enhancer among healthy individuals.

The effects of D-amphetamine on antisaccade and predictive saccade performance were evaluated by Allman et al. (2010) in a double-blind crossover design. Twenty-four healthy individuals completed an antisaccade task and a predictive saccade task at a baseline visit, and again at two subsequent visits where they were randomized to receive 0.3 mg/kg D-amphetamine or placebo (with the opposite condition assigned at the third visit). Unlike findings reported by Allman et al. (2012) no effect of drug was observed on the frequency of predictive saccades during the predictive saccade task. On the antisaccade task, however, error rate significantly decreased after D-

amphetamine administration regardless of the baseline performance level whereas the effect of drug administration on antisaccade latency depended on baseline performance level. Among those individuals who had shorter antisaccade latencies at baseline (i.e., good performance), D-amphetamine resulted in a prolongation of antisaccade latencies suggesting an adverse effect for this set of individuals. In contrast, those individuals with longer antisaccade latencies at baseline had reduced latencies following drug administration, consistent with a beneficial effect. These findings are consistent with an inverted-U relationship between dopamine activity level and performance. Importantly, this study illustrates that the effects of a drug on oculomotor performance may depend on pre-exposure performance levels.

18.4.4 Benefits and Limitations to Studying Drug Effects in Healthy Individuals

We will conclude this part of our chapter by briefly evaluating the overall approach of studying pharmacological effects on eye movements in healthy individuals. There are both limitations and benefits to this approach.

A major benefit is that the influence of confounds often present in studies with clinical samples are diminished. These confounds may include illness chronicity, co-morbid conditions, polypharmacy, and prior treatment exposure, all of which can obscure any effect of the drug or dose that is under investigation. Specifically, increasing efforts are now placed on including potential biomarkers of clinical endpoints earlier in the drug evaluation process. This can be complicated if patients are included, given heterogeneity with respect to disease severity and chronicity, and concomitant or prior treatment. However, most studies with healthy individuals are limited by use of acute rather than chronic treatment and the obvious absence of disease characteristics, which may be necessary when trying to evaluate efficacy (Table 18.3).

18.5 Findings from Pharmacological Effects on Eye Movements in Patient Groups

There are several reasons why there is utility in studying effects of clinical pharmacological treatments on eye movements in psychiatric and neurologic patient groups. First, eye movement tasks are relatively easy to perform, require relatively minimal engagement or cooperation from participants, and can be completed in patient groups across a range of ages and levels of clinical acuity. Second, the neurotransmitter systems and neural circuitry regulating eye movements are well characterized (Kobayashi & Isa, 2002; Leigh & Zee, 2006). Third, the increasing appreciation for cognitive deficits as underlying poor functional outcomes for patients, and how

Table 18.3 Summary of pharmacological effects on eye movements in healthy individuals (Reilly et al., 2008)

Pharmacological groups and agents	Presumed neurotransmitter system(s) influenced	Effects on saccades	Effects on pursuit
<i>Sedatives</i>			
Benzodiazepines	GABA agonist	Dose-dependent decrease in prosaccade peak velocity (Ball et al., 1991; Bittencourt et al., 1981)	Dose-dependent decrease in SPEM Velocity (Green et al., 2000; Bittencourt et al., 1983)
Diazepam		Decrease in prosaccade peak acceleration/deceleration (Ball et al., 1991)	Decrease in SPEM velocity (Pardoan et al., 1992)
Lorazepam		Increase in prosaccade latency (Masson et al., 2000); increase in antisaccade latency and error rate (Green & King, 1998)	Increase in SPEM latency and reduced SPEM gain (Masson et al., 2000)
<i>Antipsychotics</i>			
First Generation	DA antagonist	Dose-dependent decrease in prosaccade peak velocity (Lynch et al., 1997; King et al., 1995)	
Chlorpromazine		No effect on pro latency except at highest doses (Green & King, 1998); higher antisaccade error rate (Barrett et al., 2004)	
Haloperidol		Increase in antisaccade error (Barrett, 2004)	
Second Generation	DA antagonist	Decrease in prosaccade peak velocity (Barrett et al., 2004)	
Risperidone	5-HT antagonist	Increase in antisaccade error rate (Barrett et al., 2004)	

