THE RELATIONSHIP BETWEEN TWO ENDOPHENOTYPES OF PSYCHOSIS IN VOLUNTEERS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER

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DEDICATION

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Background: Deficits in smooth pursuit eye movements are an established endophenotype for schizophrenia (SZ) and are being investigated as a potential biomarker for psychotic bipolar disorder (BDP). While the molecular determinant of the physiological deficit is still unclear, considerable research has shown deficits in the predictive mechanism of eye movements in SZ using target masking techniques, as well as with a more recent novel prediction eye movement task. The questions of whether this deficit is related to working memory alterations in SZ and extends to other psychotic disorders like BDP were a focus

of this investigation. Methods: Volunteers with schizophrenia (SZ, n = 38), bipolar I disorder with psychotic features (BDP, n = 31), and healthy controls (HC, n = 17) performed a novel eye movement task to assess the predictive mechanism of smooth pursuit. Subjects also completed a battery of neuropsychological tasks that included measures of working memory. Results: Individuals with SZ and BDP performed similarly on both neuropsychological and eye tracking tasks. Both groups evidenced reduced predictive pursuit velocity and worse performance on the Wechsler Spatial Span task compared with healthy controls. Further, a small but significant correlation ($r = .27$, $p = .03$) between predictive pursuit gain and working memory performance on Spatial Span was obtained, without statistically significant correlations in other cognitive domains. Conclusions: Individuals with SZ and BDP showed similar deficits on the predictive pursuit eye movement task, suggesting that this alteration could be a characteristic of the psychosis domain. The a priori prediction that the predictive pursuit task is associated with working memory mechanisms was supported in part by its significant and selective correlation with a measure of working memory.

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Avila MT, Hong LE, Moates A, Turano KA, Thaker GK. The Role of Anticipation in Schizophrenia Related Pursuit Initiation Deficits. J Neurophysiol. 2006 Feb; 95(2): 593-601.

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LIST OF DEFINITIONS

Endophenotype – a measure that is associated with a syndrome, heritable, state-independent, and co-segregates in families while being expressed in unaffected family members (Gottesman & Shields, 1973).

Smooth pursuit eye movement (SPEM) – continuous slow eye movement that smoothly rotates the eyes to compensate for motion of the object being followed with the eyes.

Saccadic eye movements (saccades) – discrete, fast eye movements that quickly direct the eye toward a target, moving the image of the target from a peripheral location to the fovea, a region of the central retina where visual acuity is greatest (Krauzlis & Stone, 1999).

Gain – during smooth pursuit of a moving target performance is conventionally evaluated by a measurement of eye velocity divided by target velocity, a ratio referred to as gain. During ideal smooth pursuit where the eye does not lag behind the target, gain would be close to 1.0; the more the eye lags behind the target, the lower the gain ratio will be.

Smooth pursuit initiation – The initial smooth pursuit response (1st 100 ms), which is mostly based on motion of the target image on retina, without the feedback information from the motor regions (hence referred to as open-loop response).

Velocity error – differences in speed between an object an its representation across the retina, which motivates the eye to generate smooth pursuit to keep the image of the object on the fovea and minimize error

Maintenance pursuit – Once the eye catches up with the target and moves at about the same speed, pursuit is maintained by predictive eye movements mostly based on the internal representation of the target motion (e.g., copy of the motor command, also called the efference copy), and minor corrections driven by visual input.

Extraretinal – motion information from internal sources (memory trace of previous motion) when no current retinal information is available (visible)

Predictive pursuit – eye behavior based on extraretinal information, using memory for the target's previous position and speed to guide eye behavior when no motion is available (traditionally measured by target blanking)

Novel predictive pursuit task – an alternative to traditional target blanking techniques, where the computer moves the target on the screen based on the subject's eye movement, thus stabilizing the target on the fovea without the subject's awareness. The target does not disappear from sight. During this task a target moves back and forth several times and the eye follows (ramps); when the target speed slows to a velocity of zero as it reaches one side of the screen and briefly stops to reverse direction, a predictive window is triggered to open. During this brief window (1 second in duration) the target is driven by the subject's eye movement without their awareness. During this window memory of the target's previous speed and position drives the eye and is perceived by the brain as movement, so that the target continues to move but is actually being driven by the eye. In other words, the target follows the movement of the eye, without the subject's awareness, and the subject continues to "pursue" the target although they are actually leading it (Hong et al., 2008). Because the brain is not aware that target motion has stopped and thus has not signaled the eye to stop, a more refined measure of eye behavior can be collected.

SECTION ONE

Journal-Ready Manuscript

Title: The Relationship Between Two Endophenotypes of Psychosis in Volunteers with Schizophrenia and Bipolar Disorder

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Abstract

Background: Deficits in smooth pursuit eye movements are an established endophenotype for schizophrenia (SZ) and are being investigated as a potential biomarker for bipolar I disorder with psychotic features (BDP). While the molecular determinant of the physiological deficit is still unclear, considerable research has shown deficits in the predictive mechanism in SZ using target masking techniques, as well as with a more recent novel prediction task. The questions of whether this deficit is related to working memory alterations in schizophrenia and extends to other psychotic disorders like BDP, is addressed here.

Methods: Volunteers with schizophrenia (n = 38), bipolar I disorder with psychotic features (n = 31), and healthy controls (n = 17), diagnosed using the SCID interview, performed a novel eye movement task to assess the predictive mechanism. Subjects also completed neuropsychological tasks of working memory and other cognitive domains.

Results: Individuals with schizophrenia and psychotic bipolar disorder performed similarly on both neuropsychological and eye tracking tasks. Both groups evidenced reduced predictive pursuit gain and worse performance on the Wechsler Spatial Span task compared with healthy controls. Further, a small but

significant correlation ($r = .27$, $p = .03$) was found between predictive pursuit gain and one working memory task.

Conclusions: Individuals with SZ and BDP each showed similar deficits on the predictive pursuit eye movement task, suggesting that this alteration could be a characteristic of the psychosis domain. The a priori prediction that the predictive pursuit task is associated with working memory mechanisms was supported in part by its significant and selective correlation with a measure of working memory.

Introduction

Studies measuring neuronal activity with both electrophysiology and functional imaging techniques in humans and animals have significantly increased our understanding of the neural substrates involved in smooth pursuit eye movements (SPEM). The anatomic pathway for smooth pursuit is hypothesized to begin with two subsystems. The first subsystem begins with retinal ganglion cells that specialize in processing stimuli characteristics such as color and shape, also referred to as the thalamic parvocellular pathway. This pathway extends beyond the lateral geniculate nucleus (LGN) as the dorsal pathway (Leigh & Zee, 1991). The second subsystem contains larger, faster conducting neurons that process spatial and movement information, also referred to as the magnocellular pathway, which extends beyond the LGN as the ventral pathway via the primary visual cortex, including V1, Broadmann area 17, and the striate cortex (Leigh & Zee, 1991). Additional projections extend from the striate cortex to the middle temporal visual area, which also contains neurons responsible for encoding information about speed and direction of moving stimuli. Additional projections extend to the posterior parietal cortex and the frontal and supplementary eye fields (FEF and SEF) and then to pontine nuclei (Leigh & Zee, 1991). Research in non-human primates has used single cell neuron recording to generate stimulation techniques to localize neurons in a specific region of the FEF that are involved during the initiation and maintenance of smooth pursuit eye movements, but do

not seem to be involved in the generation of catch-up saccades (MacAvoy et al., 1991). Based on the pattern of deficits observed in individuals with schizophrenia (SZ), specifically, reduced gain and a preserved ability to use saccadic eye movements to catch up and track a target, MacAvoy and Bruce (1995) hypothesized that the SPEM abnormality found in schizophrenia may be due to an abnormality in the FEF; this conclusion was supported by a report from Sweeney et al. (1998) in which this pattern was demonstrated by a sample of first episode, treatment naïve individuals with schizophrenia. Further, frontal dysfunction in SZ has also been reported using neurobehavioral (Park & Holzman, 1993) and neuroimaging techniques (Weinberger et al., 1986).

Detecting specific dysfunction in smooth pursuit eye movements (SPEM) has been increasingly studied and refined over the past several decades to reflect underlying brain alterations in a variety of neurological and psychiatric conditions, testing specific hypotheses about their neural mechanisms. An abundance of evidence of SPEM deficits in individuals with schizophrenia (see Levy et al., 1994, O'Driscoll et al., 2008) and their relatives (see Calkins et al., 2008, for a review) has led to increasing interest in refining the measurement of SPEM as an endophenotype for the disorder. SPEM deficits have also been reported in patients with psychotic and nonpsychotic variants of affective disorders (Abel et al., 1991, Tien et al., 1996, Sweeney et al., 1999, Kathmann et al., 2003), providing evidence for potential overlap across these disorders,

particularly across the dimension of psychosis. A number of hypotheses regarding the exact nature of the SPEM deficit in schizophrenia and associated brain regions have been tested in the literature, including deficits in inhibition of the saccadic system, implicating dysfunction in the FEFs and tempo-parietal regions (Levin, 1984) deficits in voluntary control of saccades with implication of impairment in the frontal cortex, and deficits in the motion processing system, mediated in the middle temporal and medial superior temporal areas (Chen et al., 1999). Further, deficits in SPEM have been hypothesized to be related to dysfunction in predictive eye movements mostly based on the internal representation of the target motion, mediated in the prefrontal cortex and posterior parietal cortex (Thaker et al., 2003). Alterations of these mechanisms in SZ are consistent with hypotheses implicating dysfunction of the prefrontal cortex within the FEFs in schizophrenia pathophysiology.

