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Pharmacological treatment effects on eye movement control

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Abstract

The increasing use of eye movement paradigms to assess the functional integrity of brain systems involved in sensorimotor and cognitive processing in clinical disorders requires greater attention to effects of pharmacological treatments on these systems. This is needed to better differentiate disease and medication effects in clinical samples, to learn about neurochemical systems relevant for identified disturbances, and to facilitate identification of oculomotor biomarkers of pharmacological effects. In this review, studies of pharmacologic treatment effects on eye movements in healthy individuals are summarized and the sensitivity of eye movements to a variety of pharmacological manipulations is established. Primary findings from these studies of healthy individuals involving mainly acute effects indicate that: (i) the most consistent finding across several classes of drugs, including benzodiazepines, first- and second-generation antipsychotics, anticholinergic agents, and anticonvulsant/mood stabilizing medications is a decrease in saccade and smooth pursuit velocity (or increase in saccades during pursuit); (ii) these oculomotor effects largely reflect the general sedating effects of these medications on central nervous system functioning and are often dose-dependent; (iii) in many cases changes in oculomotor functioning are more sensitive indicators of pharmacological effects than other measures; and (iv) other agents, including the antidepressant class of serotonergic reuptake inhibitors, direct serotonergic agonists, and stimulants including amphetamine and nicotine, do not appear to adversely impact oculomotor functions in healthy individuals and may well enhance aspects of saccade and pursuit performance. Pharmacological treatment effects on eye movements across several clinical disorders including schizophrenia, affective disorders, attention deficit hyperactivity disorder, Parkinson's disease, and Huntington's disease are also reviewed. While greater recognition and investigation into pharmacological treatment effects in these disorders is needed, both beneficial and adverse drug effects are identified. This raises the important caveat for oculomotor studies of neuropsychiatric disorders that performance differences from healthy individuals cannot be attributed to illness effects alone. In final sections of this review, studies are presented that illustrate the utility of eye movements for use as potential biomarkers in pharmacodynamic and pharmacogenetic studies. While more systematic studies are needed, we conclude that eye movement measurements hold significant promise as tools to investigate treatment effects on cognitive and sensorimotor processes in clinical populations and that their use may be helpful in speeding the drug development pathway for drugs targeting specific neural systems and in individualizing pharmacological treatments.

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Keywords

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1. Introduction

Methodological approaches such as functional magnetic resonance imaging (fMRI) (see glossary), positron emission tomography (PET) (see glossary) and high density electro-encephalography (EEG) (see glossary) have contributed to increased knowledge about disturbances in functional brain systems in psychiatric and neurologic disorders. Paralleling these advances, investigators are increasingly using eye movement paradigms to probe distributed cortical and subcortical systems involved in sensorimotor and cognitive processes and to gain insight into whether such systems are intact or disturbed in clinical populations (Leigh & Kennard, 2004; Sweeney, Levy, & Harris, 2002). With greater use of oculomotor tasks to understand functional disturbances of brain systems in clinical disorders, attention to pharmacological treatment effects on these brain systems is important for several reasons. First, it is important to differentiate disease and drug treatment effects when eye movement testing is used for pathophysiology research with patient populations or as intermediate phenotypes in family genetic research. Second, this work is important for broadening the understanding of neurochemistry supporting sensorimotor and cognitive processes assessed by eye movement paradigms. This is essential for continued refinement of sorely needed sensitive and specific translational neurobehavioral indices of pharmacological effects to guide drug development and evaluate treatment effects in order to individualize patient care.

Use of eye movement measurements to evaluate pharmacological effects on functional brain systems is advantageous for several of the same reasons why these paradigms are important tools for understanding dysfunction in clinical disorders. First, the neurophysiologic and neurochemical basis to oculomotor control in the nonhuman primate brain has been well characterized from single unit recording studies (Bruce & Goldberg, 1985; Hikosaka & Wurtz, 1989; Munoz & Wurtz, 1993). Second, functional imaging studies with healthy humans have established that there are homologous regions involved in oculomotor control in the nonhuman primate and human brain (O'Driscoll et al., 1995; Rosano et al., 2002; Sweeney et al., 1996) (see Lencer & Trillenberg; 2008; Ilg & Thier, 2008; McDowell, Dyckman, Austin, & Clementz, 2008; Johnston & Everling, 2008). Third, work in behavioral pharmacology has clarified the effects of certain drugs on specific brain regions that are important for subserving discrete aspects of eye movement control. Perhaps the clearest example of this is in the work of Goldman-Rakic and colleagues demonstrating the dopaminergic modulation of spatial working memory (see glossary) using the oculomotor delayed response task (Arnsten & Goldman-Rakic, 1998; Sawaguchi & Goldman-Rakic, 1991; Sawaguchi & Goldman-Rakic, 1994). Fourth, oculomotor performance can be reliably measured and quantified (see Smyrnis, 2008) which is important for pre- and post-treatment comparisons. Fifth, eye movement tasks are relatively easy to perform and place overt few cognitive demands on subjects, which is of importance when studying psychiatric and neurologic disorders across the age span and over a wide range of illness severity. Sixth, different parameters within paradigms can be systematically manipulated to differentiate reasons underlying performance deficits, such as deficits due to sensory guided vs. internally generated processes. And finally, oculomotor paradigms may be used to examine dose dependent effects (i.e., how eye movement parameters may change across a range of medication doses) in certain clinical samples or after an acute or chronic pharmacologic intervention. Drawing from the experience with animal models of drug effects on eye

movement activity in different task conditions, predictions and interpretations of drug effects in both healthy and clinically affected individuals can be made. This line of work has the potential to develop eye movement measurements as translationally based biomarkers for monitoring drug effects on oculomotor outcomes that have been linked to specific functional brain systems. Thus, eye movement tasks provide an important translational bridge between behavioral pharmacology research in animal models and clinical investigations.

In this paper, the effects of CNS-active drugs on saccadic and smooth pursuit eye movements are reviewed to provide a broad overview of current knowledge about drug effects on eye movements. Summaries of relevant neural systems, and of disorder and age-span effects, are provided by other papers in this special issue. Studies of pharmacological effects with healthy individuals, the majority of which evaluated acute effects of drug administration to characterize the degree and/or time course of sedative or other effects, are reviewed. Next, investigations of pharmacological treatment effects using eye movement paradigms in clinical populations including schizophrenia, bipolar disorder, attention deficit hyperactivity disorder, Parkinson's disease, and Huntington's disease are considered, with an emphasis on those studies that compared patients on or off certain treatments or when comparisons between treatments were made. In the latter half of this review, we present studies that highlight the potential of using eye movement paradigms to guide drug discovery and how eye movement measurements can be useful as biomarkers for understanding pharmacodynamic effects and their modification by genetic factors. With the development of new treatments for preserving and enhancing cognition in many disorders such objective specific bio-markers of drug effect are urgently needed.

2. Pharmacologic effects on eye movements in healthy individuals

Historically, phase 1 pharmacological studies have been concerned with tolerability and pharmacokinetics in healthy individuals, with less attention at this stage given to efficacy. Increasing efforts are now placed on including potential biomarkers of clinical endpoints earlier in the drug evaluation process than in phase 2 studies, in part to provide early proof of concept support for continued development of a particular drug. This can be complicated if patients are included, given heterogeneity with respect to disease severity and chronicity, and concomitant or prior treatment. Most studies with healthy individuals, however, are limited by use of acute rather than chronic treatment and the obvious absence of disease characteristics, alterations in which are needed to create the basis for efficacy. In the work reviewed below, the effects of several classes of CNS-active drugs on eye movements in healthy individuals are presented, the vast majority of which were conducted to determine tolerability. While there are yet few examples of a systematic evaluation of biomarkers for evaluating drug effects in healthy individuals, there is growing need for such methods given the pressure for earlier decisions in the drug development pathway, and for ways to directly bridge animal and human studies where similar biomarker outcomes can be used. Eye movements remain viable candidates for such efforts (de Visser, van der, Pieters, Cohen, & van Gerven, 2001; de Visser et al., 2003) and examples showing the potential of this approach are highlighted below.

2.1. Benzodiazepines and other sedatives

Benzodiazepines are among the most commonly prescribed pharmacological agents for the treatment of anxiety disorders. The anxiolytic effects of benzodiazepines are believed to be mediated through agonism of the GABA-benzodiazepine chloride receptor complex, specifically, $GABA_A$ α2 and $GABA_A$ α3 receptors. Use of eye movements as a measure of benzodiazepine effects on brain functions is particularly relevant because of the well established impact of GABA-ergic drugs on eye movements.

Studies with nonhuman primates have established that GABA-ergic projections from the caudate nucleus to the substantia nigra pars reticulata, and from the nigra to the superior colliculus (see glossary), play important roles in the generation of saccades (Hikosaka & Wurtz, 1983; Hikosaka & Wurtz, 1985; Schurr, Miller, Payne, & Rigor, 1999; Spencer, Wang, & Baker, 1992). Local injection of the GABA agonist muscimol into the superior colliculus decreases peak velocity and to a lesser extent amplitude and increases latency of saccades made to visual targets or to remembered locations in the absence of targets (Hikosaka & Wurtz, 1985). In contrast, the GABA antagonist bicuculline injected into the superior colliculus results in a facilitation of saccades (i.e., decreased latency) and deficits in fixating gaze due to increased spontaneous saccade activity. Consistent with this, findings of prolonged latency following muscimol injection and fixation deficits after bicuculline injection into the frontal eye fields (FEF) (see glossary) have been reported (Dias, Kiesau, & Segraves, 1995; Dias & Segraves, 1999). Deficits in smooth pursuit also have been reported following muscimol inactiviation within the smooth eye movement region of the primate FEF (Shi, Friedman, & Bruce, 1998).

Consistent with the findings from animal models, several studies with healthy humans have established that saccade peak velocity is slowed by benzodiazepines such as diazepam, lorazepam, midazolam, and tenazepam (Ball, Glue, Wilson, & Nutt, 1991; Glue, 2007; Rothenberg & Selkoe, 1981) as well as their metabolites (Mandema et al., 1992), presumably through their GABA-ergic agonism. This reduction of saccade velocity is dose-dependent and a consistent log linear relationship with serum concentrations has been demonstrated for several drugs within this class (Bittencourt, Wade, Smith, & Richens, 1981; Hommer et al., 1986; Roy-Byrne, Cowley, Radant, Hommer, & Greenblatt, 1993). In a recent review of potential bio-markers of the effects of benzodiazepines in healthy individuals, de Visser et al. (2003) reported that decreased saccade velocity was the most consistently reported effect, and one that has been shown to be far more sensitive to effects of benzodiazepines than visual analog scores (VAS) of alertness or neuropsychological measures of attention or psychomotor speed (Blom, Bartel, de Sommers, van der Meyden, & Becker, 1990; Casucci, Di Costanzo, Riva, Allocca, & Tedeschi, 1991; Salonen, Aaltonen, Aantaa, & Kanto, 1986). Despite the robustness of this effect, marked variability (as great as fourfold) in the magnitude of saccade peak velocity slowing after single administration of benzodiazepines has been reported (van Steveninck et al., 1992). Studies have established that peak saccade velocity is also a sensitive indicator of tolerance effects that emerge over chronic vs. acute exposure (Griffiths, Tedeschi, & Richens, 1986; Tedeschi, Griffiths, Smith, & Richens, 1985).

Less robust findings of benzodiazepines on other saccade parameters have been reported. In a study with healthy volunteers performing a prosaccade task (see glossary) using a baseline pre-infusion and saline infusion control conditions, intravenous administration of incremental doses of the benzodiazepine midazolam (6 and 12 λg/kg) resulted in a dose-dependent decrease in peak saccade velocity, peak acceleration and deceleration, and saccade error (hypometria, see glossary), although this latter effect was transient as a return to baseline values was reported within minutes after infusion which was far more rapid than the recovery time for other parameters (Ball et al., 1991). These performance decrements were reversed by administration of the benzodiazepine antagonist flumenazil, demonstrating the pharmacological specificity of midazolam's effects on saccade control. Saccade latency was unaffected by midazolam.