(continued)

Table 18.3 (continued)

Pharmacological groups and agents	Presumed neurotransmitter system(s) influenced	Effects on saccades	Effects on pursuit
<i>Antidepressants</i>			
Selective Serotonin Reuptake Inhibitors	5-HT agonist	No change in peak prosaccade velocity (Morrens et al., 2007)	Increase in SPEM velocity and gain (Friedman, Jesberger, & Meltzer, 1994; Gijnsman et al., 2002)
<i>Stimulants</i>			
Dextroamphetamine		Decrease in antisaccade error rate (Allman et al., 2010)	
Methylphenidate	NE and DA reuptake inhibitor	Decrease in prosaccade latency, increase in prosaccade peak velocity (Allman et al., 2012)	Increase SPEM gain and decrease in saccades during tracking (Allman et al., 2012)
Nicotine	ACh agonist	Possible decrease in antisaccade latency and increase in error rate (Rycroft et al., 2006)	Increase in SPEM velocity to faster targets (Domino et al., 1997)
<i>Anticonvulsants/mood stabilizers</i>			
Carbamazepine	NE antagonist, DA and GABA agonist	Decrease in prosaccade peak velocity and increase in prosaccade duration (Noachtar et al., 1998)	
Gabapentin	Glutamate antagonist	Decrease in prosaccade peak velocity (Noachtar et al., 1998)	
Lamotrigine	Glutamate antagonist, possible weak 5-HT, DA, and NE antagonist	No reported effects on prosaccades (Cohen et al., 1985)	No reported effects on SPEM (Cohen et al., 1985; Peck, 1991)
Lithium	Modulation of glutamate, though mechanism still largely unknown		No reported effects on SPEM (Flechner et al., 1992)

(continued)

Table 18.3 (continued)

Pharmacological groups and agents	Presumed neurotransmitter system(s) influenced	Effects on saccades	Effects on pursuit
<i>Other</i>			
Ketamine	NMDA antagonist	Dose-dependent decrease in peak prosaccade velocity and increase in prosaccade latency (Radant et al., 1998)	Dose-dependent decrease in SPEM gain and increase in catch-up saccade frequency and amplitude (Radant et al., 1998)

these deficits are impacted by existing treatments from a neural systems basis. Lastly, drugs targeting cognitive deficits in patient groups are, in the near term, likely to be adjunctive to existing treatments thereby increasing the importance for understanding the effect of such treatments on cognitive systems. In this section we provide exemplary discussions of three clinical disorders and how their corresponding medications impact eye movements.

18.5.1 Effects of Antipsychotic Medications in Schizophrenia

The effects of pharmacological treatments on eye movements in patients with schizophrenia are well documented. Schizophrenia is a chronic psychiatric illness that is characterized by positive and negative symptoms. Positive symptoms include hallucinations, delusions, and thought disorder, while negative symptoms include anhedonia, alogia, avolition and asociality (Tamminga, Buchanan & Gold, 1998). Cognitive deficits are also a characteristic of individuals with schizophrenia that appears independent of positive symptoms and are more closely related to negative symptoms. These cognitive deficits include attention, working memory, episodic memory and executive functioning, which is a set of cognitive processes that underlie reasoning, planning, problem solving, and mental flexibility. The general consensus is that schizophrenia is a complex disorder with a multifactorial etiology with multiple genes of small effect interacting with environmental insults leading to the development of the disorder (Siever & Davis, 2004).

In terms of the pathophysiology underlying schizophrenia, much research has supported the hypothesis that increased levels of striatal dopamine are related to positive symptomatology, and that such symptoms are reduced by antipsychotic medications through blockade of dopamine D2 receptors. Reduced function of the NMDA receptor leading to reductions in glutamate also likely plays a role and may further contribute to symptoms as well as associated cognitive deficits. This notion is also supported by studies that have shown that drugs such ketamine or phencyclidine,

both of which are NMDA receptor antagonists, can induce the positive and cognitive symptoms characteristic of schizophrenia (as discussed above).