The presence of frontal lobe abnormalities in neurobehavioral studies of schizophrenia further supports the implication of frontal dysfunction in psychosis. (Weinberger et al., 1986, Snitz et al., 1999). Reports of working memory deficits in SZ further support frontal lobe dysfunction in schizophrenia pathophysiology. Baddeley (1986) described working memory as a cognitive process requiring mental representation of information to be held "online", not unlike in short term memory, but distinct from short term memory in that the online information undergoes some manipulation or transformation. Baddeley also noted some

overlapping features between working and short term memory, such as the limited capacity for how much information can be stored at any one point in time. Goldman-Rakic (1987, 1991) reported activation of neurons in the principle sulcus of the dorsolateral prefrontal cortex in non-human primates performing a DRT that involved remembering the location of a food reward over a time delay (Goldman-Rakic, 1987). Park and Holzman (1992) first reported that individuals with SZ were impaired on delayed response tasks (DRT), adapted from Goldman-Rakic's classic working memory paradigm. Park and Holzman also reported an association between working memory on an oculomotor DRT and SPEM (1993), providing evidence for a relationship between these cognition and oculomotor tasks of frontal function in SZ. Several other studies have examined the relationship between domains of cognition and eye movements. Litman et al. (1991) found a correlation between performance on the Wisconsin Card Sorting Test (WCST), a task of mental flexibility and set-shifting, and gain during smooth pursuit, although this has not been consistently replicated (Friedman et al., 1995). Two independent investigations reported a positive correlation between errors on a task of saccadic inhibition (anti-saccade task) and perseverative errors on the Wisconsin Card Sorting Test (Rosse et al., 1993, Tien et al., 1996). However a direct examination of the relationship between working memory performance and smooth pursuit eye movement function has not been reported in individuals with

BDP, despite evidence of overlapping patterns of deficits in these areas with SZ patients (Ivleva et al., 2010).

While the predictive mechanism of smooth pursuit has traditionally been measured by recording eye behavior in response to a briefly masked (invisible) target (Barnes and Asselman, 1992, Thaker et al., 1998), measurement with a novel technique that stabilizes the target image on the fovea of the eye without removing it from visibility has demonstrated impairment in individuals with SZ and their first-degree relatives (Hong et al., 2008). Because the eye behavior during this task is based on extra-retinal information (e.g. the internal representation and memory of target position and speed), it is hypothesized that a contribution of the working memory system is required to provide the predictive response (Thaker, 2008).

The current study aimed to characterize the relationship between deficits in predictive pursuit and working memory across two main psychotic illnesses (SZ and BDP) and healthy comparison subjects based on the hypothesis that working memory contributes to the predictive pursuit mechanism, and both may be promising endophenotypic markers of psychosis. We measured the predictive mechanism of eye behavior using a novel predictive pursuit task, utilizing a technique wherein the computer switches control of target movement to be contingent on the subject's eye movement without their awareness, and subsequent movement is based on the subject’s memory of previous target

position and speed (Hong et al., 2008). A previous study using this technique found robust predictive pursuit deficits in both individuals with SZ and their first-degree relatives (Hong et al., 2008). The current study examined whether similar deficits also exist in BDP in order to contribute to the evidence that individuals with SZ and BDP share aspects of brain pathology. Further, the relationship between working memory and predictive pursuit was explored in both disorders, based on the prediction that working memory is intimately involved in the performance of the predictive pursuit task. Two commonly used measures of working memory were included. For comparison purposes, performance on a battery of tasks tapping dimensions of attention, episodic memory, executive functioning and general intelligence were also included.

Methods

Participants

Thirty-eight individuals with a lifetime diagnosis of schizophrenia (SZP) and 31 individuals with bipolar I disorder with psychotic features (BDP) were included. In addition, 17 healthy comparison subjects (HC) without a history of Axis I or II diagnoses were included and no first degree relative with a psychotic illness. Diagnoses were determined at consensus conferences using all available clinical data, including results from the Structure Clinical Interview for DSM-IV (SCID, Modules A – E) (First et al., 1995). All individuals were recruited concurrently through advertising and by referral from community mental health centers in and around Dallas, TX and from the University of Texas Southwestern Medical Center outpatient clinics. Inclusion criteria limited ages between 16 and 58 years. Subjects with a history of major neurological or decompensated medical illness, mental retardation, traumatic brain injury, substance abuse within the last month or substance dependence within the last 3 months were excluded from the study. To screen participants for current illicit drug use, a urine toxicology test was performed at the initial visit and on a case by case basis at subsequent visits for those with problematic substance use histories or reported use. The study was approved by the institutional review board of UT Southwestern Medical Center and participants provided written informed consent.

Experimental Procedures

Horizontal eye movements were recorded with infrared reflection technology (EyeLink II eyetracker, SR Research, Osgoode, Canada) sampling at 500 Hz in a room with controlled luminance of 2 lux. A target (a cross in a .25 x .25 - degree box with a photometric contrast of 2.1 log units) was presented on a 22-inch flat screen monitor (ViewSonic, P225f Professional System) set to 120 Hz, placed 60 cm in front of the subject.

The digital data were filtered off-line using a low pass filter at two cutoff frequencies, 75 and 20 Hz, using data acquisition and analysis software (AcqKnowledge Version 3.7.3, Goleta, CA and IGOR Pro Version 5.0, Wavemetrics, Inc.). Data were all inspected visually to eliminate artifacts (blinks) and saccades. Saccades were identified based on velocity (> 35 degrees/sec) and acceleration (>600 degrees/sec^2) criteria. All saccades and artifacts were identified as missing data points.

Predictive Pursuit Task

The experimental procedures for this task have been described in detail elsewhere (Hong et al., 2008) and are summarized here. The predictive pursuit task consisted of two 4-minute sessions. Each session included 12 trials. A trial started with calibration steps at + and – 12 degrees, followed by 1 – 3 seconds of center fixation. The target traversed horizontally across the screen at a steady velocity of either 9.9 degrees/sec or 18.7 degrees/sec (a ramp). After 1-3 ramps, a virtual window was triggered to open during which the software covertly

switched the driver of the target from the computer to the eye (Hong et al., 2008). During this window the subject's memory of the target position and speed drives the target without the subject's awareness. All subjects were naïve to the task. Most literature indicates differences between patient and control groups are more evident at higher target speeds (higher difficulty load), between 15-20 degrees/second, and that differences are not as robust at lower target speeds (Thaker et al., 2003). The current paradigm included trials at both 9.9 (low difficulty) and 18.7 (higher difficulty) degrees/second with the expectation that differences would be more evident at the high difficulty load.

Neuropsychological Tasks

Subjects underwent a battery of neuropsychological tests tapping several different cognitive domains. The following neuropsychological measures were used to examine performance across four cognitive domains known to be affected in psychosis: *working memory* - Letter Number Sequencing and Spatial Span subtests from the Wechsler Memory Scale – Third edition (WMS-III) (Wechsler, 1997b); *episodic memory* - Logical Memory II (delayed recall) from the WMS-III and the Word and Face Recognition subtests from the Warrington Recognition Memory Test (Warrington, 1984); *executive function* - perseverative error score from the Wisconsin Card Sorting Test (Heaton et al., 1993), Letter Fluency (PRW) total score from the Controlled Oral Word Association (Benton et al., 1994), and the Trail Making Test, Part B (Reitan & Wolfson, 1985);

attention/vigilance - Trail Making Test, Part A (Reitan & Wolfson, 1985) and Digit – Symbol Coding subtest of the Wechsler Adult Intelligence Scale – Third edition (WAIS-III) (Wechsler, 1997a). In addition, an estimate of general intellectual level was obtained based on Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001). Demographically corrected T-scores, which have a mean of 50 and standard deviation of 10, were obtained for all measures except the WTAR IQ estimate, which has a mean of 100 and standard deviation of 15. Composite scores were then calculated for the four cognitive domains by computing the mean of the subtest T-scores for that domain. Performance was examined for the subtests individually as well as by composite.

Statistical Analysis

Statistical analyses were conducted using SPSS version 12.0 (SPSS, Inc., Chicago IL). Descriptive statistics were examined for demographic and neuropsychological characteristics of the three groups. In addition to the individual neuropsychological working memory test scores, composite scores for the domains of working memory, episodic memory, executive functioning and attention/vigilance were calculated for each group. A one-way analysis of variance (ANOVA) with a subsequent post hoc Tukey HSD test was used to examine between-group differences in socio-demographic and neuropsychological performance. Yates corrected chi-square test was used to evaluate between-group differences on nominal variables.

Smooth pursuit gain was calculated during the 1-second window (predictive pursuit gain) as well as during the preceding ramp (maintenance pursuit gain) using the artifact-free (saccades and blinks removed) eye velocity divided by the target velocity. Predictive pursuit gain and neuropsychological performance were examined using a Pearson product moment correlation.

