LEVERAGING PUPILLOMETRY TO EVALULATE TRANSDIAGNOSTIC MOTIVATIONAL NEGATIVE SYMPTOM MECHANISMS IN SCHIZOPHRENIA AND BIPOLAR DISORDER

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ABSTRACT

Motivational negative symptoms of schizophrenia (SZ) are predictors of poor functional outcome and are notoriously difficult to treat. These symptoms also occur in bipolar disorder with psychotic features (BPP), although it is unclear how they are developed and maintained both within and across diagnoses (SZ or BPP). Pupillometry can be used as a tool to clarify said mechanisms. Blunted dilation as a function of cognitive demands has been interpreted as a metric of diminished effort while blunted constriction to light has been interpreted as a metric of blunted autonomic balance and both have been found to be reduced in individuals with schizophrenia and related to increased motivational negative symptom severity. However, associations between these two sets of findings in the same individuals have not yet been investigated. Blunted cognitive-related dilation has also been observed in individuals with BPP compared to healthy controls, but relationships with motivational negative symptoms have not been examined. To investigate these two lines of research, I first computed correlations between blunted constriction and blunted dilation in individuals with schizophrenia (n = 55) and then used multi-level modeling (MLM) to determine whether motivational negative symptoms in BPP (n = 30) and SZ (n = 55) are significant predictors of blunted dilation. Results indicate a significant positive correlation between both pupil metrics not explained by motivational negative symptoms. Blunted dilation was replicated in SZ relative to HC but was not found in BPP relative to HC nor SZ. Motivational negative symptoms did not predict blunted dilation. These findings provide, for the first time, evidence for a shared mechanism linking blunted pupil response to light and cognitive demands in SZ. Individuals with schizophrenia may show reduced attentional resource allocation to internal versus external goals. No conclusion can be made as to pupil/symptom relationships in SZ nor transdiagnostically in BPP.

This thesis is dedicated to Olivier and Beverley Delay and my loving brothers Matthieu and Joven. Thank you for always supporting my goals and aspirations.

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1. Introduction

Schizophrenia is a severe mental illness affecting 0.25 to 0.64% of the US population (Kessler et. al, 2005; Wu et. al., 2006). Although prevalence rates are relatively low, the burden related to the illness is tremendous. Schizophrenia is responsible for 12.9% of years lived with disability worldwide (Vos et. al., 2017), and life expectancy is reduced by up to 20 years (Correll et. al., 2022) due in part to increased risk for co-morbid medical conditions (Suvisaari et. al., 2016; Kritharides, Chow & Lambert, 2017; Li et. al., 2014) and suicide (Hor & Taylor, 2010). Full symptom remission is rare, even with treatment (Robinson et. al., 2004; Jääskeläinen et al., 2013) and even after achieving symptomatic remission (Lambert et. al., 2010), individuals living with the diagnosis are faced with a whole host of economic (Lin et. al., 2022; Foster et. al., 2012; Chong et. al., 2016), and social (Awad & Voruganti, 2012; Palumbo et. al., 2015) difficulties that negatively impact quality of life. Treatment development is thus at the forefront of clinical needs; however, a lack of understanding into mechanisms of symptoms complicates this endeavor.

Schizophrenia is a highly heterogenous disorder, both symptomatically and genetically (Takahashi, 2013). A diagnosis of schizophrenia is based upon the presence of positive symptoms and/or a combination of negative and/or disorganized symptoms (Glasheen et.al., 2016). Positive symptoms include hallucinations and delusions which are additive and disorganized symptoms reflect disorganized thinking patterns. Negative symptoms are characterized by lessening or absence of normal behavior and functions directly related to motivation, interest, and verbal/emotional expression (Correll & Schooler, 2020). These negative symptoms are not only especially prevalent (Azar et. al., 2018; Bobes et. al., 2009), persisting outside of periods of acute psychosis (Buchanan, 2007), but are significant predictors of