18.5.1.1 Effects of Antipsychotic Medications on Saccadic Eye Movements in Schizophrenia

Straube, Riedel, Eggert, and Muller (1999) and Muller, Riedel, Eggert, and Straube (1999) evaluated the effects of antipsychotic medications on eye movement performance in a group of first-episode schizophrenia patients who were either antipsychotic-naïve at the time of testing or had been antipsychotic free for at least four weeks prior to testing, as well as after antipsychotic treatment among a subset of these patients. Subjects completed gap and overlap visually guided saccade and antisaccade tasks and two different memory guided saccade tasks - one that involved memory of a single target location and another that involved memory for an ordered sequence of three target locations. Eye movement performance was compared between groups of medicated and unmedicated patients and healthy controls. First or second generation antipsychotic treatment resulted in a reduction in peak saccade velocity; this effect was larger for internally guided saccades (i.e. antisaccade and memory guided saccade) than for externally triggered saccades (i.e. visually guided saccade). There were no differences in saccadic velocity between the unmedicated patients and controls. Only mild and nonsignificant reductions in antisaccade latency and memory-guided saccade gain were observed in the medicated group compared to unmedicated group. Lastly, there were no significant treatment effects on antisaccade error rate, which is consistent with findings from studies with first-episode schizophrenia patients (Ettinger & Kumari, 2003; Harris, Reilly, Keshavan, & Sweeney, 2006; Hutton et al., 1998; Reilly et al., 2008).

Burke & Reveley (2002) examined prosaccade and antisaccade performance in schizophrenia patients in a within subject cross-over design that involved switching from a first-generation antipsychotic to the second-generation antipsychotic risperidone, or vice versa. A reduction in antisaccade error rate was observed in patients who switched from a first-generation antipsychotic to risperidone, while patients who switched from risperidone to a first-generation drug had increased antisaccade error rate. Thus, risperidone treatment was associated with improved antisaccade performance in this study.

Another study, which used a randomized treatment design, compared the effects of two second-generation antipsychotic medications, risperidone and olanzapine, on visually guided saccade, antisaccade and memory guided saccade tasks in first-episode patients with schizophrenia and healthy controls (Broerse, Crawford, & Den Boer, 2002). Compared to controls, patients made more errors on the antisaccade task, inhibition errors on the memory guided saccade task, and had reduced amplitudes of memory guided saccades; these effects were comparable between the two medication groups.

Several longitudinal (i.e., within group) studies of first-episode patients have examined antipsychotic treatment effects on saccadic eye movements over time after

treatment initiation. A sample of antipsychotic naïve patients were evaluated before and after 6 weeks of treatment of the first-generation antipsychotic haloperidol or second-generation antipsychotic risperidone in comparison to healthy individuals followed over a similar time period (Harris, Wiseman, Reilly, Keshavan, & Sweeney, 2009; Harris et al., 2006; Reilly, Harris, Keshavan, & Sweeney, 2005; Reilly, Harris, Keshavan, & Sweeney, 2006). Prior to treatment initiation, patients demonstrated significantly faster visually guided saccade latencies compared to healthy controls. After 6 weeks of treatment with risperidone this atypical speeded response latency was not present among those taking risperidone but persisted among those taking haloperidol (Reilly et al., 2005). In addition, risperidone treatment was associated with a reduction in peak velocity, a modest decrease in prosaccade gain (Reilly et al., 2005), and a reduction in antisaccade latency (Harris et al., 2006).

Another study examined antipsychotic-naïve patients with schizophrenia performing an oculomotor delayed response (or memory guided saccade) task. Prior to treatment and early in the course of the illness, schizophrenia patients demonstrated an impairment in maintaining spatial location information in working memory (i.e. reduced memory guided saccade gain) at only the longest delay period duration (8 s) compared to controls (Reilly et al., 2006). After 6 weeks of risperidone treatment and clinical improvement, these deficits significantly worsened, such that patients demonstrated impaired gain across all delay period durations. Similar findings of reduced predictive saccade gain were also observed in these first-episode patients after treatment with risperidone (Harris et al., 2009), suggesting that accuracy of saccades made according to internal representation may be particularly susceptible to antipsychotic treatment effects.