In addition, to further describe the characteristics of smooth pursuit, eye velocity was averaged across trials by 50-ms epochs across the duration of the 1 – second predictive windows at the two target speeds, 9.9 degrees/second and 18.7 degrees/second. For comparison, maintenance pursuit gain from the preceding ramp was also analyzed by 50-ms epochs at each of the two target speeds. In analysis, subjects whose values were based on less than 5 trials with valid data were not included as calculating mean velocity using 4 or fewer trials may produce unreliable results. In the 18.7 degrees/second condition, this excluded 5 SZ, 4 BDP, and 6 HC' in the 9.9 degrees/second condition, 4 SZ, 6 BDP, and 3 HC were excluded. Eye velocity during predictive and maintenance pursuit at each target speed was evaluated for the three groups using individual repeated measures analysis of variance tests, with subsequent post hoc Tukey HSD tests for significant results. For these repeated measures ANOVAS, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity. Age was used as a covariate in these analyses due to its known influence on eyetracking

performance. For all analyses, probability values below .05 were considered significant.

Results

Demographic characteristics

The characteristics of the study populations are shown in Table 1. No group differences were observed in gender (female/male: 15/23, 20/11, and 7/10 in SZ, BDP, and HC, respectively; $\chi^2 = 4.78$, $p = .092$), ethnicity (Caucasian: African-American: Hispanic: other: 24:12:1:1, 22:3:4:2, 13:3:1:0, respectively; $\chi^2 = 8.44$, $p = .208$), or years of education (mean ± SD: 13.58 ± 2.27, 13.65 ± 2.39, and 13.59 ± 1.58, respectively; F (2, 83) = .008, $p = .992$). Age was significantly different between the patient groups and thereafter used as a covariate in relevant subsequent analyses (F (2, 83) = 4.542, $p < .001$; post hoc Tukey HSD: SZ vs. BDP, $p = .014$; SZ vs. HC, $p = .140$; BDP vs. HC, $p = .895$). All SZ volunteers were medicated with either typical or atypical neuroleptic medication at time of testing. In addition, 10 individuals with BDP were taking atypical neuroleptics and 12 BDP volunteers were taking lithium carbonate (Table 2). No individuals in the HC group were taking psychoactive medication.

Neuropsychological performance

Neuropsychological performance analyzed using composite scores for working memory, episodic memory, and attention/vigilance showed no differences between the SZ, BDP and HC groups (statistics reported in Table 3). The HC group performed significantly better than SZ or BDP on the executive

functioning composite (F (2, 69) = 5.25, p = .008*;* post hoc Tukey HSD: SZ vs. BDP, p =.819; SZ vs. HC, p = .006; BDP vs. HC, p = .020).

On the individual measures of working memory, both SZ and BDP performed worse than the HC group on Spatial Span (F (2, 75) = 5.88, p = .004; post hoc Tukey HSD: SZ vs. BDP, p = .934, SZ vs. HC, p = .010, BDP vs. HC, p = .005). No differences were seen between SZ, BDP, and HC on the other measure of working memory, Letter Number Sequencing (F (2, 69) = 0.54, p = .585).

Results of the exploratory analysis of the individual neuropsychological tests are shown in Table 4. In addition to Spatial Span, four other individual subtests showed significant differences between diagnostic groups. Individuals with SZ performed worse than HC on the Wechsler Digit Symbol-Coding task (F (2, 69) = 3.91, post hoc Tukey HSD: SZ vs. BDP, p = .153, SZ vs. HC, p = .034, BDP vs. HC, p = .421). Differences were also seen on the Trail Making test, part B (F (2, 69) = 3.37, p = .040). Post hoc comparisons showed scores on the Trail Making test, Part B were significantly higher in HC than BDP (p = .039), and at a trend level compared to SZ (p = .051). Performance on the WCST was worse in SZ and BDP than HC (F (2, 67) = 3.62, p = .032), as was performance on the Logical Memory II task (F (2, 69) = 3.55, p = .034; post hoc Tukey HSD: SZ vs. BDP, p = .946, SZ vs. HC, p = .048, BDP vs. HC, p = .032).

The three study groups did not differ in estimated intelligence or education.

Specifically, no significant differences emerged in WTAR estimated full scale IQ (F (2, 66) = .270, p = .76), with each of the three groups scoring in the average range (SZ = 99.58 ±13.35, BDP = 101.24 ±10.71, HC = 102.56 ±11.23). Further, education years were similar across groups (mean ± SD: SZ= 13.58 ± 2.27, BDP = 13.65 ± 2.39, and HC = 13.59 ± 1.58; F (2, 83) = .008, p = .992).

Eyetracking performance

Individuals with psychosis demonstrated lower eye velocity during maintenance pursuit compared with HC in the condition where the target was moving at a speed of 18.7 degrees/second (high difficulty). At this speed, the three groups differed significantly on the maintenance pursuit velocity (F (1, 67) = 3.41, $p < 0.05$). Post hoc comparisons showed that maintenance velocity in BDP was lower than in HC ($p < 0.05$) and lower in SZ compared to HC at a trend level compared to HC ($p = 0.06$) (Figure 1). When the target speed was slower, moving at 9.9 degrees/second (low difficulty), the 3 groups did not differ in maintenance velocity (F (1, 69) = .455, NS) (See Figure 2).

Regarding the predictive pursuit mechanism, measured during the 1-second window where eye behavior was based on memory of target position and speed, the three groups again showed differences during the high difficulty condition with the faster target speed of 18.7 degrees/second (F (1, 67) = 3.2, $p < .05$) (Figure 3). Post hoc comparisons showed that the predictive pursuit velocity was lower in both BDP and SZ compared to HC ($p \leq 0.05$); SZ and BDP did not differ

on predictive velocity (p = .986). During the slower condition, where the target was moving at 9.9 degrees/second, the 3 groups did not differ in predictive pursuit velocity (F (1, 69) = 1.602, NS) (Figure 4).

These analyses examined all 50ms epoch velocities over the course of the predictive window. We also examined the initial smooth pursuit response (mean acceleration of the eye during the first 100 ms of the predictive window), an eye behavior based mostly on residual motion of the target image on retina. A one-way analysis of variance showed significant differences between groups on this additional measurement of eye behavior (F (2, 67) = 4.438, p =.015) (Figure 5).

Due to the potential negative effects of lithium on eye tracking performance (Holzman et al., 1991, we conducted an exploratory analysis of individuals with BDP taking lithium (n = 9; in total, 12 individuals with BDP were taking lithium, however 3 were already excluded from analysis at 18 degrees/second due to having less than 5 usable trials) and those who were not (n = 18). No differences were found between these two groups on the predictive gain measure at 18 degrees/second (t (25) = -.939, p = .357).

Relationship between eyetracking and neuropsychological performance

In order to establish the relationship between the eye tracking alterations and cognitive performance, correlations between domains of cognition, especially working memory, and the predictive component of eye tracking performance were examined. There was a significant correlation between predictive pursuit

gain at 18 degrees/second and performance on Spatial Span (r = 0.27, p = .03; see Figure 6); no significant correlation was obtained with predictive pursuit gain and Letter Number Sequencing performance (r = .17, p = .19). Similarly, correlations between predictive pursuit gain and the four composite scores (working memory, attention/vigilance, executive functioning, and episodic memory) were not statistically significant (Figures 7, 8, 9 and 10).

Discussion

Individuals with schizophrenia and psychotic bipolar disorder performed similarly on both putative working memory endophenotypes based on the neuropsychological and eye tracking tasks. Both groups evidenced reduced predictive pursuit velocity and worse performance on the Wechsler Spatial Span task compared with healthy controls.

The neuropsychological results from the current sample demonstrated similar neuropsychological performance in SZ and BDP, which is in contrast to previous reports describing more severe impairments in SZ than BDP (Altshuler et al., 2004, Burdick et al., 2006); however, these earlier reports often included individuals with non-psychotic Bipolar I disorder and may have been lower functioning than our groups. In contrast, the current sample of BDP was comprised of only bipolar individuals who exhibited current or past psychotic symptoms, and the presence of psychosis has been shown to be related to poorer neuropsychological outcome in individuals with bipolar disorders (Glahn et al., 2007). As the presence of psychosis may be a better indicator of common impairment than traditional diagnostic categories (Ivleva et al., 2010), it is not surprising that individuals who all share this dimension of psychopathology would perform similarly on these measures.

The current sample is unique in that it contained individuals with

psychosis and non-affected individuals all with mean estimated IQ scores in the average range. As other reports often find lower IQ and education in patient volunteer groups, these results suggest that level of intelligence may not mediate these alterations in eye movements in relation to working memory. Therefore, these results represent a report of neuropsychological functioning in SZ and BDP comparing groups similar in overall intellectual functioning and who are of average intelligence.

Lower performance by individuals with SZ on Digit Symbol Coding, a task known to be sensitive to nonspecific brain dysfunction, could have been moderated by differential effects of neuroleptic medications (Knowles, et al., 2010). Digit Symbol Coding is generally considered to be a task of psychomotor processing speed and attention and may possibly have been impacted by the role of extrapyramidal side effects in the SZ group (8 individuals with SZ and 0 individuals with BDP were taking typical antipsychotic medication at time of testing). However, it is not possible to conclude that medication affected performance on this task as the current study did not include any measurement of extrapyramidal side effects.