functional outcome (e.g., recovery and social and occupational functioning, Piskulic et. al., 2012; Campellone, Sanchez & Kring, 2016; Devoe et. al., 2020; Ventura et. al., 2009; Rabinowitz et. al., 2012; Hunter & Barry, 2012; Foussias et. al., 2009; Foussias et. al., 2014) over and above the more outwardly apparent positive symptoms (Buchanan, 2007). The omnipresent and debilitating nature of negative symptoms in schizophrenia therefore makes them a key treatment target (Sarkar et. al., 2015; Strauss et. al., 2021; Boonstra et. al., 2012), and of central focus to many researchers in the field of psychosis. However, efforts to treat negative symptoms have been unsuccessful. Research has shown only moderate effects of antipsychotic medications on negative symptoms (Leucht et. al., 2009; Hasan et. al., 2013; Harvey, James, & Shields, 2016; Möller & Czobor, 2015), with some antipsychotics even exacerbating these symptoms (Aleman et. al., 2017). While existing studies have attempted to target negative symptoms during cognitive behavioral therapy (Velthorst et. al., 2015; Klingberg et. al., 2011; Velligan et. al., 2015), little consensus exists as to whether symptom reductions are persistent or clinically meaningful. Therefore, although negative symptoms are central to impaired functioning, there is no consensus method to effectively treat them.

A lack of conceptual clarity regarding negative symptoms (Dollfus & Lyne, 2017) has stymied treatment development efforts. While negative symptoms were traditionally considered a unidimensional construct (Arndt, Alliger & Andreaasen, 1991; Grube, Bilder & Goldman, 1998), more recent evidence supports two (or more) distinct negative symptom domains: diminished expression (expressive negative symptoms) and motivation and pleasure (motivational negative symptoms) (Marder & Gladerisi, 2017; Strauss et. al., 2019). These two domains contain subfactors, such as: blunted affect (reduced facial and vocal expression) and alogia (decreased thought and speech production) which make up expressive negative symptoms,

and asociality (difficulty engaging or persisting in social interaction), anhedonia (reduced experience of pleasure from previously enjoyable activities), and avolition (disturbances in motivation) which make up motivational negative symptoms. These motivational negative symptoms are most strongly associated with aspects of functioning (Kring et. al., 2014; Strauss et. al., 2013) and thus may be key intervention targets (Thonon et. al., 2020). Within these motivational negative symptoms, avolition may be a particularly important target, as the presence of avolition is thought to cause or worsen other negative symptoms (Strauss et. al., 2021), and successful remediation of avolition has been shown to lead to global improvements in the entire constellation of negative symptoms. These findings suggest that improvements in avolition should be expected to lead to cascading improvements in negative symptoms and functional outcome, establishing the need for targeted interventions specifically aimed at reducing avolition.

To develop effective treatments for avolition, we must first understand the mechanisms leading to its occurrence. Pupillometry, a non-invasive tool capable of indexing internal functioning (Laeng & Alnaes, 2019; Mathôt, 2018; Unsworth & Robison, 2018) may provide a feasible means of doing so for several reasons. First, pupil metrics can serve as an objective readout of cognitive and emotional processes directly affected by motivational negative symptoms (Kring & Barch, 2014; Brown & Pluck, 2000). Previous studies have shown that pupil size indicates changes in attention (Kang, Huffer & Wheatley, 2014; Wierda, van Rijn & Taatgen, 2012), decision making (de Gee, Knapen & Donner, 2013; Gilzenrat et. al., 2010; Jepma & Nieuwenhuis, 2011; Einhäuser, Koch & Carter, 2010), cognitive control (Mackie, Van Dam & Fan, 2013; Kool et. al., 2017), emotional processing (Vanderhasselt et. al., 2014) and emotional regulation (Kinner et. al., 2017).

Second, pupil pathways are incredibly well understood (Einhäuser, 2017) and autonomic nervous system activity, which is dysregulated in individuals with schizophrenia (Stogios et. al., 2021), is reflected in pupil size (Turnbull et. al., 2017). Pupil size is controlled by two muscles, the iris sphincter muscle (initiation constriction) and the iris dilator muscle (initiation dilation). The iris sphincter muscle is innervated by the parasympathetic branch of the autonomic nervous system, which regulates the body's "rest and digest" activities. During constriction, light hitting the retina is turned into neuronal impulses which are sent to the pretectal nucleus, innervating the Edinger-Westphal (EW) nucleus. The EW nucleus then releases acetylcholine at multiple synapses, innervating the iris sphincter muscle. On the other hand, the iris dilator muscle is innervated by the sympathetic branch of the autonomic nervous system, which is responsible for the body's "fight or flight" response. During dilation, the iris dilator muscle is innervated via an all-excitatory projection from the locus coeruleus (LC) involving release of norepinephrine at multiple synapses to preganglionic sympathetic neurons which then release acetylcholine at multiple synapses to innervate the iris dilator muscle. In addition, the LC also projects an inhibitory response to the EW nucleus, inhibiting parasympathetic constriction. Higher cortical regions also influence pupil size, through projections to the LC (Joshi & Gold, 2020).