18.5.1.2 Effects of Antipsychotic Medications on Smooth Pursuit in Schizophrenia

Several studies have also evaluated antipsychotic treatment effects in schizophrenia patients performing smooth pursuit tasks. Specifically, untreated patients have demonstrated comparable impairment in reduced smooth pursuit gain and more frequent catch up saccades to patients who were treated with first-generation antipsychotics (Ettinger & Kumari, 2003; Gooding, Iacono, & Beiser, 1994; Reilly et al., 2008; Sweeney et al., 1999; Thaker et al., 1999). For example, Campion and colleagues (1992) assessed smooth pursuit eye movement in healthy controls, and in drug-naïve, chronic, and residual schizophrenia patients. Smooth pursuit gain was reduced across schizophrenia groups, and groups did not differ from each other. Taken together, these findings suggest that pursuit eye movements may not be impacted by first-generation antipsychotic treatment, but that smooth pursuit impairments may be related to extent of illness chronicity or may represent a trait marker of schizophrenia.

In another study examining smooth pursuit performance in schizophrenia, Hutton and colleagues (2001) conducted a study comparing smooth pursuit performance in groups of first-episode and chronic patients schizophrenia, as well as healthy controls. First-episode schizophrenia patients with less than 12 weeks of cumulative lifetime

antipsychotic exposure and first-episode patients who were untreated at the time of testing, were compared on a smooth pursuit task to chronic schizophrenia patients who were either medicated with first-generation antipsychotics or were antipsychotic free for at least 6 months before testing. Chronic schizophrenic patients demonstrated significantly reduced velocity gain, longer latency to change in target direction, and increased catch-up saccades than first-episode patients and controls. There were no differences between antipsychotic-naïve and treated first-episode patients. Antipsychotic-free chronic patients demonstrated less impairment in velocity gain than matched treated chronic patients. These findings suggest that impairment in pursuit performance may be worsened by chronic antipsychotic treatment.

The effects of second-generation antipsychotics on pursuit performance in schizophrenia patients is less known, although some studies have observed worsening pursuit performance in clozapine treated patients (Friedman, Jesberger, & Meltzer, 1992). To evaluate antipsychotic medication treatment effects on pursuit performance more directly, Lencer et al. (2008) evaluated smooth pursuit performance among antipsychotic naïve first-episode patients before and after 6 weeks of treatment with either risperidone or olanzapine and compared performance to controls studied in parallel. Before treatment latency of pursuit was shortened, pursuit gain was impaired (under conditions when tracking less predictable ramp targets requiring a relative high degree of sensorimotor processing), and catch-up saccade frequency was increased (when tracking predictable targets) compared to controls. After 6 weeks of treatment, pursuit gain decreased further to less predictable ramp targets while predictable pursuit performance did not change, suggesting that there may be a selective effect on second-generation antipsychotic treatment on tasks that require a greater extent of sensorimotor processing.

18.5.1.3 Pharmacogenetic Effects of Antipsychotics on Eye Movement in Schizophrenia

As discussed above (see Sect. 18.3.1), pharmacogenetic studies evaluate how genetic variation influences the response to a particular medication or class of medication. Recently, pharmacogenetic studies have demonstrated that the influence of antipsychotic medications on oculomotor measures in schizophrenia patients may be influenced by particular polymorphisms, indicating that genetic variation underlies much of the heterogeneity of treatment related response often observed in groups of patients. While studies have demonstrated an adverse response to risperidone on the accuracy of memory guided saccades after approximately 6 weeks of treatment (Reilly, Harris, Khine, Keshavan, & Sweeney, 2007, Reilly et al., 2006), considerable variability was observed in the extent and magnitude of this adverse effect across patients. In a subsequent study including some of these patients, Bishop et al. (2015) evaluated whether polymorphisms of the Type-3 metabotropic glutamate receptor gene (*GRM3*) and selected variants in candidate dopamine genes were associated with antipsychotic induced changes in memory guided saccade performance. The worsening of memory guided saccade accuracy observed after antipsychotic treat-