In a double-blind placebo-controlled design, the effects of the benzodiazepine diazepam and the 5-HT_{1A} partial agonist buspirone were investigated using a prosaccade task with a fixation point gap overlap manipulation (see glossary) (Fafrowicz et al., 1995). Both drugs are used to treat anxiety disorders, but buspirone which also has mixed agonist/antagonist

effects on postsynaptic dopamine receptors and no apparent GABA-ergic effects, is much less sedating. Gap overlap conditions refer to the introduction of a temporal gap between the offset of the fixation target and peripheral cue, or the persistence of the fixation target after the appearance of the peripheral cue, respectively. These manipulations result in a significant shortening of saccade latencies in gap trials due to a release of visual fixation, or the lengthening of latencies in overlap trials due to persistent fixation related activity after peripheral target appearance (see Hutton, 2008). In eight healthy volunteers 1 h after a single (5 mg) dose of diazepam, saccade latencies were significantly longer in both trial types, suggesting a general sedating effect of the drug on response times regardless of whether attention is engaged or disengaged from central fixation. A comparable dosage of buspirone did not affect saccade latencies of either trial type suggesting that the 5-HT_{1A} serotonergic agonist effects had little impact on saccadic reaction times. Consistent with this, neither acute nor chronic dosing of buspirone has been shown to affect peak saccade velocity or latency, whereas these were both adversely effect by the benzodiaze-pine bromazepam (Schaffler & Klausnitzer, 1989).

Another placebo-controlled double-blind cross-over study examined the effect of the benzodiazepine lorazepam on prosaccades using a gap and overlap paradigm (Masson et al., 2000). Similar to the findings with diazepam, saccades of healthy individuals 2 h after a single 1 mg dose of lorazepam compared to placebo had significantly longer latencies, and this increase in reaction time was comparable in gap and overlap trials reflecting a generalized slowing effect. Saccade amplitude and peak velocity were also reduced after lorazepam administration. Thus, benzodiazepines, even at relatively low doses in healthy volunteers, result in a slowing of saccade latencies but do not appear to selectively influence the release or maintenance of visual fixation or the mechanisms underlying disengagement and reengagement of attention.

The effects of benzodiazepines on smooth pursuit in healthy subjects, most consistently decreased pursuit velocity, are similar to those from saccade tasks (Padoan, Korttila, Magnusson, Pyykko, & Schalen, 1992) and are consistent with effects reported in monkeys performing pursuit tasks after intramuscular injection (IM) benzodiazepine administration (Ando et al., 1983). The finding that smooth pursuit velocity was correlated to serum concentrations of benzodiazepines led to the conclusion that this is a sensitive, reliable, quantitative measure for benzodiazepine pharmacodynamics (Bittencourt, Wade, Smith, & Richens, 1983; Green, King, & Trimble, 2000; Jansen, Verbaten, & Slangen, 1988; Rothenberg & Selkoe, 1981; Roy-Byrne et al., 1993). Bittencourt et al. (1981) established a dose-dependent log-linear relationship effect of serum concentration of lorazepam and tenazepam on pursuit velocity. In a placebo-controlled double blind study in 14 volunteers, lorazepam significantly increased smooth pursuit latency, reduced pursuit gain (see glossary) and increased catch-up saccade activity to correct for reduced eye tracking velocity (Masson et al., 2000). More specifically, low doses of lorazepam ranging from 0.5 to 1 mg did not have an effect whereas 3 h after the application of 2 mg of lorazepam smooth pursuit velocity error was significantly increased in 20 healthy subjects as demonstrated by another study (Green et al., 2000). Benzodiazepine binding in the cerebellum (see glossary) that reduces neural output is believed to play a role in all of these drug effects (Rothenberg & Selkoe, 1981).

As summarized in Table 1, the most consistently reported finding for the effects of benzodiazepines on eye movements in healthy individuals is a dose dependent slowing of peak saccade and pursuit velocity. These findings are demonstrable after single doses and have been shown to be more sensitive markers of the sedative effects of these drugs compared to measures of psychomotor speed, attention, or self ratings of alertness. In addition, benzodiazepines have also been shown to increase latencies and decrease accuracy

of both saccade and pursuit eye movements, although these findings are less robust than those reported for velocity.

2.2. Antipsychotics

The clinical effectiveness of antipsychotic medications is believed to result, in part, from their ability to competitively block central dopamine receptors, particularly D_2 receptors, a property shared by all agents within this class. D2 antagonism by these agents appears to be necessary for the amelioration of psychotic symptoms. However, the extensive affinity to D2 receptors which these agents share to varying degrees is associated with the emergence of extrapyramidal side effects. In this review, first-generation (typical) antipsychotics refer to those agents developed in the 1950s and first used to treat symptoms of psychosis, often at doses that caused significant sedation and adverse extrapyramidal effects. Second-generation (atypical) antipsychotics, the first of which was clozapine marketed in 1990, have historically been differentiated from first-generation antipsychotics by lower rates of extrapyramidal effects resulting from these medications at therapeutic doses. While second generation antipsychotics have no single mechanism of action, they additionally block 5-HT receptors and their increased tolerability and efficacy over earlier medications may be due to their degree of 5-HT_2 to D_2 antagonism.

Investigations of antipsychotic medication effects on eye movements of healthy individuals have most frequently used saccadic eye movement tasks. The most consistent finding of acute dose administration has been decreased saccadic peak velocity. Studies have shown that a single 100 mg dose of the first-generation anti-psychotic chlorpromazine results in a comparable slowing of peak saccade velocity to that seen after single doses of the benzodiazepine lorazepam (Green, McElholm, & King, 1996). This is believed to reflect the general sedating effects of these medications, but the specific regional brain effects that account for this effect are not yet clear (de Visser et al., 2001; King, 1994).

In a randomized placebo controlled cross-over design, 15 healthy individuals performed eye movement tasks prior to and 2, 4, and 6 h after single doses of the benzodiazepine lorazepam (2.5 mg) or the first-generation antipsychotic haloperidol (2, 4, or 6 mg) (Lynch, King, Green, Byth, & Wilson-Davis, 1997). Haloperidol resulted in a dose-dependent decrease in peak saccade velocity on a prosaccade task which at 4 and 6 mg doses was comparable to the decline in saccade velocity after lorazepam administration. There was no effect of haloperidol on saccade latency at any dosage. There was no adverse effect of haloperidol on accuracy, velocity, or saccadic intrusions of smooth pursuit. These findings are consistent with other studies that demonstrated first-generation antipsychotics slowed peak saccade velocity and does not adversely impact smooth pursuit (Holzman, Levy, Uhlenhuth, Proctor, & Freedman, 1975; King et al., 1995). However, Malaspina and colleagues reported that low dose (2 mg) of haloperidol, alone or in combination with amphetamine (0.3 mg/kg), in healthy individuals, resulted in increased small saccadic intrusions during pursuit that was not apparent in amphetamine alone or placebo conditions (Malaspina et al., 1994). In monkeys repeatedly exposed to methyphenidate, apomorphine, and haloperidol pursuit was disrupted by all three agents; however, tolerance developed for all but the haloperidol treatment suggesting that the adverse effects of haloperidol on pursuit that result from persistent dopamine blockade are effects which tolerance mechanisms can not reduce over time (Ando, Johanson, & Schuster, 1986).

Fewer studies have examined antipsychotic effects on oculomotor paradigms assessing cognitive or attentional control. In one of the few studies to examine effects of antipsychotic medication on healthy individuals using an antisaccade task (see glossary), Green and King (1998) compared performance on visual fixation, prosaccade, and antisaccade tasks in volunteers 3 h after single doses of lorazepam (2 mg), chlorpromazine (50, 75, and 100 mg)

and placebo in a randomized cross-over design. Chlorpromazine administration resulted in a dose-dependent decrease in peak saccade velocity (for both antisaccades and prosaccades) similar to that observed with the single dose of lorazepam, but it did not impact antisaccade latency, error rates, or fixation. At only the highest dose did chlorpromazine slow prosaccade latency. In contrast, lorazepam increased both antisaccade errors and fixation errors (i.e., saccades to targets when fixation was supposed to be maintained at central fixation) (Green & King, 1998).

Relatively fewer studies exist on effects of second-generation antipsychotic medications on eye movements of healthy individuals. In a parallel group placebo controlled study, the effects of acute doses of the second-generation antipsychotic amisulpride (300 mg) and risperidone (3 mg) and the first-generation antipsychotic chlorpromazine (100 mg) were evaluated in healthy volunteers performing saccade tasks (Barrett, Bell, Watson, & King, 2004). Risperidone and chlorpromazine, but not amilsupride, slowed peak saccade velocity which may reflect the greater sedating properties sometimes associated with these medications. Risperidone and chlorpromazine also resulted in higher rates of errors on an antisaccade task, which in the case of risperidone was associated with drug-induced akathisia. No effects on either prosaccade or antisaccade latencies were reported for any antipsychotic in these studies of healthy volunteers.

The effects on saccadic eye movements of the second-generation antipsychotic olanzapine, the first-generation antipsychotic haloperidol, and the selective serotonin re-uptake inhibitor (SSRI) paroxetine were compared to placebo in a double blind cross-over design (Morrens et al., 2007). After acute administration of olanzapine (10 mg), peak saccade velocity was significantly reduced compared to placebo whereas saccade velocity was significantly increased with paroxetine (20 mg). There was no change from placebo after haloperidol administration (2.5 mg). It is possible that the slowing of saccade velocity after olanzapine administration relative to the lack of change from placebo or haloperidol might be attributed to olanzapine's greater affinity for histaminergic receptors with corresponding greater sedative effects.

Similar to the sedative effects reported for benzodiazepines, antipsychotic medications result in a slowing of peak saccade velocity although this has only been shown to be dose-dependent among first-generation antipsychotics (Table 1), and at higher doses this effect is comparable to the slowing observed with benzodiazepines. Unlike benzodiazepines, however, antipsychotic medications do not appear to adversely effect initiation of saccades in so far as latencies (prosaccade or antisaccade) appear to be unaffected by administration of either first- or second- generation anti-psychotics in healthy individuals. Antipsychotic effects on pursuit among healthy individuals has been limited to studies of first generation agents and these do not appear to adversely effect pursuit velocity; however evidence is mixed as to whether first-generation antipsychotics increase saccadic intrusions in healthy individuals during pursuit.

2.3. Antidepressants

The common mechanism underlying the efficacy of antidepressant medications is increased availability of catecholamines (norepinephrine and dopamine) and serotonin typically caused by blocking the reuptake of these neurotransmitters by the presynaptic transporter. While the effects of anxiolytic and to a certain extent, anti-psychotic, medications on eye movements in healthy individuals have been relatively well studied, fewer investigations have examined the effects of antidepressant medications on eye movements. Further, findings on the effects of serotonin reuptake inhibitors (SSRIs), now the most widely prescribed antidepressants, on eye movements among healthy individuals have been mixed.

In a study comparing the effects of the SSRI, sertraline, and lorazepam, Green et al. (2000) examined performance on fixation, prosaccade, antisaccade, and pursuit tasks in healthy young individuals in a balanced placebo cross-over design. Three hours after a single dose of sertraline (20 mg) there were no effects relative to placebo on maintenance of visual fixation, velocity, or latency of prosaccades or antisaccades, or antisaccade errors. In contrast lorazepam (0.5., 1.0, and 2.0 mg) adversely impacted these parameters in a dose-dependent manner (Green et al., 2000). As reported above, in the study by Morrens et al. (2007), an increase in the peak velocity of prosaccades was reported among healthy individuals after single administration of 20 mg paroxetine which was also consistent with the effects reported for the SSRI minaprine (Mercer et al., 2007).

In one of the few studies that examined the effects of maintenance treatment, rather than single dose effects, Wilson, Bailey, Alford, Weinstein, and Nutt (2002) examined the effects of 5 weeks of administration of the SSRI fluoxetine (20 mg/day) and the tricyclic antidepressant dothiepin (titrated up to 150 mg/day) to placebo in a randomized cross-over design with healthy individuals performing a prosaccade task. No drug effects were observed 10 days after initiation of drug treatment, however, after 5 weeks of fluoxetine treatment, peak prosaccade velocity, and saccade acceleration and deceleration velocity were greater than after either placebo or dothiepin. There were no drug effects on saccade error, latency, or peak acceleration (Wilson et al., 2002).