Pinpointing when and where cognitive and emotional processes are affected through pupil motility may therefore allow us to make rich mechanistic inferences and identify key neural circuits implicated in avolition and the broader negative symptom construct. It is furthermore a feasible and non-invasive measurement tool.

Current efforts towards understanding the etiology of negative symptoms broadly using pupillometry as a tool have focused on cognitive changes and the pupil's response to cognitive effort. In healthy individuals, the pupil dilates in response to increased cognitive demands (Van

der Wel & van Steenbergen, 2018), indicating increased cognitive effort. However, individuals with schizophrenia show reduced dilation (potentially reflecting reduced effort) on cognitive tasks (Strauss et. al., 2016), and less cognitive-related dilation has been shown to relate to more severe motivational negative symptoms, albeit inconsistently (McGovern et. al., 2020; Granholm et. al., 2016; Granholm et. al., 2007; Granholm et. al., 1998; Granholm et. al., 2004). Difficulty assessing the subjective costs of cognitive effort (Culbreth, Westbrook & Barch, 2016), anticipating future rewards (Gard et. al., 2007), and increases in defeatist performance beliefs (i.e., over-generalized negative thoughts about one's ability to successfully perform goal-directed behavior, Couture et. al., 2011; Grant & Beck, 2009) serve as potential explanations for this association between pupil dilation and motivational negative symptoms. In addition, as processing demands of cognitive tasks increase (Granholm et. al., 2018) individuals with schizophrenia show an additional reduced pupil dilation response, reinforcing the notion that individuals with schizophrenia may tend to "give up" as tasks become more difficult and require more mental resources.

The pupil not only dilates during cognitively demanding tasks, but even during basic action preparation (Moresi et. al., 2008; Wang et. al., 2015), signaling that individuals *prepare* to allocate attentional and cognitive resources in anticipation of future goals. Individuals with schizophrenia show deficits in willed activity reflecting an inability to link goals with actions required for their initiation (Langdon et. al., 2007). The ability to recruit attentional resources to initiate actions may therefore be present, but the motivation to *prepare* for effortful action may be impaired. Indeed, individuals with schizophrenia are less likely to prepare to engage attentional resources to cognitively difficult tasks (Reuter et. al., 2006) and show decreased pupil dilation during the preparation of an eye movement compared to healthy controls (Karpouzian-

Rogers et. al., 2022). Our lab has expanded on these findings, showing that reductions in pupil dilation during action preparation are associated with greater motivational negative symptom severity (Thakkar et. al., 2018). Taken together, the pupil findings reviewed above would suggest that individuals with schizophrenia show reductions in effort and motivation both *during* and *in preparation* for cognitive tasks, and that these reductions are related to motivational negative symptoms. Further research is thus required to investigate whether these reductions are related to avolition specifically, however.

Potentially complicating the interpretation that relationships between reduced cognitive related dilation and motivational negative symptoms can be explained by altered effort and resource allocation are recent findings from our lab showing that motivational negative symptoms are not just related to cognitive and preparatory related dilation, but also to a blunted response to light in people with schizophrenia. Individuals with schizophrenia show impairments in the pupil light reflex (PLR) including reduced constriction in response to light (Bär et. al., 2008; Okada et. al., 1978; Steinhauer et. al., 1979), longer constriction latency (Okada et. al., 1978), and slower re-dilation to light offset (Rubin & Barry, 1976). More recently, smaller constriction amplitude has been associated with greater severity of motivational negative symptoms (Fattal et. al., 2022) and working memory deficits. In an attempt to provide a parsimonious explanation for the blunted pupil light reflex, Fattal et. al., 2022 proposes disordered reactivity of the LC in people with schizophrenia. It may show greater reactivity to an external stimulus, such as light, leading to increased dilation (and thus a reduced PLR). At the same time, there may be decreased LC reactivity based on internal goals leading to a reduced ability to recruit and allocate adequate cognitive resources as well as initiate cognitive effort and thus resulting in blunted cognitive dilations. If this is the case, blunted pupil light reflex and

blunted cognitive dilation—both of which have been related to the severity of motivational negative symptoms—should therefore be related in the same group of participants.