The current study has a limited sample size of healthy controls which limits statistical power. Some cases were excluded from analysis based on criteria of having at least 5 valid trials to calculate averages in the eye movement task, which further limited the N. It is possible differential effects of medications

across patient groups also contributed to differences observed. Future investigations should include the recruitment of individuals with psychosis who are medication – free in order to further explore the potential effects of medication on eyetracking performance. Further, the current study included two neuropsychological tasks of working memory that tap different modalities (auditory and visual). It has been reported in the literature that conventional neuropsychological tests may lack the sensitivity and specificity to reliably characterize neurocognitive endophenotypes in psychotic disorders (Barch & Carter, 2008), which may contribute to the small relationship we observed between predictive pursuit gain and working memory. Including more specific tasks of working memory such as the Sternberg item recognition paradigm, which has been demonstrated to activate the dorsolateral prefrontal cortex using functional imaging methods (Manoach et al., 1999) may provide a measurement of the working memory deficit in individuals with psychosis that might show a stronger relationships with eyetracking results, although this remains to be seen. Selecting working memory tests that bear a closer relationship to the underlying neuroanatomy of eyetracking mechanisms may also be informative.

Individuals with SZ and BDP each showed similar deficits on the predictive pursuit eye movement task, suggesting that this alteration could be a characteristic of the psychosis domain. The largest group differences in both maintenance and predictive velocity between individuals with psychosis and

healthy controls were observed during the 18.7 degrees/second (high difficulty) target condition, consistent with literature reporting that group differences are maximized at higher target speeds (Thaker et al., 1998, Thaker et al., 1999). These impairments in psychosis have been hypothesized to be related to a working memory component of prediction, and higher target speeds may require more effort on the part of the individual tracking to keep up with the target than slower speeds. While impairments in individuals with SZ and their relatives have been reported using this novel predictive pursuit task (Hong et al., 2008), this study is the first to report data on the performance of individuals with BDP using this method. The a priori prediction that the predictive pursuit task relies on working memory mechanisms was supported in part by its significant and selective correlation with a measure of working memory.

Table 1.Demographic Information

	SZ (N = 38)	BDP (N = 31)	HC (N = 17)	Statistic	*p*
Age M *(SD)*[1]	41.97 *(9.52)*	35.29 *(9.76)*	36.59 *(9.56)*	$F(2,83) = 4.54$	<.001
Gender, female - N (%)	15 *(39.5)*	20 *(64.5)*	7 *(41.2)*	$\chi^2(2) = 4.78$	.092
Left-handed - N (%)	5 *(13.2)* •	4 *(12.9)* •	1 *(5.9)* •	$\chi^2(6) = 6.58$	.361
Years of Education M *(SD)*	13.58*(2.27)*	13.65*(2.39)*	13.59*(1.58)*	$F(2, 83) = .008$	.992
Ethnicity - N (%)					
Caucasian	24 *(63.2)*	22 *(71.0)*	13 *(76.5)*	$\chi^2(6) = 8.44$	.208
African-American	12 *(31.6)*	3*(9.7)*	3 *(17.6)*		
Hispanic	1 *(2.6)*	4 *(12.9)*	1 *(5.9)*		
Other	1 *(2.6)*	2 *(6.5)*	0 *(0)*		

SZ –schizophrenia, BDP –psychotic bipolar disorder, HC – healthy controls.

[1] post hoc Tukey HSD: SZ vs. BDP, $p = .014$; SZ vs. HC, $p = .140$; BDP vs. HC, $p = .895$

• Cells with missing data.

Table 2.Concomitant Medications

	SZ (N = 35) •	BDP (N = 30) •
Off medications - N (%)	0 (0)	1 (3.3)
Typical AP - N (%)	9 (23.7)	0 (0)
Atypical AP - N (%)	25 (65.8)	17 (54.8)
Antidepressants - N (%)	16 (42.1)	15 (48.4)
Anxiolytics/Hypnotics - N (%)	10 (26.4)	16 (51.6)
Stimulants - N (%)	0 (0.0)	2 (6.5)
Lithium - N (%)	0 (0.0)	12 (38.7)

SZ –schizophrenia, BDP –psychotic bipolar disorder, HC – healthy controls.

• Total number of subjects that provided responses is shown in each cell.

Table 3.Composite Neurocognitive Test T-Scores by Group

	SZ (N = 34)	BDP (N = 29)	HC (N = 9)	Statistic	*p*
Working Memory (Letter Number, Spatial Span)	47.65 *(8.95)*	47.53 *(7.63)*	54.07 *(8.34)*	$F(2,69) = 2.36$	.102
Episodic Memory (Logical Memory II, Warrington Words and Faces)	46.41 *(9.29)*	45.82 *(7.71)*	52.10 *(5.20)*	$F(2,69) = 2.08$	.133
Executive Functioning (WCST Perseverative errors, COWAT, Trails B)	42.61 *(7.80)*	43.90 *(9.27)*	52.54 *(5.46)*	$F(2,69) = 5.25$	.008
Attention/Vigilance (WAIS-III Coding, Trails A)	41.24 *(8.67)*	43.94 *(7.97)*	48.09 *(9.95)*	$F(2,69) = 2.48$	.092

SZ –schizophrenia, BDP –psychotic bipolar disorder, HC – healthy controls.

[1] post hoc Tukey HSD: SZ vs. BDP, p =.819; SZ vs. HC, p = .006; BDP vs. HC, p = .020

*****Composites represent the mean of T-score on subtests contained within each composite

Table 4.Neurocognitive Performance by Group (T-scores)

	SZ (N = 34)	BDP (N = 29)	HC (N = 9)	Statistic	*p*
Letter Number Sequencing	47.35 *(10.04)*	47.93 *(8.61)*	51.11 *(11.54)*	$F(2, 69) = 0.54$	.585
Spatial Span	47.98 *(10.31)*	47.13 *(9.33)*	56.67 *(7.89)*	$F(2, 75) = 5.88$ •	.004[1]
Logical Memory II	50.98 *(10.93)*	50.11 *(11.25)*	60.74 *(8.13)*	$F(2, 69) = 3.55$	.034[2]
Warrington Words Recall	48.24 *(13.61)*	47.36 *(11.1)*	54.44 *(8.16)*	$F(2, 69) = 1.22$	.302
Warrington Faces Recall	40.0 *(12.06)*	40.0 *(14.14)*	41.11 *(7.26)*	$F(2, 69) = .031$	.969
Wisconsin Card Sorting Test Perseverative Errors	41.50 *(11.35)*	44.79 *(16.23)*	56.29 *(4.75)*	$F(2, 67) = 3.62$ ••	.032[3]
Controlled Oral Word Association Test	42.41 *(11.08)*	43.38 *(9.50)*	48.33 *(6.70)*	$F(2, 69) = 1.24$	.295
Trail Making Test, part A time	41.0 *(12.79)*	42.38 *(9.60)*	46.56 *(12.19)*	$F(2, 69) = .829$	.441
Trail Making Test, part B time	44.03 *(9.91)*	43.41 *(12.05)*	53.89 *(11.47)*	$F(2, 69) = 3.37$	.040[4]
Digit Symbol-Coding	41.47 *(7.75)*	45.5 *(9.27)*	49.62 *(8.89)*	$F(2, 69) = 3.91$	.025[5]
WTAR Estimated Full Scale IQ	99.58 *(13.35)*	101.24 *(10.71)*	102.56 *(11.23)*	$F(2, 66) = .270$	.764

SZ – schizophrenia, BDP – psychotic bipolar disorder, HC – healthy controls.

• One SZ subject had unusable Spatial Span data; 7 additional HC completed SS

•• Two HC subjects had unusable data on the WCST

[1] post hoc Tukey HSD: SZ vs. BDP, $p = .934$, SZ vs. HC, $p = .010$, BDP vs. HC, $p = .005$

[2] post hoc Tukey HSD: SZ vs. BDP, $p = .946$, SZ vs. HC, $p = .048$, BDP vs. HC, $p = .032$

[3] Levene statistic = 4.614, $p = .013$; therefore a nonparametric median test was conducted: median = 45.50, $\chi 2\ (2) = 7.98$, $p = .019$

[4] post hoc Tukey HSD: SZ vs. BDP, $p = .973$, SZ vs. HC, $p = .051$, BDP vs. HC, $p = .039$

[5] post hoc Tukey HSD: SZ vs. BDP, $p = .153$, SZ vs. HC, $p = .034$, BDP vs. HC, $p = .421$