Consistent with the finding that enhancing serotonergic transmission with SSRIs may improve performance on eye movement tasks, studies with 5-HT agonists have reported improvement on both pursuit and saccade measures. Friedman, Jesberger, and Meltzer (1994) demonstrated that administration of MK-212 (6-chloro-2[1-piperazinyl]-pyrazine), a direct acting serotonergic agonist, resulted in an increase in pursuit gain and a reduction in catch-up saccade frequency for both slow and fast pursuit targets (Friedman et al., 1994). Administration of meta-chlorophenylpiperazine (mCPP), a 5-HT2_C receptor agonist commonly used as a challenge drug in MDMA research, or the 5-HT agonist dexfenfluramine, resulted in an increase of peak saccade velocity (Gijsman et al., 1998; Gijsman et al., 2002). Interestingly, fluoxetine has been shown to increase eye movements in REM sleep among depressed patients and patients with obsessive compulsive disorder relative to placebo suggesting that the disinhibited release of saccades results from potentiation of serotonergic neurons that inhibit brain-stem omnipause neurons which, in turn, inhibit saccadic eye movements (Armitage, Trivedi, & Rush, 1995; Schenck, Mahowald, Kim, O'Connor, & Hurwitz, 1992).

The effects of SSRIs or direct serotonergic agonists in healthy individuals indicate that increased levels of serotonin do not adversely impact pursuit or saccade performance to the same degree as anxiolytics and antipsychotics, and may well enhance these and pursuit eye movements (see Table 1). The mechanism underlying this effect is not entirely clear but may result from an alteration of the serotonergic modulation arising from the dorsal raphae nucleus to the burst and pause neurons in the brain-stem that are responsible for determining the speed of eye movements. Consistent with this possibility, are the findings from animal models that iontophoretic application of serotonin to the pause neurons markedly decreases their firing rate thereby disinhibiting burst neurons (Ashikawa, Furuya, & Yabe, 1991), and that lesions to the dorsal raphae nuclei slows peak saccade velocity due to a reduction in the inhibitory regulation of the pause cells (Kaneko & Fuchs, 1991).

2.4. Stimulants

Stimulants include a range of therapeutic agents and drugs of abuse that render their effects, both beneficial and adverse, through augmentation of synaptic action of several neurotransmitter systems principally norepinephrine and dopamine, and serotonin to a lesser

extent. Within restricted doses, there are several central nervous system enhancing effects of stimulants including mood elevation, increased alertness, increased psychomotor speed and reaction time, and reduced fatigue.

2.4.1. Amphetamines—Amphetamines are a structurally defined group of drugs that produce a variety of effects on the central nervous system through the release of norepinephrine and dopamine from presynaptic nerve terminals. In a study examining the effects of either oral or intravenous administration of dextroamphetamine (d-amphetamine) (15 mg) on prosaccades and smooth pursuit among healthy individuals, no effects of either administration were reported for pursuit and oral administration did not affect saccade performance (Tedeschi, Bittencourt, Smith, & Richens, 1983). Intravenous delivery of d-amphetamine, however, resulted in maintenance of pre-infusion saccade velocity and latency, parameters which declined over time under placebo conditions presumably due to fatigue effects (Tedeschi et al., 1983). In the study by Malaspina et al. (1994) mentioned above, no effects of an amphetamine challenge (.3 mg/kg) were reported for the quality of smooth pursuit compared to placebo. Among healthy individuals exposed to d-amphetamine (30 mg) over repeated testing sessions in a randomized placebo controlled cross-over design, there was no change reported in anti-saccade latency or error rates compared to placebo (Wonodi, Cassady, Adami, Avila, & Thaker, 2006). Thus, except perhaps under conditions likely to elicit fatigue, there do not appear to be adverse or enhancing effects of amphetamines on saccade or pursuit eye movements among healthy individuals.

2.4.2. Nicotine—Nicotine is a cholinergic agonist that binds to nicotinic acetylcholine receptors which are widely distributed throughout the central nervous system. The presence of these receptors on presynaptic nerve terminals of dopaminergic, cholinergic, and glutamatergic neurons facilitates the release of these neurotransmitters and potentiates their effects throughout the brain. Nicotine's beneficial effects on psychomotor speed, sustained attention, and other cognitive tasks requiring higher order cognitive control have been widely reported. Cholinergic inputs to brainstem oculomotor structures, namely the superior colliculi, influences motor outputs involved in saccade generation (Kobayashi & Isa, 2002). For example, firing of cells in the substantia nigra has been shown to dramatically increase in animals exposed to nicotine, thereby increasing inhibitory input to the fixation zone of the colliculus with effects likely to reduce gaze stabilization and shorten saccade latencies (Clarke, Hommer, Pert, & Skirboll, 1985). Express saccades (saccades with shortened latencies typically less than 80–100 ms; see Hutton, 2008, and glossary) have been facilitated in monkeys after injection of nicotine into the superior colliculus (Aizawa, Kobayashi, Yamamoto, & Isa, 1999).

In a study examining the effects of acute nicotine administration via chewing gum (4 mg dose), Larrison and colleagues examined the performance of prosaccade and antisaccade tasks among psychiatrically healthy smokers who had abstained from cigarette use 2 h prior to eye movement testing (Larrison, Briand, & Sereno, 2004). Relative to a placebo controlled condition, performance after nicotine exposure resulted in a significant reduction in antisaccade error rates as has been reported among healthy control groups of studies with psychiatric patients (Depatie et al., 2002; Powell, Dawkins, & Davis, 2002). Among a subgroup of those subjects tested repeatedly over a 3 week period, this reduction in antisaccade errors was accompanied by a slight (10 ms) but significant reduction in antisaccade latencies. No effects were observed among subjects on prosaccade latencies which is consistent with findings from other studies which also reported no nicotine effect on prosaccade accuracy or peak velocity (Depatie et al., 2002; Sherr et al., 2002).

Rycroft, Hutton, and Rusted (2006) examined the effect of nicotine, administered in the form of a single cigarette, on antisaccade performance among psychiatrically healthy

smokers evaluated over two consecutive test sessions. Similar to the findings of Larrison et al. (2004), nicotine exposure resulted in a decrease in antisaccade error rates and latencies, but this effect was present only among subjects who smoked during the first session (Rycroft et al., 2006). Thus, it is possible that the enhancing effects of nicotine are apparent when subjects are task naïve and performance is less optimal. That is, it appears that potential beneficial effects of nicotine are less apparent once practice effects have been achieved. More recently this group reported on the effects of nicotine (2 mg, delivered via nasal spray) and the non-amphetamine psychostimulant modafinil (200 mg capsule) on antisaccade performance in a double blind dummy-drug design (Rycroft et al., 2007). For both the nicotine and modafinil exposed individuals, a reduction in correct antisaccade latencies were reported over the 5 h study period although there were no differences from placebo in the rate of decline over time in antisaccade errors.

Smoking has been shown to induce transient effects on pursuit eye movements of healthy individuals characterized by reduced upward tracking velocity and an increase in saccadic square-wave jerks on both vertical and horizontal tracking eye movements, deficits that were related to tobacco-induced nystagmus (see glossary) (Sibony, Evinger, & Manning, 1988). In a study examining nicotine effects on pursuit performance, Domino, Ni, and Zhang (1997) studied healthy non-smokers and smokers before and after inhalation of a sham or verum cigarette. An increaseof smooth pursuit velocity when tracking a 15°/s velocity stimulus was reported for both smokers and non-smokers indicating an enhancement of pursuit tracking by nicotine exposure (Domino et al., 1997). This effect was not found at slower (6°/s) target speeds. More recent studies, however, have reported conflicting effects of nicotine exposure among healthy individuals on pursuit performance. Olincy, Ross, Young, Roath, and Freedman (1998a), Olincy, Ross, Young, Roath, and Freedman (1998b) reported that healthy smokers abstinent from cigarettes for several hours prior to testing failed to show any change in pursuit gain or leading saccades (i.e., saccades ahead of the target during pursuit) 10 and 20 min after smoking (Olincy et al., 1998a; Olincy et al., 1998b). Sherr et al. (2002) reported improvement in closed loop gain after healthy individuals were exposed to nicotine via nasal spray (1 mg), regardless of their smoking history. In contrast, Avila, Sherr, Hong, Myers, and Thaker (2003) reported no change among healthy non-smokers after nicotine nasal spray (1 mg), whereas healthy smokers demonstrated a reduction of leading saccades during pursuit following nicotine exposure (Avila et al., 2003).

It thus appears that nicotine may result in improved antisaccade performance among healthy individuals in so far as there is some evidence that antisaccade latencies and error rates are reduced after nicotine exposure. Prosaccades do not appear to be influenced by nicotine exposure. The magnitude of these potential drug-induced enhancements on antisaccade performance among healthy individuals may be influenced by methodological differences that contribute to variation in pre-exposure performance levels. They thus may be bound by floor effects because error rates may be otherwise too low in healthy individuals to be reduced by drug administration. Conflicting findings have also been reported for nicotine's effects on pursuit performance, with some evidence for enhancement of pursuit (increase in gain and decrease in leading saccades).

2.5. Other cholinergic drugs

Other cholinergic drugs have similarly been demonstrated to impact eye movements. For example, the anticholinesterase inhibitor pyridostigmine decreased visual smooth pursuit in nonhuman primates while not impacting manual tasks (Vercher, Dusticier, Ebihara, Nieoullon, & Gauthier, 1990). The acetylcholine receptor antagonist scopolamine has been demonstrated to impair stability of visual fixation, decrease saccade accuracy and increase latency, and robustly decrease peak saccade velocity in healthy individuals even at low

doses (Oliva, Bucci, & Fioravanti, 1993). And, atropine, another anticholinergic drug, impairs smooth pursuit performance at doses where changes in neuropsychological measures of attention were not detected (Penetar, Haegerstrom-Portnoy, & Jones, 1988).

2.6. Anticonvulsants and mood stabilizers

Anticonvulsant and mood stabilizing medications, such as lithium, are commonly used acute and prophylactic treatments for bipolar disorder. The anticonvulsant drug carbamazepine is a norepinephrine antagonist and dopaminergic and GABA-ergic agonist. It has been shown to adversely impact eye movements of healthy individuals in so far as a decrease in peak prosaccade velocity after acute administration has been reported for dosages used clinically (e.g., 400–600 mg) (Hoffmann et al., 1993; Noachtar, von Maydell, Fuhry, & Buttner, 1998; Peck, 1991; Tedeschi et al., 1989). Similar effects have been reported among clinical samples of partial epilepsy patients maintained at these doses (Hoffmann et al., 1993) and case reports of downbeat nystagmus oscillopsia have been reported among patients at toxic levels (Chrousos et al., 1987). Some studies have also reporting prolonged saccade latency and decreased saccade gain (Remler, Leigh, Osorio, & Tomsak, 1990; Tedeschi et al., 1989). A reduction in smooth pursuit gain has also been reported (Bittencourt, Gresty, & Richens, 1980; Hoffmann et al., 1993) although this effect has not been consistent (Holzman et al., 1975; Noachtar et al., 1998; Pieters et al., 2003; Tedeschi et al., 1989). In a comparison of the effect on smooth pursuit performance of carbamazepine vs. a newer structurally similar agent, oxcarbazepine, in a double blind cross-over design, carbamazepine reduced tracking velocity to a greater degree than oxcarbazepine (Zaccara et al., 1992).

In a double blind placebo controlled cross-over design investigating the effects of the newer anticonvulsant gabapentin (600 mg), a glutamatergic antagonist, were compared to carbamazepine (400 mg) in healthy individuals who performed a prosaccade and smooth pursuit tasks 2, 5, and 7 h after medication administration (Noachtar et al., 1998). Gabapentin and carbamazepine both resulted in reduced peak saccade velocity (and increased saccade duration), although the time course of these effects differed. Gabapentin's effects were present at 2 h with restoration at later time points whereas carbamazepine effect was delayed in onset and apparent at only 7 h.