ment was associated with variation in *GRM3* polymorphisms, such that those patients with the rs1468412_TT genotype exhibited a substantial worsening saccade accuracy compared to those with the rs1468412_AA genotype. While variants in candidate dopamine genes were associated with memory guided saccade performance, they were not associated with changes in performance following antipsychotic treatment. These findings suggest variation related to altered glutamate signaling exhibit increased sensitivity to the adverse effects of D2 antagonism from antipsychotic drugs on working memory.

In another pharmacogenetic study, Lencer et al. (2014) examined whether polymorphisms of two candidate genes, the dopamine receptor D2 gene (*DRD2*) and *GRM3*, were associated any antipsychotic medication related changes after approximately 6 weeks of treatment in first-episode schizophrenia patients. Variants of the -141C Del/Ins polymorphism in *DRD2* contributed to differences in the extent of slowed initial velocity gain during pursuit in patients, such that deletion carriers had significantly slower velocity gain compared to CC insertion carriers. While no effect of treatment on genotype differences was observed on initial velocity gain, treatment resulted in an increase in pursuit latency to a greater extent in CC insertion carriers compared to -141C deletion carriers. With regard to *GRM3* there was a significant association of rs274622 with maintenance velocity gain, such that rs_274622_CC carriers had poorer sustained pursuit maintenance than T-carriers. There was no differential treatment effect on sustained pursuit performance between genotypes.

18.5.1.4 General Comments Regarding Antipsychotic Medication Effects on Eye Movements in Schizophrenia

In sum, both first- and second- generation antipsychotic medications result in a reduction in peak saccade velocity and decreased saccade gain. Decreased gain is more apparent for internally driven saccades (i.e. memory-guided), than for externally driven (i.e. visually guided), suggesting that this effect may disproportionately affect accuracy of eye movements based on internal representations versus those driven by visual input. Additionally, antipsychotic treatment may result in lengthening of atypically shortened prosaccade latencies observed in untreated psychosis, suggesting some improvement in the regulation of visual attention. Generally, antisaccade error rate remains elevated in comparison to healthy controls despite antipsychotic treatment. Deficits on smooth pursuit tasks persist despite treatment and may be worse in chronically treated patients, suggesting potential cumulative adverse medication effects on pursuit systems (Reilly et al., 2008). Finally, more recent studies have suggested that pharmacogenomic effects may account for some of the observed changes in saccade and pursuit performance among patients after starting antipsychotic medication treatment, and that genetic variation may account for heterogeneity of treatment response in patient groups.

18.5.2 Effects of Stimulants in Attention Deficit Hyperactivity Disorder (ADHD)

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by symptoms of inattentiveness and hyperactivity/impulsivity. Inattentive symptoms include difficulty maintaining focus, becoming easily distracted, and difficulties with organization. Hyperactive/impulsive symptoms include excessive talking, fidgeting, impatience, and interrupting others. If these symptoms are present in several different settings (i.e. work, school, etc.), are present before the age of 12, and interfere significantly with quality of daily functioning, an ADHD diagnosis may be likely. Under current diagnostic nomenclatures (DSM-V, American Psychiatric Association, 2013), subtypes of ADHD include a predominantly inattentive type, predominantly hyperactive type, and a combined type with features of both inattention and hyperactivity. The pathology of ADHD may be due to deficits in the frontal-striatal pathway, the neural pathway underlying executive functions that links the frontal lobe to the basal ganglia. Stimulants such as methylphenidate are an effective treatment for ADHD, as these medications increase the amount of dopamine and norepinephrine available at the synapse, which in turn modulates neural circuits including the frontal lobe and basal ganglia (Reilly et al., 2008).