Figure 1. Maintenance Pursuit Velocity at 18.7°/sec: Eye following target

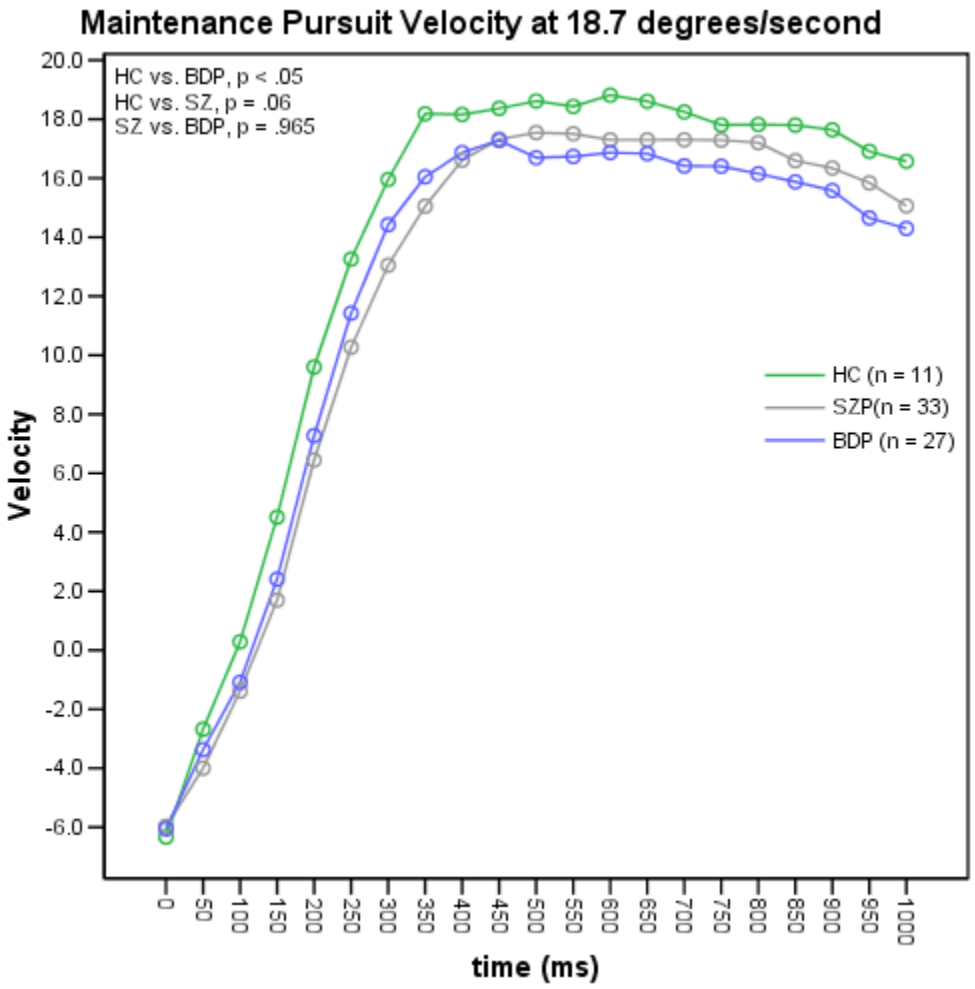


Figure 2. Maintenance Pursuit Velocity at 9.9 °/sec: Eye following target

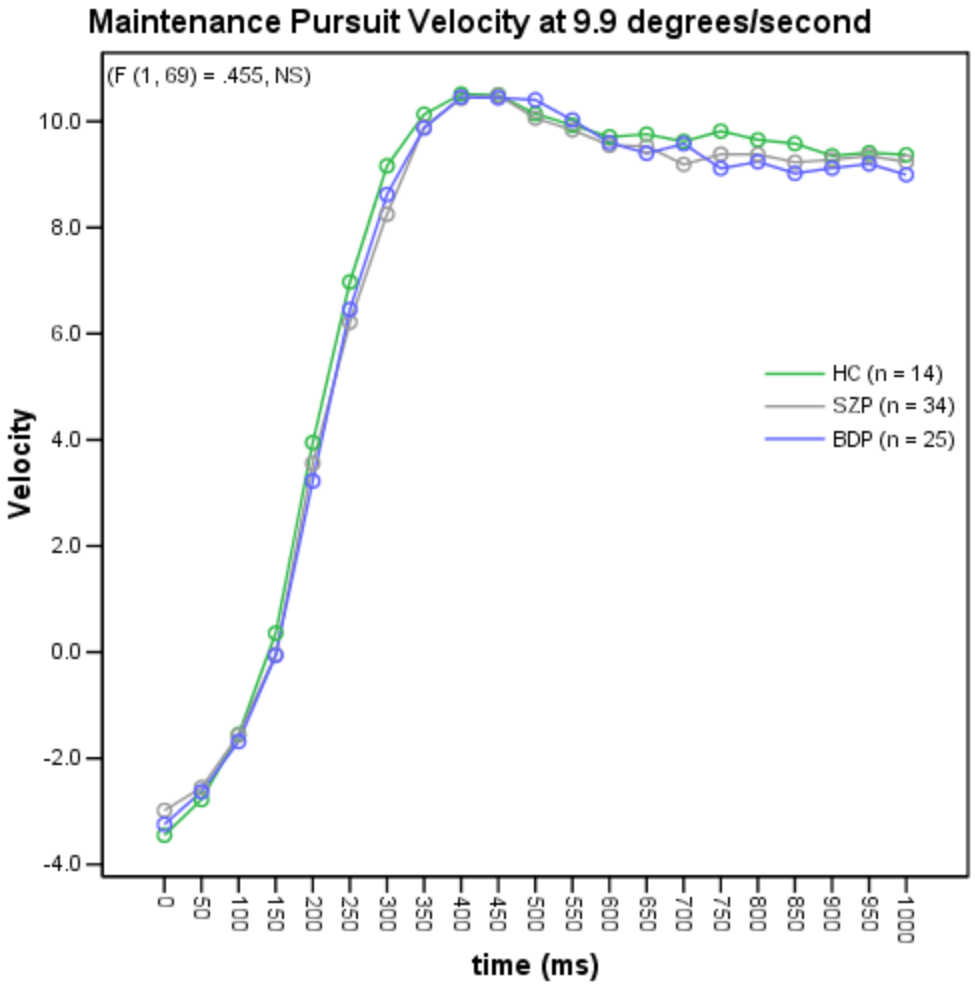


Figure 3. Predictive Pursuit Velocity at 18.7°/sec: Eye driving target

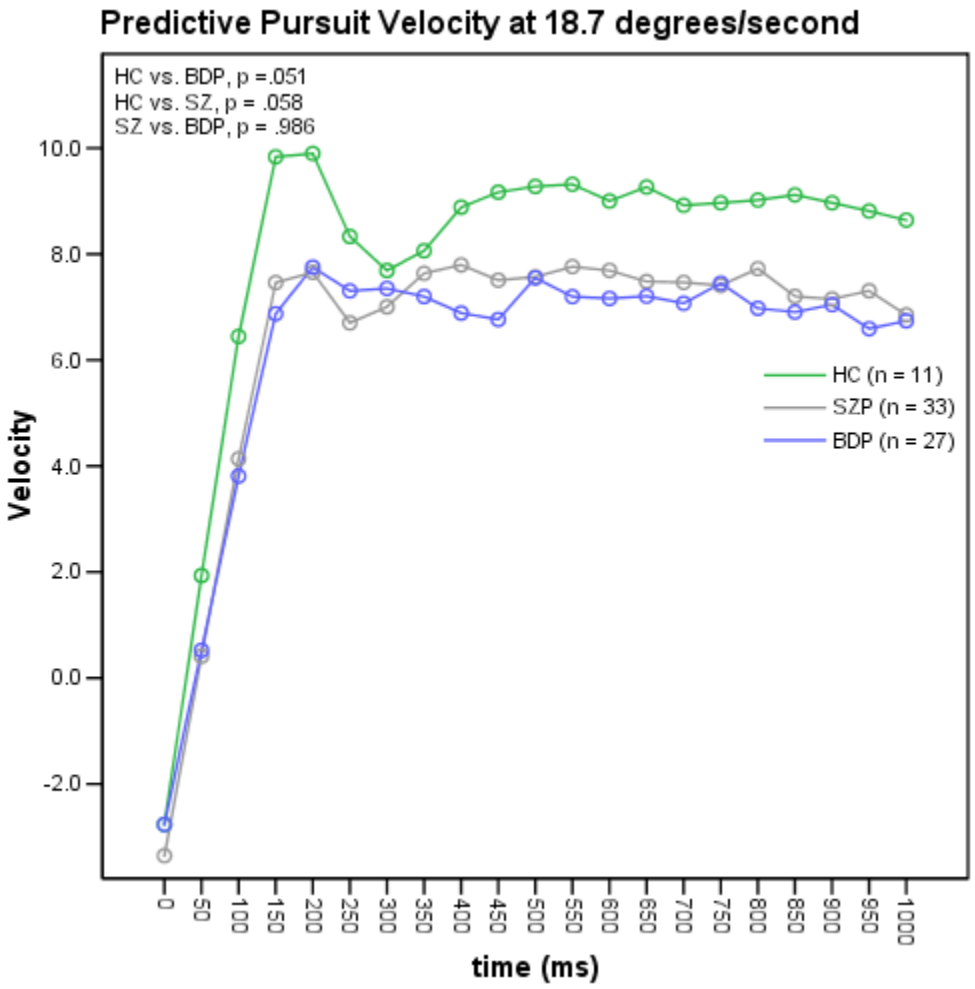


Figure 4. Predictive Pursuit Velocity at 9.9°/sec: Eye driving target

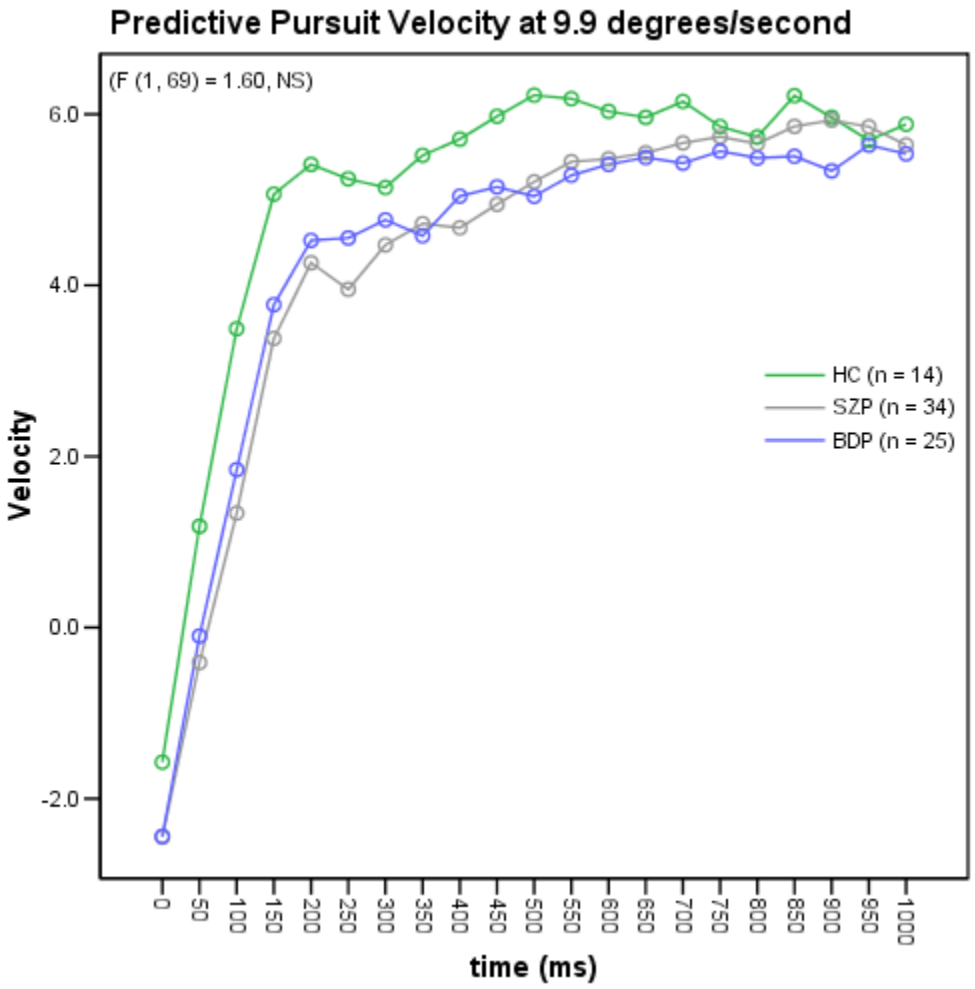