Lamotrigine, which is a glutamatergic antagonist and 5-HT agonist, is another relatively newer antiepileptic drug being used as mood stabilizer in the treatment of affective disorders. In contrast to older antiepileptic drugs such as phenytoin and carbamazepine, no adverse effects on smooth pursuit tracking were seen in healthy individuals after lamotrigine administration (Cohen et al., 1985; Hamilton et al., 1993; Peck, 1991). No consistent effects of lithium have been reported on smooth pursuit performance among healthy individuals (Flechtner, Mackert, Thies, Frick, & Muller-Oerlinghausen, 1992).

2.7. Other: Ketamine

Ketamine and phencyclidine are noncompetitive *N*-methyl-$_D$-aspartate (NMDA) antagonists. Administration of these agents produces dissociative, cognitive, and perceptual abnormalities similar to those of schizophrenia (Krystal et al., 1994). Thus, these are potentially useful pharmacological models of NMDA receptor hypofunction as hypothesized in schizophrenia. Investigating prosaccade, antisaccade, and smooth pursuit eye movements under ketamine infusion in healthy subjects revealed a clear performance deficits including a dose-dependent decrease in saccade velocity, dose-independent increase in saccade latency, and dose-independent nystagmus during pursuit (Radant, Bowdle, Cowley, harasch, & Roy-Byrne, 1998). There was no reported effect of ketamine on antisaccade performance. In contrast, in animal models ketamine has been demonstrated to causes a failure in gaze

holding and increased antisaccade error rates and prolonged antisaccade latencies (Condy, Wattiez, Rivaud-Pechoux, & Gaymard, 2005; Godaux, Cheron, & Mettens, 1990). In other pursuit studies ketamine disrupted closed loop gain and open loop acceleration but not non visual pursuit provided by extraretinal mechanisms (Weiler, Thaker, Lahti, & Tamminga, 2000). Ketamine has also been shown to significantly increase the number of leading saccades, especially at lower target speeds, in healthy individuals, a pattern that was also observed in drug-free relatives of schizophrenia patients (Avila, Weiler, Lahti, Tamminga, & Thaker, 2002). The authors concluded that the generation of disruptive leading saccades is mediated by the frontal-thalamic cerebellar circuitry involving NMDA receptors in the cerebellum.

2.8. Summary of pharmacological effects on eye movements in healthy individuals

In consideration of the studies examining pharmacological effects on eye movements in healthy individuals and how these can inform our understanding of treatment effects in clinical samples, it is important to keep in mind that much of this work in healthy individuals was done to examine the effects of single doses with an emphasis on characterizing tolerability. As summarized in Table 1, the most consistent finding across several classes of drugs, including benzodiazepines, first- and second- generation antipsychotics, anticholinergic agents, and anticonvulsant/mood stabilizing drugs is a decrease in saccade velocity and reduction in smooth pursuit velocity (or increase in saccades during pursuit). These oculomotor effects largely reflect the general sedating effects of these medications on central nervous system functioning. In many cases changes in oculomotor functioning are more sensitive indicators of pharmacological effects than other measures including self-report measures of alertness and performance on neuropsychological tasks of attention and motor speed. Other agents, including antidepressants (SSRIs), direct serotonergic agonists, and stimulants including amphetamine and nicotine, do not appear to adversely impact oculomotor functions in healthy individuals and may well enhance saccade and pursuit performance.

3. Investigations of pharmacologic effects on eye movements in clinical disorders

Historically, it is generally surprising that there is such a limited tradition of using neurophysiologic markers to study drug effects in clinical disorders (Chang, Steiner, & Ketter, 2000; Spohn, Coyne, Lacoursiere, Mazur, & Hayes, 1985; Spohn, Lacoursiere, Thompson, & Coyne, 1977; Tecce & Cole, 1972) and eye movements are no exception to this. The majority of studies examining pharmacological treatment effects on eye movements in clinical disorders provide only indirect examination of drug effects since comparisons are typically made between groups of patients treated with different (and often heterogeneous) medications, or between patients on a particular medication vs. those who had been withdrawn or were untreated at the time and thus often in a different clinical state. Few studies follow patients longitudinally over time to examine changes in performance on eye movement tasks associated with treatment initiation and with few exceptions, treatment administration have not been randomized. Moreover, there are often methodological differences in eye movement paradigms that complicate comparison of different studies. However, as reviewed below, some consistent effects of clinical treatments in patients have emerged which underscore the importance of appreciating the contribution of pharmacologic effects to patients' impairments when administering eye movement tasks in clinical studies.

3.1. Schizophrenia

3.1.1. Effects of antipsychotics—Among studies of treatment effects in clinical disorders, effects of antipsychotics on eye movements of schizophrenia patients are perhaps

the most common. They illustrate the heterogeneity of study design and patient characteristics with respect to medication history and status at the time of testing. A selection of these studies are summarized in Table 2 and described below, with emphasis provided on findings that address effects of first- and second-generation antipsychotics on eye movement performance in schizophrenia patients.

Crawford, Haeger, Kennard, Reveley, and Henderson (1995) examined the effects of clinician selected first-generation antipsychotic medications on several saccadic eye movement tasks in chronically ill patients with schizophrenia and bipolar disorder. Patients in both diagnostic groups were either on antipsychotic medication or had not been on any antipsychotic medication for at least six months. Both patient groups taking antipsychotics demonstrated reduced gain on prosaccade, memory guided (see glossary), and predictive saccade (see glossary) tasks compared to those patients not on antipsychotic treatment. This difference was especially large on the predictive task. There were no interactions of diagnosis and medication status. No effects of medication or diagnosis were reported on saccade latencies and antisaccade error rates were not influenced by medication status (but were highest in schizophrenia patients) (Crawford et al., 1995).

Straube, Riedel, Eggert, and Muller (1999) and Muller, Riedel, Eggert, and Straube (1999) examined the effects of antipsychotic medications on saccadic eye movements in a group of predominantly first-episode schizophrenia patients who were either antipsychotic-naïve at the time of testing or had been antipsychotic free for at least 1 month. Antipsychotic treatment (which included both first- and second-generation agents) resulted in a decrease in peak saccade velocity for prosaccades but even more so for antisaccades and memory guided saccades. In contrast to these effects on peak velocity, mild and nonsignificant reductions in antisaccade latency and gain of memory guided saccades were reported for antipsychotic treated vs. untreated patients. No significant treatment effects on antisaccade error were found (Muller et al., 1999; Straube et al., 1999), consistent with the findings from studies with first-episode schizophrenia patients evaluated after treatment initiation (Harris, Reilly, Keshavan, & Sweeney, 2006; Hutton et al., 1998; see review by Ettinger and Kumari (2003)).

More recent studies have examined the effects of second-generation antipsychotics on saccadic eye movements. Burke and Reveley (2002) reported a reduction in antisaccade errors in a small sample of patients who switched from a first-generation antipsychotic to the second–generation drug risperidone. In turn, the switch from risperidone to a first-generation drug worsened antisaccade performance and these effects occurred independently from the degree of symptomatic change (Burke & Reveley, 2002). In the only published study using a randomized treatment design, Broerse, Crawford, and Den Boer (2002) compared the effects of risperidone and olanzapine on prosaccade, antisaccade and memory guided saccade tasks. While patients committed more antisaccade errors and had reduced amplitudes of memory guided saccades, the two medication groups did not differ across any saccade parameter (Broerse et al., 2002).

Longitudinal studies of antipsychotic-naïve first-episode patients followed over time after treatment initiation have begun to shed more light on antipsychotic treatment effects on oculomotor control. Prior to treatment, patients performing a prosaccade task demonstrated significantly faster latencies compared to healthy individuals and this abnormality was no longer present after 6 weeks of treatment in those patients receiving risperidone but not among those taking haloperidol (Reilly, Harris, Keshavan, & Sweeney, 2005). Risperidone treatment was associated with decreased peak velocity and a modest decrease in prosaccade gain (Reilly et al., 2005) and reduction in antisaccade latency (Harris et al., 2006). These effects observed with risperidone were not observed with haloperidol (Harris et al., 2006;

Sweeney et al., 1997). In another study of antipsychotic-naïve patients performing a memory guided saccade task with a variable delay period duration, schizophrenia patients prior to treatment demonstrated a delay dependent impairment with reduced gain of saccade to remembered locations at only the longest delay period duration compared to controls (Reilly, Harris, Keshavan, & Sweeney, 2006). After 6 weeks of risperidone treatment patients' pretreatment deficits significantly worsened, such that they demonstrated uniformly impaired gain across all delay period durations. This adverse effect was sustained throughout a 1 year follow-up period in these patients. The effect of greater impairment in the accuracy of memory guided saccades after antipsychotic treatment was replicated in a second longitudinal study of antipsychotic-naïve first episode schizophrenia patients (Reilly, Harris, Khine, Keshavan, & Sweeney, 2007), and is consistent with the effects suggested by earlier group comparisons of medicated and unmedicated patients (Muller et al., 1999; Straube et al., 1999). Moreover, worsened accuracy of memory guided saccades after antipsychotic treatment is consistent with pharmacologic studies of nonhuman primates performing similar oculomotor delayed response tasks (Castner, Williams, & Goldman-Rakic, 2000).

Comparisons of antipsychotic-naïve schizophrenia patients or treatment withdrawn patients to those who are treated with (mostly) first generation medications revealed similar pursuit impairments reflected in lower maintenance gain and more frequent catch-up saccades as contrasted to healthy subjects (Campion et al., 1992; Gooding, Iacono, & Beiser, 1994; Karson, 1979; Litman, Hommer, Radant, Clem, & Pickar, 1994; Spohn, Coyne, & Spray, 1988; Sweeney, Haas, Li, & Weiden, 1994; Sweeney et al., 1999; Thaker, Ross, Buchanan, Adami, & Medoff, 1999; see review by Ettinger & Kumari, 2003).

In longitudinal studies in which pursuit performance was monitored over time, there was no association with antipsychotic medication dose (Flechtner, Steinacher, Sauer, & Mackert, 2002; Levy, Lipton, Holzman, & Davis, 1983; Muir, St.Clair, Blackwood, Roxburgh, & Marshall, 1992; Saletu, Kufferle, Grunberger, & Anderer, 1986; Schlenker & Cohen, 1995; Sweeney et al., 1998). A study by Hutton et al. (1998) reported that smooth pursuit velocity gain in untreated but not in treated first episode schizophrenia patients was lower than in controls, implying that antipsychotic medication may normalize disturbed smooth pursuit performance in first-episode patients (Hutton et al., 1998). However, other studies have reported that patients treated with mostly first-generation antipsychotics performed worse than untreated patients giving rise to the hypothesis that antipsychotic medication may impair smooth pursuit (Bartfai, Levander, Nyback, Berggren, & Schalling, 1985; Bartfai, Levander, & Sedvall, 1983; Kufferle et al., 1990). Another study with nine schizophrenia patients showed that although qualitative smooth pursuit ratings remained unaltered during a 4 weeks follow-up period under first generation antipsychotic medication, the nature of catch-up saccade responses to pursuit gain disturbances changed significantly, with a 57% increase in small saccades and a 77% reduction in larger catch up saccades (Rea, Sweeney, Solomon, Walsh, & Frances, 1989).

The effects of second-generation antipsychotic medications on smooth pursuit performance have not been directly and systematically evaluated with the exception of clozapine, which has been shown to worsen smooth pursuit in schizophrenia. These effects have included reduced pursuit gain and increased catch-up saccade frequency and amplitude (Friedman, Jesberger, & Meltzer, 1991; Litman et al., 1994). This finding was attributed to the effect of clozapine not only on dopamine receptors but also on the serotonergic system. The strong sedative effects of clozapine are another potentially contributing factor (Flechtner et al., 2002; Friedman et al., 1991; Litman et al., 1994).

Hutton et al (2001) investigated whether smooth pursuit abnormalities in schizophrenia were comparable in samples of first-episode and chronic schizophrenia patients who differed in their lifetime antipsychotic treatment exposure and their antipsychotic treatment status at the time of testing. Sixty-seven first-episode schizophrenia patients with less than 12 weeks of cumulative lifetime antipsychotic exposure, 20 of whom were antipsychotic-naïve at the time of testing, were compared on a smooth pursuit task to 36 chronic schizophrenia patients of which 16 were antipsychotic free for at least 6 months preceding the time of testing. Approximately half of the treated first episode patients were on second-generation antipsychotics and the remaining first episode patients and all of the chronic patients were taking first-generation antipsychotics. The chronic schizophrenia patients demonstrated a greater impairment in pursuit velocity gain relative to the first episode patients, and the degree of this effect was mediated by the effects of long term antipsychotic treatment. Smooth pursuit velocity gain was significantly better in chronic patients who were presently withdrawn from antipsychotics for at least 6 months compared to those who had been continuously treated. Moreover, the chronic untreated patients did not differ from either first-episode antipsychotic treated patients and were impaired on a trend level from the antipsychotic-naïve first-episode patients. The performance impairments among the chronically treated patients were not explained by demographic factors or characteristics of illness severity (Hutton et al., 2001).