Klein, Fischer, Fischer, and Hartnegg (2002) studied prosaccade and antisaccade performance in patients (ages 10–15 years) on or off methylphenidate in two separate eye movement sessions. In order to limit any confound of practice effects, pediatric patients were randomized to a different testing order, either on-off medication or off-on medication. Subjects completed a prosaccade overlap condition and antisaccade gap condition. Methylphenidate resulted in faster latencies on both the prosaccade and antisaccade tasks, reduced antisaccade error rate, and improved error corrections. Collectively, these findings suggested that under treatment with methylphenidate, individuals with ADHD demonstrate a greater control of the voluntary attention systems.

These findings of improved voluntary attentional control were supported by another study that examined the effects of methylphenidate on executive control and response inhibition in children with ADHD compared to controls (O'Driscoll et al., 2005). In addition to prosaccade, antisaccade and predictive saccade tasks, this study also used a task switching paradigm which required subjects to perform either a prosaccade or antisaccade depending on the color of the central fixation. Children with ADHD, inattentive and combined types, were compared to controls under a baseline condition, and were then evaluated in a double blind crossover trial of a single dose of methylphenidate or placebo, with the order of drug administration counterbalanced. When compared to placebo, methylphenidate administration resulted in decreased prosaccade and antisaccade latency, as well as a decrease in antisaccade error rate comparably in both subtypes, and did not impact performance on task switching. These findings suggest that improved executive control is evident during methylphenidate treatment for either clinical subtype.

In a study assessing smooth pursuit performance in individuals with ADHD, 20 children with ADHD were compared to 20 age-matched healthy controls on a smooth pursuit eye movement task (Bylsma & Pivik, 1989). Individuals with ADHD were assessed both on and off medication. Smooth pursuit performance was characterized by velocity arrests, or periods where pursuit velocity reached below 2 degrees per second, and root mean square errors, or eye position error relative to target error. Greater velocity arrest scores were observed in unmedicated children with ADHD compared to healthy controls; however, there were no differences in smooth pursuit error. Furthermore, there were no changes in smooth pursuit performance when comparing patients evaluated on or off methylphenidate.

18.5.3 Effects of Dopamine Agonists in Parkinson's Disease

Parkinson's disease (PD) is a progressive, neurodegenerative disorder of the central nervous system. PD is characterized by motor abnormalities including difficulty initiating or continuing (eye) movements, problems with balance and walking, and tremors (see chapter by Müri et al. in this volume). Symptoms of PD are caused by dopaminergic disruption in the basal ganglia, which plays a central role in (oculo)motor control. The pathology of PD is attributed abnormalities in the nigrostriatal pathway, a dopaminergic pathway that connects the substantia nigra to the striatum. Specifically, levels of dopamine in individuals with PD are greatly reduced. The basal ganglia also has connections to regions responsible for executive control and cognitive processing, and therefore individuals with PD may develop a range of cognitive difficulties, including executive impairment and memory loss, as well as oculomotor abnormalities (Hood et al., 2007). Levodopa (L-Dopa) is pharmacological treatment for Parkinson's disease that is considered a pre-cursor to dopamine. Once it crosses the blood brain barrier it is converted to dopamine by dopamine-decarboxylase, thereby increasing concentrations of dopamine in the brain.

Prior studies examining pharmacological effects on eye movements in PD have been somewhat mixed. A study conducted by Hood and colleagues (2007) examined the effects of levodopa on individuals with PD. Patients with PD completed eye movement testing both on and off their optimal dose of levodopa, and were also compared to a healthy control group. All subjects completed a prosaccade and antisaccade task, with a gap overlap manipulation. Patients had significantly higher error rate on the antisaccade task (both on/off levodopa) when compared to healthy controls. However, when on levodopa, patients demonstrated had fewer antisaccade errors when compared to their off-levodopa baseline. Patients had slower prosaccade latencies when under on versus off conditions, findings that have been reported by others (Michell et al., 2006). Thus, levodopa may improve voluntary cognitive control, and may slow reflexive responses. Improvements in prosaccade accuracy, which are hypometric in PD, have also been reported in patients on levodopa (Gibson, Pimlott, & Kennard, 1987; Rascol et al., 1989), although not consistently (Nakamura et al., 1991).