Figure 5. Smooth Pursuit Initiation at points 0, 50ms, and 100 ms

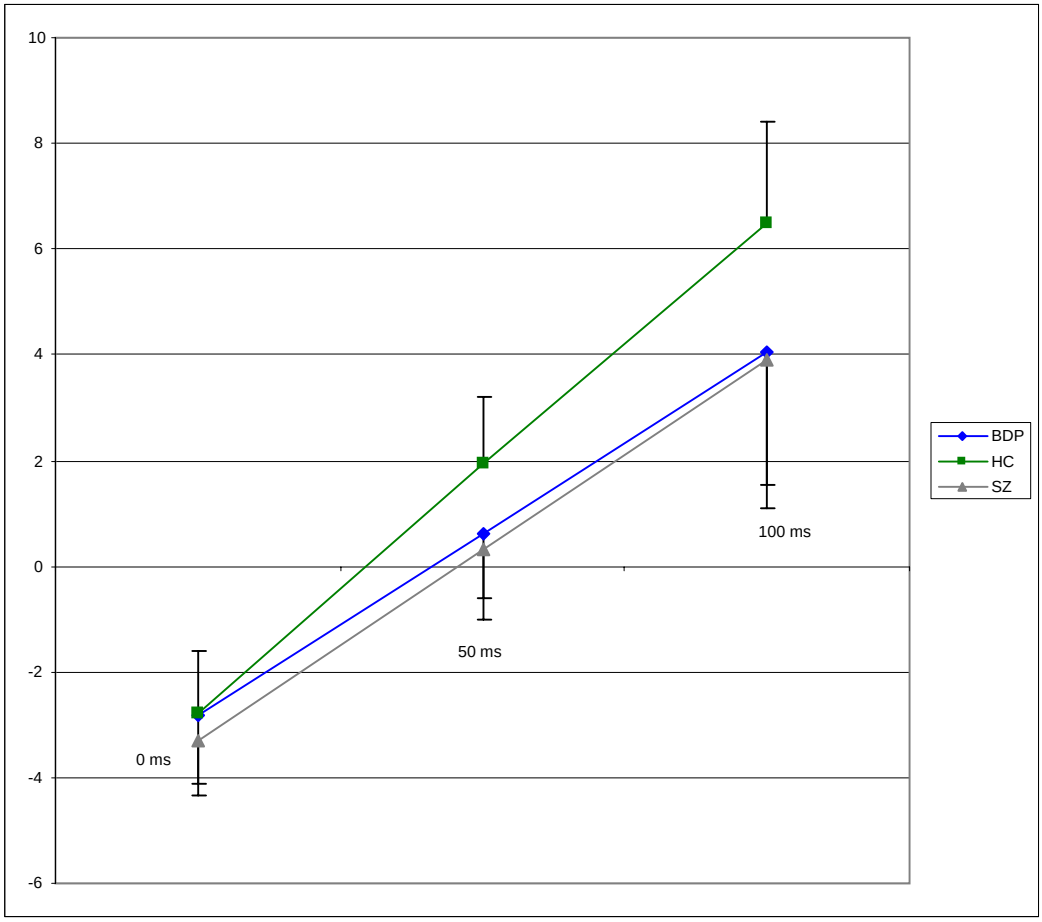


Figure 6. Scatterplot of Spatial Span by Predictive Pursuit Gain

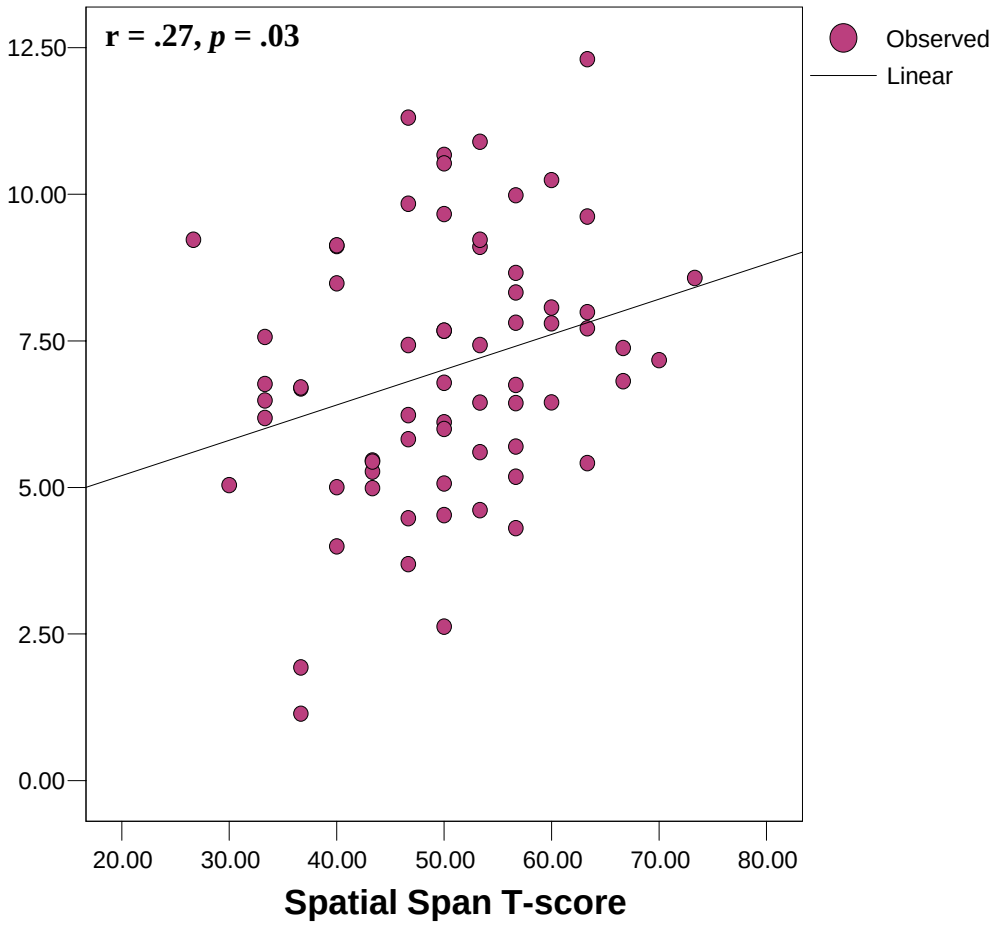


Figure 7. Scatterplot of Working Memory Composite by Predictive Pursuit Gain

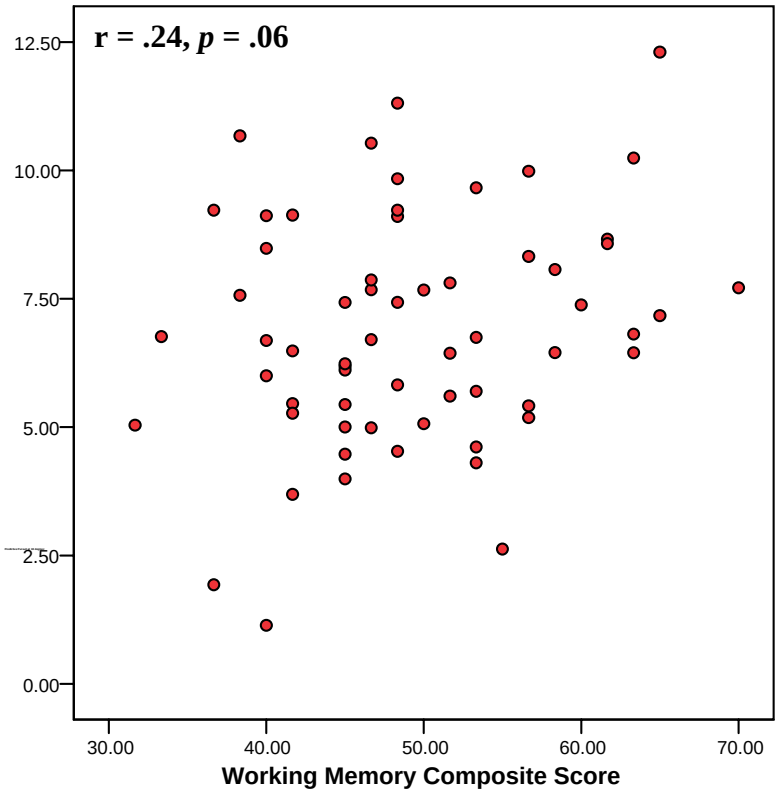


Figure 8. Scatterplot of Attention/Vigilance Composite by Predictive Pursuit Gain