Despite methodological confounds including few studies following patients longitudinally after treatment initiation, underpowered post-hoc comparisons, and heterogeneous patient and treatment groups, some tentative conclusions regarding antipsychotic treatment effects on eye movements of schizophrenia patients can be drawn. First, both first- and second-generation antipsychotic medications reduce peak saccade velocity, similar to the effects reported from single dosing studies with healthy individuals, and tolerance to this effect does not appear to develop. Second, decreases in saccade gain (increased hypometria) are observed with antipsychotic treatment, and this is most pronounced for internally generated saccades (e.g., memory guided and predictive saccades) compared to those made to visual targets. Prosaccade latencies may be prolonged and antisaccade latencies reduced after antipsychotic treatment, and this finding appears to be most consistently reported after second-generation antipsychotic treatment. Antisaccade error rate does not appear to significantly change in patients after treatment and remains persistently elevated compared to healthy individuals. Patients' deficits on pursuit tasks persist despite treatment with first-generation antipsychotics and the observation that these deficits may be worse among chronically treated patients suggests possible cumulative adverse medication effects on pursuit systems. The limited studies examining second- generation medication effects suggest that these agents may more acutely worsen pursuit performance. Both saccade and pursuit studies indicate that there is a dissociation of improvement in clinical symptoms and change in eye movements (either beneficial or adverse) after antipsychotic treatment, and it is clear that more systematic investigations of these effects are needed.

3.2.2. Effects of nicotine and other cholinergic drugs—Abnormality of the nicotinic cholinergic system in schizophrenia may contribute to the underlying pathophysiology of the disorder and its associated cognitive deficits. This view is supported by evidence of disproportionately high rates of smoking in schizophrenia patients, findings of reduced nicotinic receptors in the brains of schizophrenia patients compared to healthy individuals (Freedman, Hall, Adler, & Leonard, 1995), nicotine's amelioration of sensory motor gating deficits commonly demonstrated in schizophrenia patients (Olincy et al., 1998a, 1998b) and animal studies that demonstrate sensory gating is modulated by nicotinic agonists (Stevens & Wear, 1997). Thus, drugs targeting the nicotinic cholinergic system may prove useful to treat some of the sensorimotor and cognitive deficits associated with schizophrenia (Levin & Rezvani, 2007).

In support of the notion that nicotinic modulation may be a promising target for novel agents, recent studies have documented improvement in antisaccade performance and smooth pursuit among schizophrenia patients after administration of nicotine. Larrison et al. (2004) demonstrated that nicotine (administered via chewing gum) decreased antisaccade error rates among antipsychotic treated schizophrenia patients who demonstrated the greatest deficits under placebo controlled conditions and that this effect was dose- dependent (i.e., present at 6 mg but not 4 mg dose)(Larrison-Faucher, Matorin, & Sereno, 2004). Klein and Andresen (1991) reported a reduction of large amplitude saccades among briefly abstinent schizophrenia patients who were then retested after smoking. In a study by Sherr et al. (2002), nicotine administration by nasal spray increased eye acceleration during smooth pursuit initiation and maintenance in both smoking and non-smoking schizophrenia patients whereas it had no effect on healthy controls (Sherr et al., 2002). Comparing the effects of smoking on smooth pursuit performance between 15 smoking schizophrenia patients and 15 smoking healthy controls revealed no effect on large anticipatory saccade frequency but a decrease of small amplitude leading saccade frequency in the patients after nicotine exposure and it has been suggested that leading saccades may be a measure of cholinergic inactivity and thus part of an alpha7 nicotinic receptor dysfunction assumed in schizophrenia (Olincy, Johnson, & Ross, 2003). This finding was later supported by another study demonstrating that nicotine administration reduced the number of leading saccades during a pursuit task in both smoking and non-smoking schizophrenia patients (Avila et al., 2003). The impact of alterations in the cholinergic system on smooth pursuit control was further investigated by administering procyclidine, an anticholinergic drug, to 13 schizophrenia patients in a double-blind placebo-controlled cross-over study (Ettinger et al., 2003). A mild non-significant worsening of smooth pursuit gain and increased frequency of intrusive anticipatory saccades under procyclidine treatment was reported, further supporting the role of the cholinergic system in the control of smooth pursuit.

In a recent fMRI study, the effect of nicotine on smooth pursuit was compared between 16 schizophrenia patients and 16 controls revealing reduced hippocampal activity in both groups with a larger effect in controls (Tanabe, Tregellas, Martin, & Freedman, 2006). Further a group by drug interaction was demonstrated for the anterior cingulate (see glossary) where activity was decreased by nicotine in controls but increased in patients, but no effects were shown for the core oculomotor or sensory regions such as the frontal eye fields or in area V5 (see glossary) that provides motion information to the pursuit system (Tanabe et al., 2006). These findings partly conflicted with results from the same group on nine schizophrenia patients in whom they had shown that nicotine compared to placebo was associated with increased activity in the anterior cingulate, area V5 and the precuneus on the one hand and decreased activity in the hippocampus and the parietal eye fields on the other hand (Tregellas, Tanabe, Martin, & Freedman, 2005). Tanabe et al. concluded that nicotine may improve smooth pursuit performance in schizophrenia via cholinergic stimulation of the hippocampus and the cingulate gyrus.

3.2.3. Effects of serotonergic drugs—In the only identified study of serotonergic effects on eye movements in schizophrenia patients, Chaudhry and colleagues examined the effects of the serotonergic 5-HT_{2C} antagonist cyproheptadine on antisaccade performance among a sample of chronic antipsychotic treated patients in a randomized double blind cross-over design (Chaudhry, Soni, Hellewell, & Deakin, 2002). Under cyproheptadine treatment patients' antisaccade error rates significantly improved relative to placebo condition (31% vs. 40% respectively). Interestingly, the degree of improvement on the antisaccade task observed in this sample after a 5-HT_2 antagonist is comparable to that observed by Burke & Revelely (2002) in their study of chronic patients who underwent a medication switch from a first-generation antipsychotic medication to risperidone, which similar to other second-generation medications, antagonizes 5-HT_{2C} receptors.

3.4. Affective disorders

The study by Crawford et al. (1995) reviewed above was the largest study to examine antipsychotic treatment effects on saccadic eye movements in patients with bipolar disorder. Comparable adverse effects of first-generation antipsychotic medications on saccade gain in prosaccade and predictive tasks were reported for antipsychotic treated bipolar disorder and schizophrenia patients. Several of the bipolar patients were also on antidepressant and mood stabilizer medications, so interpretation of this effect is complicated by the broader clinical treatment programs for the patients in the study. Katsanis, Kortenkamp, Iacono, and Grove (1997) examined antisaccade performance among patients with bipolar disorder, major depression, and schizophrenia who were on various combinations of medications including antispychotics, lithium, anticholinergics, antidepressants, and benzodiazepines. They examined the association between medication status (i.e., those patients who were or were not taking a particular agent) and antisaccade error rates and antisaccade latency and reported only an association for longer latencies with anticholinergic medications (Katsanis et al., 1997). Thus, as with other studies, and with appreciation of significant limitations associated with the post-hoc analyses used to examine drug effects, visually guided saccade performance was not adversely impacted by either antipsychotic or mood stabilizing medications among affectively disorder patients in these studies.

Although early studies using qualitative performance ratings of smooth pursuit suggested adverse effects of lithium treatment among bipolar disorder patients evidenced by lower gain and increased catch up saccades (Holzman, O'Brian, & Waternaux, 1991; Levy et al., 1985), studies using quantitative assessment techniques have not consistently supported this conclusion. In a study of first episode patients with major depression or bipolar disorder, those treated with lithium did not differ in their smooth pursuit performance from those who were not taking lithium (Gooding, Iacono, Katsanis, Beiser, & Grove, 1993). Re-evaluation of a subset of bipolar patients, who were initially lithium-naïve and were retested after 10 months of lithium treatment, did not reveal any change in pursuit performance. Consistent with this, other studies reported that predictive smooth pursuit performance was independent of lithium treatment among groups of chronic patients with bipolar disorder or major depression (Flechtner et al., 2002; Muir et al., 1992; Opgenoorth, Kral, & Wolf, 1986). Among a small group of remitted patients with bipolar disorder, who were off any mood stabilizing or antidepressant medication at the time of testing, no effects of acute amphetamine treatment compared to placebo conditions were observed on pursuit performance (Siever et al., 1987).

3.5. Attention deficit hyperactivity disorder

Stimulants such as methylphenidate are an efficacious clinical treatment for attention deficit/hyperactivity disorder (ADHD). These drugs increase the amount of dopamine and norepinephrine available at the synapse, which in turn modulates functioning of catecholamine-regulated neural circuits including the frontal lobe, basal ganglia (see glossary), and cerebellum. Faster latencies on either prosaccade or antisaccade tasks have been found comparing patients on or off of methylphenidate (Klein, Fischer, Fischer, & Hartnegg, 2002; O'Driscoll et al., 2005). In some studies of ADHD children evaluated on or off treatment improvement in antisaccade error rates while on methylphenidate have been reported (Klein, Fischer, Fischer, & Hartnegg, 2002; O'Driscoll et al., 2005). Although two studies reported no difference on and off medication, these studies did not clarify whether practice effects may have confounded the results (Aman, Roberts, & Pennington, 1998; Munoz, Hampton, Moore, & Goldring, 1999) and a group comparison of medicated and unmedicated ADHD children did not reveal any differences on antisaccade or memory guided saccades (Mostofsky, Lasker, Cutting, Denckla, & Zee, 2001). No change in smooth

pursuit was reported among patients evaluated on or off methylphenidate nor did these patients differ from healthy individuals under either time point (Bylsma & Pivik, 1989).

3.6. Parkinson's disease

Findings for dopaminergic treatment effects on eye movements in Parkinson's disease (PD) have been mixed. Recent studies report prolonged prosaccade latencies for PD patients in the on state of their clinical dopamine drug therapy relative to their off state (Hood et al., 2007; Michell et al., 2006). Improved prosaccade saccade accuracy (Gibson, Pimlott, & Kennard, 1987) and amplitude (Rascol et al., 1989) have been reported. On the other hand, a few studies report no effect of dopaminergic drugs on any prosaccade measures (Gibson et al., 1987; Nakamura et al., 1991). For antisaccade tasks, advanced PD patients had fewer errors while on vs. off levadopa in one study (Hood et al., 2007). L-Dopa (100 mg) administered to healthy individuals increases antisaccade errors but does not impact latencies of antisaccades or prosaccades (Duka & Lupp, 1997). Crevis, Versijpt, Hanse, & De Ridder (2000) found adding the D1 and D2 agonist pergolide to regimens already including levadopa did not change performance on an antisaccade task. Comparing measures of patients on and not on anticholinergic therapy showed higher error rates on antisaccade task in treated patients (Kitagawa, Fukushima, & Tashiro, 1994). On a saccade sequencing task, PD patients performed better when taking levadopa than when not (Benecke, Rothwell, Dick, Day, & Marsden, 1987; Vermersch et al., 1994). Consistent with these findings, monkeys treated with MPTP which results in depletion of striatal dopamine, demonstrate a significant decrease in spontaneous volitional saccades and hypometric saccades to visual targets and these effects can be temporarily alleviated with administration of L-dopa (Brooks, Fuchs, & Finocchio, 1986; Schultz et al., 1989).