Several studies have shown that patients with PD demonstrate reduced maintenance gain on smooth pursuit tasks (Bares et al., 2003; Waterston, Barnes, Grealy, & Collins, 1996). In a study of untreated patients with PD, clinical improvement with dopaminergic treatment was associated with an improvement in smooth pursuit gain (Gibson et al., 1987), suggesting that oculomotor changes in PD may be related to dopamine levels in the basal ganglia. However, in a study completed by Sharpe, Fletcher, Lang, & Zackon (1987), smooth pursuit gain did not improve after Levodopa. Specifically, patients with PD completed a smooth pursuit task during predictable off-periods and during on-periods, with no apparent change in performance.

18.6 Conclusions

There is increasing evidence that eye movements are sensitive biomarkers of drug effects on discrete sensorimotor and cognitive processes both for examining side effects in early phase studies with healthy individuals as well as in studies of potential cognitive enhancers or therapeutics in clinical settings.

In many examples reviewed above, eye movement paradigms have shown greater sensitivity to pharmacological effects than neuropsychological measures or subjective ratings, with strong dose–response effects that potentially could be used to individualize drug dosing for patients.

In addition, use of eye movements in studies involving pharmacogenetics and genetics remains highly promising and may lead to improved understanding of heterogeneity in drug response as well as in drug selection. With the need for biomarkers to support the development of new drugs and assess their efficacy, eye movement studies offer particular methodological benefits including the translational linkages to discrete neurotransmitter and neural systems, the rational manner to evaluate pharmacological effects for proof of concept/target engagement, and for understanding individual differences in drug response.

Despite these advantages, challenges for the practical implementation of eye movement biomarkers remain such as variability in laboratory set-up and paradigm characteristics, the degree of technical sophistication to data collection and analysis (which may limit transportability), and the challenge of substantiating the linkage of eye movement measurements, and drug effects upon them, to functional outcomes in patients.

18.7 Suggested Readings

Ansari A, Osser DN (2015). *Psychopharmacology: A Concise Overview for Students and Clinicians* (2nd Edition). CreateSpace Independent Publishing Platform. North Charleston, South Carolina, USA

– *An overview of the most important pharmacological therapies currently used in psychiatry.*

de Visser SJ, van der Post JP, de Waal PP, Cornet F, Cohen AF, van Gerven JM (2003). Biomarkers for the effects of benzodiazepines in healthy volunteers. *Br J Clin Pharmacol* 55(1):39–50.

– *A review underscoring the role of saccadic tasks in the assessment of sedative effects.*

Golan DE, Armstrong EJ, Armstrong AW (2017) *Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy*, 4th Edition. Wolters Kluwer Health. Philadelphia, PA, USA.

– *A comprehensive textbook of the principles of pharmacology.*

Reilly JL, Lencer R, Bishop JR, Keedy S, Sweeney JA (2008). Pharmacological treatment effects on eye movement control. *Brain Cogn* 68(3):415–35.

– *A comprehensive review of drug effects on eye movements.*

Thaker GK (2007). Schizophrenia endophenotypes as treatment targets. *Expert Opin Ther Targets* 11(9):1189–206.

– *A review of the overlap between oculomotor endophenotypes and biomarkers and their application to pharmacological studies.*

18.8 Questions Students Should Be Able to Answer

- (i) Define the terms pharmacokinetics and pharmacodynamics
- (ii) What are the advantages and disadvantages of a repeated-measures design in pharmacological studies?
- (iii) What are the most consistent effects of benzodiazepines on eye movements in healthy individuals?
- (iv) What are the advantages and disadvantages of studying pharmacological influences on eye movements in healthy individuals?
- (v) What is the pattern of effects of antipsychotics on eye movements in patients with schizophrenia?
- (vi) What are some of the challenges or limitations of studying pharmacological effects on eye movements in clinical populations?

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