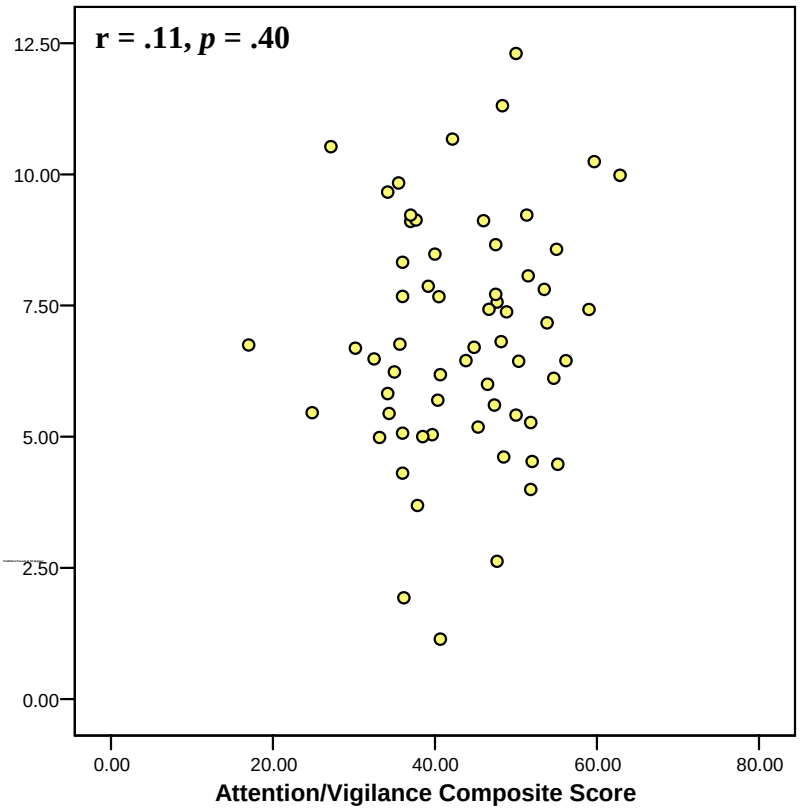


Figure 9. Scatterplot of Executive Functioning Composite by Predictive Pursuit Gain

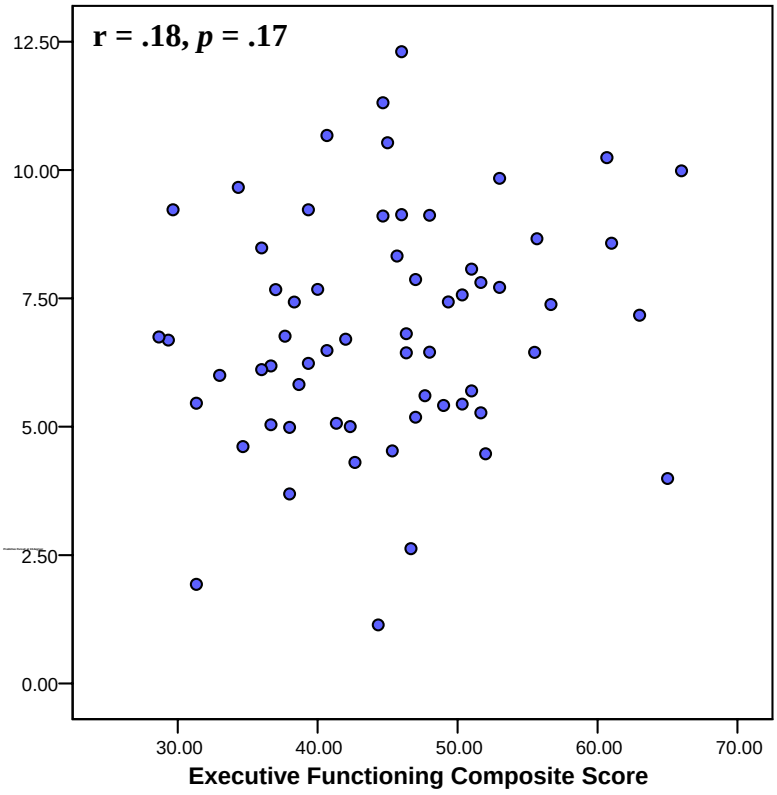
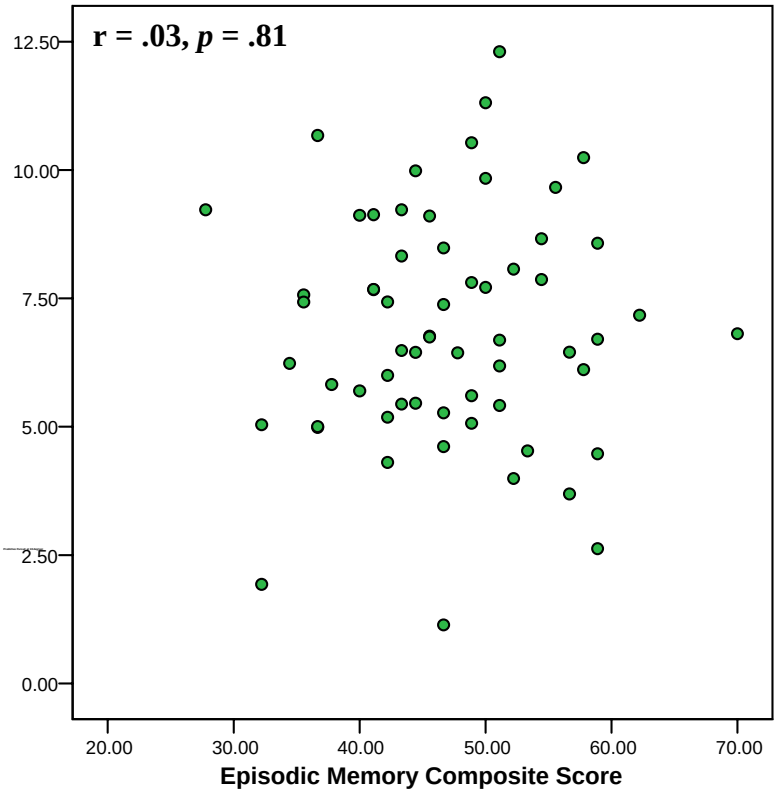


Figure 10. Scatterplot of Episodic Memory Composite by Predictive Pursuit Gain



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SECTION 3

APPENDIX I

Additional Background

GENETICS AND INTERMEDIATE PHENOTYPES OF THE SCHIZOPHRENIA-BIPOLAR DISORDER BOUNDARY – SUMMARY OF PUBLISHED LITERATURE REVIEW BY IVELVA ET AL., 2010

Our review article is a comprehensive description of the unique and overlapping genetic targets and intermediate phenotypes in schizophrenia and bipolar disorder, including a thorough discussion of the need for an alternative approach to the categorization of psychotic illnesses, moving from a dichotomous separation of schizophrenia and affective psychosis to a clinical continuum of psychosis. The overlapping symptom profiles, neurophysiology, genetics, and treatment responses and targets across these disorders, as well as inconsistent findings in large scale genetic linkage studies, highlights the need for re-thinking of traditional phenomenology-based diagnostic systems in psychiatric research. This review includes thorough discussion of not only overlapping and unique candidate genes in psychosis, but also evaluates the literature of intermediate phenotypes in SZ and BDP, including neurocognitive deficits, electrophysiological findings, eye tracking dysfunction, structural imaging, and neurological soft signs. This review paper provides a comprehensive background for the current investigation, which

examines two intermediate phenotypes of psychosis, neurocognitive deficits and eye tracking dysfunction, in individuals with both SZ and BDP classified psychosis.

Additional aspects of oculomotor abnormalities in SZ and BDP are discussed in this review, including the heritability of eye tracking dysfunction, the effects of medication on eye tracking, and associations with other biological markers that have been reported in the literature.

Ivleva, E.I., Morris, D.W., **Moates, A.F.,** Suppes, T., Thaker, G.K., Tamminga, C.A. (2010). Genetics and intermediate phenotypes of the schizophrenia-bipolar disorder boundary. *Neuroscience and Biobehavioral Reviews,* 34, 897-921.