Several studies demonstrate that patients with PD have impaired smooth pursuit performance mainly reflected by decreased maintenance gain (Bares et al., 2003; Gibson et al., 1987; Nakamura et al., 1991; Sharpe, Fletcher, Lang, & Zackon, 1987; Waterston, Barnes, Grealy, & Collins, 1996). In a study of 15 mildly affected untreated patients, clinical improvement with dopaminergic drugs was also associated with an improvement of smooth pursuit gain (Gibson et al., 1987). This was confirmed by a more recent study on L-dopa naïve patients whose impaired smooth pursuit performance improved after subcutaneous administration of apomorphine (Bares et al., 2003). However, others reported that only one out of 21 patients with Parkinson's disease who had pre-treatment impaired smooth pursuit showed a remarkable improvement under treatment with a dopaminergic drug (Nakamura et al., 1991) or that no major improvement at all could be attributed to administration of L-dopa (Waterston et al., 1996). Similarly, smooth pursuit gain was significantly reduced in PD patients during both L-dopa dose-related on and off phases (Sharpe et al., 1987).

3.7. Huntington's disease

Saccadic eye movement abnormalities have been reliably found among Huntington's disease (HD) patients. These findings support models of fronto-striatal disturbances in this patient population (Lasker & Zee, 1997). In a study by Rubin, King, Reinbold, and Shoulson (1993), a decline in prosaccade latency and velocity was reported among patients taking baclofen, a GABAb agonist, compared to those who were not (Rubin et al., 1993). Dursun, Burke, Andrews, Mlynik-Szmid, and Reveley (2000) measured the effect of the antipsychotics haloperidol and sulpride on antisaccades and found no difference in latency or error rate among patients taking either of these medications and those who were not taking an antipsychotic (Dursun et al., 2000). Some studies of treatments for Huntington's utilize a motor symptom severity rating instrument, the Unified Huntington's Disease Rating Scale (UHDRS), which includes six items qualitatively rating abnormalities of pursuit and saccadic eye movements. In a case study of a patient before and after high dose (30 mg)

olanzapine treatment, improvement was noted after 5 days (Bonelli, Niederwieser, Tribl, & Koltringer, 2002), although this patient's performance not very severely disturbed at baseline. Doses of subanesthetic NMDA antagonist ketamine have been given to HD patients to prevent neural degeneration from excitotoxicity, and at higher doses pursuit and saccade performance declined using the UHDRS (Murman et al., 1997).

4. Conclusions regarding pharmacological effects in clinical disorders

The preceding review of the pharmacological effects on eye movement control in healthy individuals and in clinical populations provides some evidence for both adverse and beneficial effects in healthy subject and in patient studies. Some general conclusions can be derived from these previous studies. First, while several promising findings support the sensitivity of eye movement measures to drug effects, study designs used in that work have generally been weak, and this is especially true in clinical studies. Treatments were rarely randomly assigned, dose effects were rarely examined in a controlled manner, and healthy subjects were often not followed in parallel to assess practice effects when patients were followed over time. Nonetheless, the data provide general support for the sensitivity of eye movement measures for evaluating drug effects across a range of targeted neurotransmitter systems and diseases. These findings are important because they suggest that eye movement measures may provide an informative biomarker for contrasting beneficial and adverse effects of different drugs and classes of drugs, for evaluating promising new treatments, for justifying plans to build translational bridges from animal to human models of drug effect monitoring, and potentially in dose ranging studies for new drugs and for individualizing care for specific patients.

The potential utility of eye movement measures for use as informative biomarkers of pharmacological treatment effects on sensorimotor and cognitive processes was illustrated in a recent study by Hill, Reilly, Harris, Khine, & Sweeney (2008) Using data from several of the longitudinal studies of antipsychotic treatment effects in University of Pittsburgh first-episode schizophrenia study reviewed above (Harris et al., 2006; Reilly et al., 2005; Reilly et al., 2006), treatment-related change in performance on prosaccade, antisaccade, and memory guided saccade tasks was directly compared to changes in performance on a neuropsychological battery in antipsychotic naïve-schizophrenia patients studied before and after 6 weeks of treatment with risperidone (Hill et al., 2008). Healthy individuals were also studied over a similar period. Several findings from this comparison of assessment strategies are of interest here. First, oculomotor tasks demonstrated greater test–retest reliability than neuropsychological measures (as evidenced by both higher intraclass correlations and Spearman rank order correlations) in both patients and healthy individuals. This stability of eye movement performance, even over periods of acute symptomatic change early in the course of treatment, is similar to reports of repeated measures in chronic samples (Flechtner et al., 2002; Gooding, Mohapatra, & Shea, 2004). The lower reliability among neuropsychological measures, particularly among healthy individuals, may result from the susceptibility of these measures to practice or carryover effects from one testing session to the next, which is an effect that may be smaller with oculomotor measures. Second, oculomotor measures were more sensitive to both beneficial and adverse treatment effects compared to neuropsychological measures. Moreover, the oculomotor changes after treatment observed in patients were consistent the findings from behavioral pharmacology and animal models of pharmacological treatments targeting specific receptors, which underscore their potential value as candidate biomarkers for neurocognitive changes associated with treatment in clinical studies (Hill et al., 2008).

A final general conclusion apparent from prior studies is that these findings raise an important caveat for oculomotor studies of psychiatric disorders. Often, findings from

patient studies using oculomotor measures are interpreted to reflect illness effects without sufficient regard for potential medication effects. Drug effects are very difficult to sort out in post hoc analyses when patients are on clinician-selected and heterogeneous drugs and doses. Post hoc analyses in these situations are often very underpowered for detecting drug effects, and sometimes are used to argue for an absence of drug effects in this context. Potential sedative effects on saccade and pursuit measures that can occur from many drug classes, and alterations of working memory systems that have rather narrow optimal ranges of catecholamine modulation, can have very robust effects on eye movement data. Both to better understand the potential confounding influence such drugs may exert, and to learn about the specific neurochemical modulation of sensorimotor and cognitive neural systems supporting different types of eye movement activity, much more behavioral pharmacology research is needed to understand drug effects on eye movement activity.

5. Role of eye movements in future pharmacological studies

One important line of research in this area involves the potential role that oculomotor measures may play in facilitating clinical pharmacological studies in coming years, including the potential to evaluate novel agents targeting specific cognitive systems. The ability to detect and quantify drug effects from subtle to profound levels with eye movement studies provides the potential to enhance the quality of pharmacodynamic investigations of psychotropic medications, including both acute and chronic effects of medications on functional brain systems. Additionally, an important but under-utilized application of eye movement studies is as biomarkers in pharmacogenetic investigations to add power in identify genetic contributions to treatment response heterogeneity.

6.1. Eye movements and pharmacokinetics and pharmacodynamics—As an example of pharmacokinetic and pharmacodynamic (see Text Box 1) application of eye movement studies, Kroboth et al (1998) investigated alprazolam-induced changes in saccadic eye movements and psychomotor function assessed with neuropsychological tasks including a digit symbol substitution task, a continuous performance task, and a manual tracking task (Kroboth et al., 1998). In a double-blind three way cross-over single dose study healthy individuals were administered alprazolam 1.5 mg immediate release and 3 mg sustained release tablet formulations on two occasions separated by a 7 day washout period. Healthy individuals were administered study medications with plasma alprazolam concentrations, psychomotor performance, and measures of the peak velocity, duration, and amplitudes of prosaccades assessed at identical increments across the 12 h study period after drug administration. Both drug formulations demonstrated a comparable time-dependent slowing of saccade velocity with more rapid recovery with the immediate release tablet formulation. However, when psychomotor performance and saccade duration to amplitude ratios were assessed for relationships with alprazolam plasma concentrations, equal concentrations of each drug formulation observed at different time points yielded disparate results. The assessment of saccade data in concert with serum concentrations illustrated a proteresis effect where the impairment of saccade velocity during the absorption phase was greater than when equal or greater concentrations were observed later in time. Moreover, saccade impairments were also slower to resolve than impairments on psychomotor assessments. The combination of pharmacokinetic and saccade pharmacodynamics in this study showed that alprazolam-induced saccade velocity impairment is both concentration and time-dependent, and that the saccade eye movements were more sensitive to pharmacologic effects mediated by the GABA-benzodiazepine receptor complex than psychomotor measures, providing further support for eye movements utility as a biomarkers for pharmacodynamic studies.

5.2. Acute vs. long-term effects of psychotropic medications

Eye movement paradigms also have potential to contribute to the understanding of acute vs. long-term effects of medications on sensorimotor and cognitive processes. This in turn provides important information on drug effects in the brain, and may have important implications for how patients are treated in the short and long-term settings. van Steveninck et al. (1997) studied benzodiazepine sensitivity in long-term (1–20 years) users of temazepam and lorazepam compared to short term exposure in a matched control group in an open, parallel, cross-sectional study with age and sex matched control subjects treated with 10–20 mg temazepam or 1–2.5 mg lorazepam. Plasma benzodiazepine concentrations along with visual analog scales of subjective alertness and attention, antero-posterior sway, and prosaccade velocity and latency were all assessed at intervals 50 min prior to drug treatment up to 8 h post-dose. The relationship between temazepam concentration and saccade measures did not differ between chronic users and single dose controls. Similarly, patients treated chronically with lorazepam did not differ from single dose controls at similar plasma concentrations. However, the area under the curve effect and slope concentration–effect plots following lorazepam administration were smaller for peak saccade velocity, saccade latency, and body sway in the chronic patients than in single dose controls. Subjective alertness and tension measures were not different in chronic and single dose control lorazepam patients, indicating the sensitivity of eye movement tasks to assessing differences in short term and chronic pharmacodynamic effects of benzodiazepines (van Steveninck et al., 1997).

5.3. Pharmacogenetic applications

Clinicians treating serious mental illness commonly see marked variability in response to different drugs within the same class, and thus far have little empirical data to guide choice of treatment or their dosing. Individual differences in genotype can have a powerful influence in determining not only drug metabolism, but the extent of beneficial and adverse effects caused by psychopharmacological therapies. While several studies have utilized eye movement measures as intermediate phenotypes in family genetic studies of schizophrenia, the potential of oculomotor studies to provide biomarkers that can be used to understand variance in treatment outcome that can be predicted with genotype information has only begun to be utilized.

Pharmacogenetics (see Text Box 2) in psychiatry has been slow to develop due to difficulties in the replication of genotype–phenotype relationships. These difficulties likely result from heterogeneities in study design and the phenotypes used as outcomes in these studies. Psychiatric pharmacogenetic researchers now recognize the benefit of using intermediate phenotypes of neurophysiological function as biomarkers for response that are more sensitive to genotype effects and also provide process- and brain region-specific outcomes that better approximate drug effects on the brain than clinical rating scales and neuropsychological assessments.

Studies have indicated that eye movements may provide an index of benzodiazepine sensitivity in both clinically affected individuals and healthy individuals who score high along certain personality dimensions (Cowley, Roy-Byrne, Greenblatt, & Hommer, 1992; Roy-Byrne, Cowley, Greenblatt, Shader, & Hommer, 1990) which may relate to underlying genotypic differences. To our knowledge, there has been only one published study using eye movements to investigate differential response to a pharmacologic agent as a function of genotype. Both smooth pursuit gain and peak saccade velocity have been shown to be less affected by diazepam in males at genetic risk for alcoholism, indicating that eye movements provide an index of individual differences in altered sensitivity of the central GABA-benzodiazepine receptor system (Cowley et al., 1994) as has been suggested previously. As

a follow-up genetic investigation of this finding, Iwata, Cowley, Radel, Roy-Byrne, and Goldman (1999) examined the effects of diazepam sensitivity as a function of an amino acid altering (Pro385Ser) variant (1236C > T) in the $GABA_A$a6 gene that was previously associated with alcohol sensitivity. In this investigation, 51 medically healthy offspring of alcoholic fathers complete prosaccade and smooth pursuit tasks prior to and after a continuous intravenous infusion of six incrementally increasing diazepam boluses over the course of 90 min (Iwata et al., 1999). Carriers of the Ser385 allele demonstrated less sensitivity to diazepam indicated by less change from baseline values in smooth pursuit gain. No genotype association was observed with peak saccade velocity. Iwata et al. (1999) reported that these findings were consistent with gene expression studies showing significant expression of $GABA_A\alpha6$ in the cerebellum which is involved with generation of smooth pursuit. Of relevance for this review, this study illustrates the potential for use of eye movements as intermediate phenotypes and bio-markers for drug response in pharmacogenetic studies.

A few studies that have identified genotype relationships with eye movement functioning in schizophrenia were published by Rybakowski and colleagues (2001, 2002, 2003) and while these were not pharmacogenetic investigations, they illustrate that genotypic differences may be readily observable by using eye movement outcomes that are themselves sensitive to pharmacological effects as reviewed above. In the first investigation, the relationship between visual fixation and smooth pursuit with the Ser9Gly polymorphism of the dopamine D3 receptor (*DRD3*) gene was examined in schizophrenia patients (Rybakowski, Borkowska, Czerski, & Hauser, 2001). The D3 receptors readily bind first- and second-generation antipsychotic drugs and the DRD3 gene is a candidate gene for sensitivity to tardive dyskinesia. Among patients who were homozygous for the Ser allele, fixation disturbance and abnormal pursuit performance (qualitative ratings) were substantially greatest, followed by those patients with the Ser-Gly and Gly-Gly genotypes. In another investigation (Rybakowski, Borkowska, Czerski, & Hauser, 2002), the relationship of visual fixation disturbance and smooth pursuit with the catechol-*o*-methyltransferase (*COMT*) Val158Met polymorphism in schizophrenia patients was examined. The 158Met allele results in a structural instability of the enzyme, reducing its capacity to metabolize dopamine in the prefrontal cortex, and has thus been investigated in cognitive studies of executive function, attention, and working memory. Among male but not female schizophrenia patients the MET allele was associated with better quality ratings of visual fixation and smooth pursuit. In a third investigation by this same research group (Rybakowski, Borkowska, Czerski, Dmitrzak-Weglarz, & Hauser, 2003), the relationship of the *BanI* polymorphism in the Phospholipase A_2 (*PLA2*) gene, which is involved in phospholipid metabolism, and visual fixation and smooth pursuit quality was evaluated in schizophrenia patients. The A2 genotype, which has been inconsistently associated with schizophrenia, was significantly associated with greater disturbance in fixation and smooth pursuit in both schizophrenia patients and controls, and there was a trend for the greater A2 allele frequency in schizophrenia patients with a higher degree of fixation and pursuit performance. While treatment data, including medication, dose, and length of exposure were not reported in these studies, it can be speculated that differential effects of genotype on these eye movement parameters may well be mediated by antipsychotic treatment either acutely or via chronic exposure.

6. General conclusions

Use of eye movement measurements has been advantageous to the understanding of neurophysiologic and neurochemical dysfunctions, and treatment effects, in a number of clinical disorders. Behavioral pharmacology studies with animal models and healthy humans exposed to various drugs indicate that oculomotor measures can provide a highly sensitive

pharmacodynamic index of drug effect on brain systems. As mentioned above and addressed more extensively by Smyrnis in press, oculomotor performance can be reliably measured and quantified which is important for pre- and post-treatment comparisons. Eye movement tasks place few overt cognitive demands on subjects which is important when studying psychiatric and neurologic disorders with a wide range of illness severity over the lifespan. Thus, eye movement paradigms provide an important translational bridge between behavioral pharmacology research in animal models, studies with healthy individuals and clinical investigations of treatment effects in patient groups.

It is clear that that more systematic consideration is needed in pathophysiological studies of pharmacologically treated patients with regard to potential effects of drug treatments on brain systems supporting oculomotor behaviors being investigated. While there are practical challenges to investigations of drug effects in clinical studies, such as the preference to study treatment-naïve patients before and after treatment initiation or patients who have undergone medication washout who are then re-tested after resumption of treatment, more attention needs to be paid to treatment-related effects when interpreting differences between clinically treated patients and healthy individuals. All too often it is assumed that differences between these groups are disease related when in fact most medications used to treat psychiatric and neurologic disorders have established effects on eye movement activity.

Evidence is accumulating that eye movements are sensitive biomarkers of drug effects on discrete sensorimotor and cognitive processes. Because they can provide a more direct measure of effects on brain systems of interest than are provided by behavioral ratings or neuropsychological testing, their role in advancing pharmacodynamic and pharmacogenetic studies is promising. Several examples already exist demonstrating the greater sensitivity of eye movements to pharmacological manipulations than neuropsychological measures or subjective ratings, with strong dose–response effects that potentially could be used to individualize drug dosing for patients. Use of eye movements in studies involving pharmacogenetics and genetics is highly promising in part because they are neurophysiological indices of brain functions directly targeted by drugs. The fact that eye movements represent a sensitive and robust measure of drug effect may allow for smaller sample sizes in proof of concept studies or studies designed to detect drug–genotype interactions compared to investigations using more common neuropsychological or phenomenological assessments of treatment effect. With the need for better measures to support the drug discovery process for agents to treat cognitive deficits in clinical disorders, eye movement measurements hold promise for speeding the development pathway for drugs targeting specific neural systems and the behaviors they support, and for individualizing pharmacological treatments.

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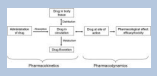
Text Box 1

Pharmacokinetics and Pharmacodynamics

- *Pharmacokinetics* and *pharmacodynamics* are two aspects of clinical pharmacology that collectively contribute to drug outcomes. *Pharmacokinetics* refers to the study of the time course and distribution of drug concentrations in the body. The classical parameters influencing the pharmacokinetics of a drug are absorption, distribution, metabolism, and elimination/excretion (often collectively abbreviated as A, D, M, and E). A primary factor affecting absorption is the bioavailability of a drug, which may refer to both the extent and/or rate at which an administered dose reaches circulation. The lipophilicity of a medication as well as the formulation (delayed vs. immediate release, etc.) are two common contributors to bioavailablility. One common measure of drug distribution is the volume of distribution (Vd). Vd relates to the amount of drug in the body relative to the concentration of drug in the blood. For example, drugs with high Vd have much higher concentrations in extravascular tissue than in the vascular areas, or compartments, of the body. Compartments where drugs are commonly distributed include: water in the body, blood/plasma, fat, and bone. Metabolism simply refers to the enzyme systems (if any) that are responsible for the transformation of parent drug to excretable metabolite(s). The cytochrome P-450 enzyme system is responsible for the metabolism of many psychotropic medications. The final aspect of pharmacokinetics is elimination/excretion. This refers to the removal of drug from the body, which largely occurs through the kidneys, liver, and lungs. One commonly referenced pharmacokinetic parameter, which is partially related to both the distribution and clearance of a drug is the half life ($t_{1/2}$), which refers to the time required for a drug to either reach 50% of its steady state, or decay to 50% of its steady state.
- *Pharmacodynamics* refers to the biological effect of a drug. Parameters characterizing the biological effects of a drug include: potency and affinity. Drug potency refers to the dependency of receptor activation on drug concentration and is commonly measured by the EC_{50}, or concentration at which the drug achieves 50% of a maximal effect. Affinity refers to the attraction between a drug and its receptor or binding site.



Text Box. 2
Pharmacogenetics

- Pharmacogenetics refers to the study of how genetic variability in an individual affects their response to a medication. Generally speaking, the term *pharmacogenetics* refers to the relationship between a single genetic variant, or a small number of selected variants in one gene, and a drug outcome. The term *pharmacogenomics* refers to the collective effects of genetic variants across the genome, or a large number of variants in many genes, on drug outcomes. Genetic variations such as single nucleotide polymorphisms (SNPs), repetitive sequences, deleted DNA sequences, inserted DNA sequences, or alterations in chromosome structure can all affect response to medications as well as disease risk. 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), drug metabolizing enzymes (e.g., cytochrome P-450 enzyme variants).

Table 1

Summary of pharmacological effects on eye movements in healthy individuals.

Pharmacologic groups and agents	Presumed neurotransmitter system(s) influenced	Effects on saccades	Effects on pursuit
Sedatives			
Benzodiazepines	GABA agonist	Dose-dependent decrease in pro peak velocity[3,6,18,22,26,33,47]	Dose-dependent decrease in SPEM velocity[6,7,21,27,46,47]
Bromazepam	($GABA_A$ α2 and $GABA_A$ α3 receptors)		
Diazepam		Decrease in pro peak acceleration/ deceleration[3]	Increase SPEM latency[34]
Lorazepam			Increase in SPEM error[2134]
Midazolam		Increase in pro latency[13,34,50]	Increase catch-up saccade frequency[34]
Tenazepam		Possible transient decrease in pro gain (hypometria)[3]	
		Increase in anti errors[20]	
Antipsychotics			
First generation	DA antagonist (D_2, D_3, & D_4 receptors)	Dose-dependent decrease in pro peak velocity[4,10,20,22,25,28,29,31]	Mixed evidenced for increase in saccadic intrusions[25,29]
Chlorpromazine		No effect on pro or anti latency except at highest doses[4,20,31]	
Haloperidol		Increase in anti errors[4]	
Second generation	DA antagonist (D_2, D_3, & D_4 receptors)	Decrease in pro peak velocity[4,36]	No identified studies
Risperidone	5-HT antagonist (particularly $5\text{-}HT_{2A}$, and also $5\text{-}HT_{2C}$)	No effect on pro or anti latencies[4]	
Olanzapine		Increase in anti error rates[4]	
Antidepressants			
Tricyclics dothiepin		No effect on pro velocity, latency, or error[55]	
Selective serotonin	5-HT agonist (via blockade of presynaptic reuptake transporter)	No change[21] or increase in peak pro velocity[35,36] including with maintenance dosing[55]	Direct serotonergic agonists (MK-212, mCPP, dexfenfluramine) increase SPEM velocity and gain, and decrease catch-up saccade frequency[15,16,17]
Reuptake inhibitors			
Sertraline			
Paroxetine		No impact on pro or anti latency[21,55]	
Minaprine			
Stimulants			
Amphetamine	NE and DA agonist	Possible attenuation of decreased pro velocity and latency associated with fatigue[52]	No reported effects on SPEM[32,52]

Pharmacologic groups and agents	Presumed neurotransmitter system(s) influenced	Effects on saccades	Effects on pursuit
Dextroamphetamine		No effect on anti latencies or error rates[56]	
Nicotine	ACh agonist, potentiates DA, ACh, GLU (due to presence of nicotinic Ach receptors on presynaptic nerve terminals)	No effect on pro latency[11,30,51]	Increased SPEM velocity to faster but not slower targets[12]
		Reduction in antisaccade latency[30,48,49]	Mixed evidence for any enhancement of SPEM gain or leading saccades[1,38,51]
		Reduction in anti error rates[11,30,43]	
Cholinergic agents			
Scopalomine	Ach antagonist	Impair stability of visual fixation	Decrease in SPEM tracking[41]
Atropine		Decrease pro velocity and gain, and increase latency[39]	
Anticonvulsants/mood stabilizers			
Carbamazepine	NE antagonist, DA and GABA agonist	Decrease in pro velocity[24,37,40,53]	Mixed evidence for reduction in SPEM gain[5,24,2,37,42,53]
Oxacarbemazepine		Increase in pro latency and decrease in gain[45,53]	Decrease in SPEM velocity[57]
Gabapentin	GLU antagonist	Decrease in pro velocity[37]	
'Lamotrigine	GLU antagonist, 5-HT agonist, GABA effects unclear	No identified studies	No reported effects[8,23,40]
Lithium	DA, 5-HT GABA, Ach agonist	No identified studies	No reported effects[14]
	NE antagonist		
Other			
Ketamine	NMDA antagonist	Dose-dependent decrease in pro velocity and dose-independent increase in latency[44]	Nystagmus induction during SPEM[44]
		No reported change on anti performance[44]	Decrease in closed loop gain and open loop SPEM acceleration[54]
		Increase in fixation instability, pro latency, and anti errors in nonhuman primates[9,19]	Increase in leading saccades[2]

5-HT, serotonin; ACh, acetylcholine; anti, antisaccade; DA, dopamine; GABA, aminobutyric acid; GLU, glutamate; NE, norepinephrine; pro, prosaccade; SPEM, smooth pursuit eye movement.

[1] Avila et al. (2003).

[2] Avila et al. (2002).

[3] Ball et al. (1991).

[4] Barrett et al. (2004).

[5] Bittencourt et al. (1980).

[6] Bittencourt et al. (1981).

[7] Bittencourt et al. (1983).

*8*Cohen et al. (1985).

*9*Condy et al. (2005).