APPENDIX II

Additional Methods

Processing of eye movement data

The novel predictive pursuit task consisted of two 4-minute sessions. Each session included 12 trials, half at a target speed of 9.9 degrees/sec and half at 18.7 degrees/sec, arranged in pseudo-random order. Data were processed off-line using algorithms (macros) written in the scoring software IGOR Pro Version 5.0 by Wavemetrics, Inc. Data were all inspected visually using both position and velocity graphs to eliminate artifacts (blinks) (Figure A) and saccades (Figure B). Saccades were identified based on the criteria of having a velocity > 35 degrees/sec and acceleration > 600 degrees/sec^2. All saccades and artifacts were identified as missing data points. Next, the one-second long predictive pursuit window was evaluated. Using the position graph, the examiner determines if the subject's eye moved in the expected target direction and for how long. In some instances, the subject did not produce any eye movement in the expected target direction. Those windows were marked as "no gaze contingent tracking occurred" and were not included in the average velocity across trials. Automated measurements of velocity were recorded every 50ms throughout the 1000ms predictive pursuit window. The velocities were multiplied by +1 during trials where the target would have moved to the right, also referred to as a positive

ramp. During trials where the target would have moved to the left, (negative ramp), the eye velocity was multiplied by – 1. Therefore when the eye moved in the expected direction of the target, the velocity measurements were all positive numbers. In some cases, the eye failed to move in the expected target direction, creating negative values, which were not included in analysis. A measurement of predictive gain was calculated by taking an average of the eye velocities over the course of the window and dividing that average by the expected target speed (either 9.9 or 18.7).

All valid trials were averaged for each subject; therefore trials marked as no gaze contingent tracking were not included. Further, some eye velocity values were extreme (high variability ranging from large negative values to positive ones). This occurs when the subject does not change direction when the target would have changed direction (therefore creating negative values), and then moving very fast when they realize that they have not changed direction. In addition values of very high eye velocity (> 1.5 times the target velocity) were also identified and removed before analysis. In all, using these criteria, approximately 5% of the raw data was not included in calculating the average gain. In analysis, subjects whose values were based on less than 5 trials with valid data were not included as calculating mean velocity using 4 or fewer trials may produce unreliable results. In the 18 degrees/second condition, this excluded 5 SZ,

4 BDP, and 6 HC; in the 9 degrees/second condition, this excluded 4 SZ, 6 BDP, and 3 HC).

Repeated measures analysis of variance examined the 50ms epoch velocities across the 3 groups. Our a priori hypothesis was that the predictive mechanism contributes to smooth pursuit over the entire course of the window where the eye drives the target; therefore all the time points were included in the analysis. Further, a one-way analysis of variance examining the mean acceleration that occurred during smooth pursuit initiation (the first 100ms of smooth pursuit) showed that groups were significantly different even at this early time period in the window (F (2, 67) = 4.438, p =.015), giving further evidence to include all the time points in analysis.

Working memory neuropsychological tasks

The Wechsler Spatial Span task is thought to tap visual working memory and is also considered a visuospatial attention task. To administer this task, the examiner touches a sequence of blocks which are attached to a board in an irregular arrangement. The subject must then touch the blocks in the same order. In the second part of this task, the subject must point to the same blocks in reverse order. During the Wechsler Letter Number Sequencing task, the subject hears a list of randomized numbers and letters in alternating order of increasing lengths (from two to eight units). The subject is asked to repeat numbers and letters from the lowest in each series, with numbers first, then letters. For example, on hearing

4, D, 7, G, the subject should respond 4, 7, D, G. This requires the subject to keep the items in mind long enough to rearrange their order. The span is increased until the subject fails all three items on one length. Normative data have shown a moderate effect of age on the Letter Number Sequencing task (Lezak et al., 2004).

APPENDIX III

Dissertation Hypotheses

Aim 1: To ask the question whether SZ and BDP, both psychotic disorders, will show a similar deficit on measures of eye movements using a novel eye tracking task of predictive pursuit compared with healthy comparison subjects.

Hypothesis 1: It was predicted that performance on predictive pursuit at target velocity 18.7 degrees per second will be worse in participants with psychosis (both SZ and BDP) compared with HC.

Hypothesis 2: Further, we predict a similar but milder impairment to be seen at 9.9 degrees per second target velocity.

Aim 2: To compare performance of individuals with psychosis on neuropsychological tasks of working memory with healthy comparison subjects.

Hypothesis 3: Individuals with psychosis will perform worse than healthy comparison subjects on Wechsler Spatial Span and Letter Number Sequencing.

Exploratory Aim: To compare performance of individuals with psychosis with healthy comparison subject on neuropsychological tasks tapping the areas of episodic memory, attention/vigilance, and executive functioning.

Aim 3: To further characterize the specific nature of the deficit in predictive pursuit

Hypothesis 4: Based on anatomical correlates, an association is predicted between deficits in predictive pursuit, as measured by predictive pursuit gain at 18 degrees/second, and the two neuropsychological tasks of working memory.

APPENDIX IV: ADDITIONAL RESULTS

Preliminary Data Analysis of Eyetracking Data from Family Members

This section describes the preliminary analysis of data from first degree family members of the patient group. This data is preliminary and is still under analysis.

Usable eye movement data was available for 18 family members of BDP probands (BPF) and 21 family members of SZ probands (SZF). Of these, 3 BPF did not complete the neurocognitive battery, and 1 BPF did not complete the entire clinical assessment battery.

Analyses were conducted by diagnostic group (BPF vs. SZF vs. HC) as well as by psychosis dimension. The psychosis dimension analysis contrasted all psychosis probands (SZ and BDP combined), all relatives, and HC. Three family members had Axis I psychotic diagnoses (2 BPF and 1 SZF); these 3 volunteers were not included in the diagnostic category analysis and were included with psychosis probands in the dimension analysis.

As in the analysis of proband data, subjects whose average velocities were based on less than 5 trials with valid data were not included in analysis (in the 18.7 degrees/second condition, this excluded 4 individuals: 3 BPF and 1 SZF; in the 9.9 degrees/second condition, 12 individuals were excluded, 5 BPF and 7 SZF).

Preliminary analysis of eye movement data by diagnostic group (SZF, BPF

and HC) did not show significant differences on predictive pursuit velocity (F (2, 28) = 1.01, NS) or maintenance pursuit velocity at 18 degrees/second (F = (2, 28) = 1.12, NS). Analysis of eye movement data by psychosis dimension showed significant group differences in predictive pursuit velocity (F (2, 101 = 4.23, $p <$ .05); post hoc Tukey HSD test showed these differences were between the psychosis probands and HC ($p < .05$) but not between the relatives and HC or relatives and probands. The same pattern was observed in maintenance velocity data.

The small number of HC limited statistical power in these preliminary analyses, and future investigations will include additional HC volunteers.

APPENDIX V: ADDITIONAL FIGURES

Figure A. Velocity Graph of an Artifact (Blink)

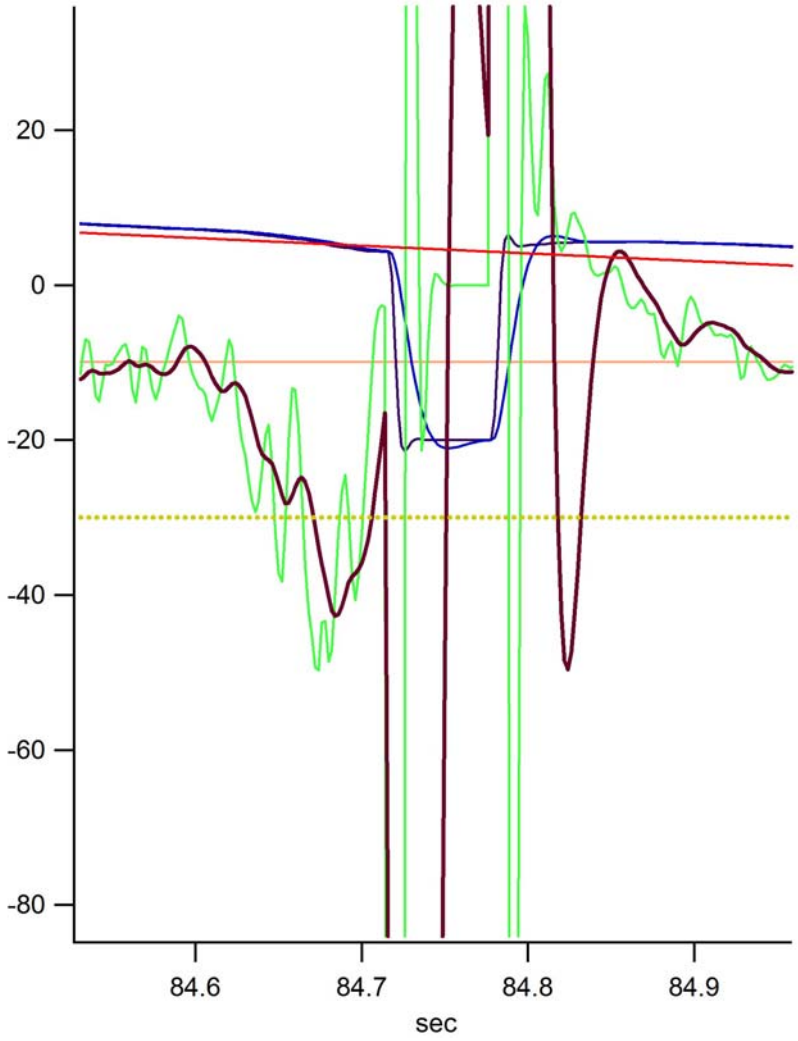

Figure B. Velocity Graph of a Saccade