*10*de Visser et al. (2001).

*11*Depatie et al. (2002).

*12*Domino et al. (1997).

*13*Fafrowicz et al. (1995).

*14*Flechtner et al. (1992).

*15*Friedman et al. (1994).

*16*Gijsman et al. (1998).

*17*Gijsman et al. (2002).

*18*Glue (2007).

*19*Godaux et al. (1990).

*20*Green et al. (1998).

*21*Green et al. (2000).

*22*Green et al. (1996).

*23*Hamilton et al. (1993).

*24*Hoffmann et al. (1993)

*25*Holzman et al. (1975).

*26*Hommer et al. (1986).

*27*Jansen et al. (1988).

*28*King (1994).

*29*King et al. (1995).

*30*Larrison-Faucher et al. (2004).

*31*Lynch et al. (1997).

*32*Malaspina et al. (1994).

*33*Mandema et al. (1992).

*34*Masson et al. (2000).

*35*Mercer et al. (2007).

*36*Morrens et al. (2007)

*37*Noachtar et al. (1998)

*38*Olincy et al. (1998a), Olincy et al. (1998b).

*39*Oliva et al. (1993).

*40*Peck (1991).

[41] Penetar et al. (1988).

[42] Pieters et al. (2003).

[43] Powell et al. (2002).

[44] Radant et al. (1998).

[45] Remler et al. (1990).

[46] Rothenberg et al. (1981).

[47] Roy-Byrne et al. (1993).

[48] Rycroft et al. (2007).

[49] Rycroft et al. (2006).

[50] Schaffler et al. (1989).

[51] Sherr et al. (2002).

[52] Tedeschi et al. (1983).

[53] Tedeschi et al. (1989).

[54] Weiler et al. (2000).

[55] Wilson et al. (2002).

[56] Wonodi et al. (2006).

[57] Zaccara et al. (1992)

Table 2

Summary of pharmacological effects on eye movements in schizophrenia samples.

Reference	Design	Reported treatment effects on eye movements
Saccade Studies		
Broerse et al. (2002)	Cross-sectional comparison of first episode patients randomized to risperidone (n = 12) or olanzapine (n = 21) and controls (n = 23)	Pro, anti, or mem parameters similar between medication groups Increased anti latency in risperidone treated patients vs. controls Increased inhibition errors and decreased accuracy on mem in olanzapine treated patients vs. controls
Burke and Reveley (2002)	Longitudinal cross-over comparison after switch from FGA (heterogeneous) to risperidone in chronic patients (n = 12) and controls (n = 12)	Decreased anti error rates in patients after risperidone vs. FGA treatment Comparable anti and pro latency under both treatment conditions
Crawford et al. (1995)	Cross-sectional comparison of FGA treated (heterogeneous) chronic patients (n = 40) to unmedicated[a] chronic patients (n = 18)	Increased error of pred and mem in FGA treated vs. unmedicated patients Comparable anti, pred, and mem latency, and inhibition errors on anti and mem
Harris et al. (2006)	Longitudinal comparison of antipsychotic-naive[b] first episode patients before and after haloperidol (n = 11) or risperidone (n = 23) treatment and controls (n = 41)	Comparable decrease in anti error rates for haloperidol and risperidone treated patients Decreased anti latency in risperidone but not haloperidol treated patients
Hommer et al. (1991)	Cross-sectional comparison of FGA fluphenazine and benztropine treated patients (n = 8) and unmedicated patients (n = 7) and controls (n = 11)	Increased pred error in treated vs. unmedicated patients Comparable pro latency between patient groups
Hutton et al. (2001)	Cross-sectional comparison of antipsychotic treated (heterogeneous) patients (n = 50) and antipsychotic-naive patients (n = 13) and controls (n = 40)	Comparable pro gain and latency in antipsychotic treated and naïve patients Comparable pred error in antipsychotic treated and naïve patients Increased in initial pred latency in naïve vs. treated patients
Hutton et al. (1998)	Cross-sectional comparison of antipsychotic treated (heterogeneous) (n = 19) and antipsychotic-naïve first episode patients (n = 17) and controls (n = 36)	Comparable pro latency and gain in treated and naïve patients Comparable increased anti error rate in treated and naïve patients Increased anti latency in naïve vs. treated patients
Katsanis et al. (1997)	Cross-sectional comparison of pharmacologically (heterogeneous) treated schizophrenia and affective disorder patients (n = 40) and unmedicated schizophrenia and affective disordered patients (n = 11)	Comparable anti latency and errors among patients taking antipsychotic, antidepressant, lithium, benzodiazepines, or anticholinergic medications
Mueller et al., 1999/ Straube et al. (1999)	Cross-sectional comparison of unmedicated (n = 30) and antipsychotic (heterogeneous) treated (n = 17) patients and controls (n = 12)	Decreased pro, anti and mem velocity in treated vs. unmedicated patients Other comparable pro, anti, and mem parameters were comparable among treated vs. unmedicated patients
Reilly et al. (2005)	Longitudinal comparison of antipsychotic-naive first episode patients before and after haloperidol (n = 13) or risperidone (n = 24) treatment and controls (n = 39)	Increased pro latency and decrease gain after risperidone but not haloperidol treatment Comparable decrease in pro velocity among risperidone and haloperidol treated patients
Reilly et al. (2006)	Longitudinal comparison of antipsychotic-naive first episode patients (n = 25) before and after risperidone treatment and controls (n = 25)	Increase in magnitude of pretreatment mem error after risperidone treatment
Reilly et al. (2007)	Longitudinal comparison of antipsychotic-naive first episode patients (n = 17) before and after SGA (heterogeneous) treatment and controls (n = 15)	Increase in magnitude of pretreatment mem error after SGA treatment
Sweeney et al. (1997)	Longitudinal comparison of antipsychotic-naive first episode patients before and after haloperidol (n = 10) or risperidone (n = 10) treatment and controls (n = 10)	Decreased pro velocity and gain and increased pro latency after risperidone but not haloperidol treatment
Pursuit Studies		

Reference	Design	Reported treatment effects on eye movements
Barfati et al. (1983)	Cross-sectional comparison of unmedicated patients with history of prior FGA antipsychotic treatment and antipsychotic-naïve patients	SPEM impairments (qualitative rating) were greater in patients with prior antipsychotic treatment vs. antipsychotic naïve patients
Barfati et al.(1985)	Cross-sectional comparison of currently medicated (heterogeneous) patients with (n = 17) and without (n = 9) history of antipsychotic treatment prior to study period	SPEM impairments (qualitative rating) were greater in patients with prior antipsychotic treatment vs. antipsychotic naïve patients
Campion et al. (1992)	Longitudinal comparison of chronic treated (n = 15), treated residual (n = 10) and antipsychotic naïve patients (n = 12) after treatment with antipsychotic (unspecified)	SPEM performance (gain, frequency of saccades) was comparable among antipsychotic-naïve patients and treated patients No change in performance (gain or frequency of saccades) in patients followed longitudinally, including patients previously naïve studied after 1 month of antipsychotic treatment
Friedman et al. (1994)	Longitudinal comparison of unmedicated patients before and after FGA (heterogeneous; (n = 6) or clozaril (n = 6) treatment and controls (n = 19; studied only once)	Increase in amplitude of saccades during after clozaril but not FGA treatment; no other reported changes in SPEM for either medication group Clozaril dose and treatment length associated with worsened pursuit (increased saccade amplitude and square-wave jerks, decreased pursuit) Longer treatment length with FGA was associated with decrease gain
Hutton et al. (1998)	Cross-sectional comparison of antipsychotic treated (heterogeneous) (n = 19) and antipsychotic-naïve first episode patients (n = 17) and controls (n = 36)	Worse performance (decrease gain) in antipsychotic naïve patients vs. controls only Patient groups did not differ in SPEM performance
Hutton et al. (2001)	Cross-sectional comparison of antipsychotic-naive (n = 20) and antipsychotic treated (n = 47) first episode patients, antipsychotic treated (n = 20) and previously treated unmedicated (n = 20) chronic patients, and controls (54)	SPEM gain did not differ between antipsychotic-naïve vs. antipsychotic treated patients whereas antipsychotic treated chronic patients were significantly more impaired vs. antipsychotic free chronic patients Other SPEM parameters (saccade frequency and amplitude) were not influenced by medication status in either first episode or chronic patients
Kufferle et al. (1990)	Longitudinal comparison of unmedicated patients with (n = 50) and without (n = 16) antipsychotic treatment before and following antipsychotic treatment (unspecified)	Greater SPEM impairment (signal to noise ratio) in patients with prior antipsychotic treatment vs. those without SPEM performance (signal to noise ration) was unchanged in both groups after acute administration of antipsychotics or after 4 weeks of maintained treatment
Levy et al. (1983)	Longitudinal comparison of unmedicated patients randomized to 4 weeks of treatment of high (n = 4) vs. low (n = 4) dose haloperidol	SPEM performance (qualitative rating) was unchanged over course of medication free and active treatment periods at either dose
Litman et al. (1994)	Longitudinal placebo-controlled cross-over from fluphenazine to clozapine (n = 16)	Clozapine worsened SPEM (decreased gain, increased frequency of saccades) compared to placebo condition, whereas there was no effect of fluphenazine
Spohn et al. (1988)	Longitudinal comparison of FGA (heterogeneous) treated patients before and after randomization to medication withdrawal (n = 64) or continued maintenance (n = 36)	Comparable SPEM impairments (signal to noise ratio and qualitative ratings) reported among patient groups over multiple repeated sessions, including during periods after medication withdrawal
Muir et al. (1992)	Cross-sectional comparison of unmedicated (n = 18) and FGA (unspecified) treated (n = 41) patients and controls (n = 145)	SPEM impairment (signal to noise ratio) comparable between unmediated and medicated patients
Rea et al. (1989)	Longitudinal comparison over 4 week course of FGA antipsychotic treatment (unspecified) (n = 9) and controls (n = 8)	SPEM performance (qualitative ratings) stable over course of treatment Increase in small amplitude saccade frequency and decrease in large amplitude saccade frequency observed, the latter of which was correlated with FGA dose
Saletu et al. (1986)	Longitudinal comparison of patients before and after randomized treatment with haloperidol (n = 10) or fluphenazine (n = 10)	SPEM impairment (signal to noise ratio) comparable in both treatment groups
Sweeney et al. (1994)	Cross-sectional comparison of antipsychotic-naive (19) and previously treated unmedicated patients (n = 22) and controls (n = 52), with longitudinal follow-up of naïve (n = 10) and unmedicated (n = 14) patients after FGA treatment (heterogeneous)	Comparable SPEM impairments (decreased gain, greater catch-up saccade frequency and amplitude, and frequency of square-wave jerks) in both patient groups prior to treatment

Reference	Design	Reported treatment effects on eye movements
		No changes in SPEM gain after treatment initiation in either patient group Decrease in frequency of anticipatory saccades after treatment for both groups
Sweeney et al. (1998)	Longitudinal comparison of antipsychotic-naive patients (n = 12) before and after haloperidol treatment and controls (n = 10)	SPEM impairments (delayed initiation and decreased gain) from pretreatment remained unchanged from baseline to post treatment across multiple follow-ups over a 2 year period
Sweeney et al. (1999)	Cross-sectional comparison of antipsychotic naive first epidose (n = 20) and unmedicated chronic (n = 12) patients and controls (n = 24)	Comparable decrease in SPEM gain among antipsychotic-naive and chronic unmedicated patients Initiation of SPEM was slowed among chronic unmediated but not antipsychotic-naïve patients
Thaker et al. (1999)	Cross-sectional comparison of chronic antipsychotic medicated (n = 21) or recent onset (n = 18, 8 of whom were antipsychotic medicated and 10 of whom were unmedicated) patients and controls (n = 25)	Comparable SPEM impairment (decreased closed loop gain and decreased predictive gain) among unmedicated and medicated patients (both chronic and recent onset)

Anti, antisaccade; FGA, first-generation antipsychotic; Mem, memory guided saccade; Pred, predictive saccade; Pro, prosaccade; SGA, second-generation antipsychotic; SPEM, smooth pursuit eye movement.

[a] Unmedicated refers to no medication treatment at time of study (see reference for length of medication free period).

[b] Naive refers to no prior exposure.