This question formed one aim of the current study. In patients with a diagnosis of schizophrenia, I aimed to replicate findings of blunted preparatory pupil dilation during a cognitive task and blunted constriction to light relating to motivational negative symptoms (Thakkar et. al., 2018; Fattal et. al., 2022). I then tested whether putatively blunted preparatory pupil dilation is related to blunted pupillary constriction to light (Fattal et. al., 2022) in the same group of individuals. The presence of such a relationship may suggest a similar mechanism for these two sets of pupil findings in individuals with schizophrenia and thus a parsimonious explanation for correlations between motivational negative symptoms and a blunted pupillary response to both light and the demand to act. In line with the findings of Strauss et. al., 2021, as an exploratory aim, I investigated whether blunted cognitive-related dilation and blunted constriction are related to avolition specifically.

In addition to investigating the mechanisms of avolition, I explored the transdiagnostic nature of the relationship between motivational negative symptoms and blunted pupil dilation. Negative symptoms are not unique to individuals with schizophrenia, but also present themselves in bipolar disorder (Popolo et. al., 2017), especially in bipolar disorder with psychotic features (Lindenmayer et. al., 2008). These individuals show similar positive and negative symptom levels (Lindenmayer et. al., 2008) as well as substantial genetic overlap (Tamminga et. al., 2013) with individuals diagnosed with schizophrenia. However, there is evidence to suggest the nature and mechanisms of negative symptoms may be different in these two conditions. For one, negative symptoms appear to be less related to each other in individuals with schizophrenia than in bipolar disorder (Strauss et. al, 2019), making them more treatment resistant (Zamani et. al.,

2018). In addition, avolition is tightly coupled and strongly related to other negative symptoms (i.e. central) in schizophrenia (Strauss et. al, 2021), whereas anhedonia is central in bipolar disorder (Strauss et. al., 2019), indicating that treatments for schizophrenia and bipolar disorder should target distinct negative symptom mechanisms. Given the limited research investigating negative symptoms transdiagnostically, further exploration of negative symptom mechanisms may provide substantial clinical implications.

Examining pupillary correlates of negative symptoms in both bipolar disorder and schizophrenia might shed light on shared versus unique mechanisms of negative symptoms across these two disorders. Recent research investigating preparatory pupil dilation in individuals with schizophrenia and bipolar disorder suggests that both groups show significantly reduced pupil dilation at equivalent magnitudes when compared to healthy controls (Karpouzian-Rogers et. al., 2022). However, the authors failed to find a significant association between blunted preparatory dilation and psychotic symptom severity, perhaps due to a lack of separation between negative and positive symptoms. As negative symptoms comprise both expressive and motivational and previous studies have reported relationships between pupil kinematics and only motivational negative symptoms (Granholm, et. al., 2016; Thakkar et. al., 2018), Karpouzian-Rogers et. al., 2022 may have benefited from exploring this same relationship in their study. In addition, the authors failed to report whether the relationship between psychotic symptoms and pupil dilation differs between diagnostic groups. It may be the case that individuals with schizophrenia and bipolar disorder show different relationships between preparatory dilation and motivational negative symptoms due to different symptom mechanisms.

The present study therefore also aimed to evaluate the transdiagnostic nature of the preparatory pupil dilation- motivational negative symptom relationship in people with

schizophrenia and bipolar disorder. I first expected to replicate findings of blunted preparatory pupil dilation in both individuals with schizophrenia and bipolar disorder. I then examined whether putative relationships between motivational symptoms and preparatory pupil dilation differed in both groups. I expected that if blunted pupil dilation is associated with motivational negative symptoms in a transdiagnostic fashion, that there would be an effect of motivational negative symptoms on pupil dilation but no diagnosis-by-symptom-severity interaction (that is, the relationship is the same in both groups). If pupil-negative symptom relationships differed across diagnostic categories, I expected a diagnosis-by-symptom-severity interaction (e.g., association between pupil dilation and motivational negative symptoms in schizophrenia but not in bipolar disorder). As an exploratory aim, I investigated whether an avolition and blunted preparatory dilation relationship existed in individuals with schizophrenia and/or transdiagnostically in individuals with bipolar disorder with psychotic features.

Overall, the current project aimed to elucidate potentially transdiagnostic mechanisms of motivational negative symptoms. Tying blunted pupil dilation with blunted constriction in individuals with schizophrenia, both of which represent objective measures of autonomic function, could allow us to infer that deficits in motivation may be linked to deficits in autonomic regulation. In my second aim, investigating the transdiagnostic nature of the relationship between motivational negative symptoms and cognitive-related pupil dilation may shed light on shared and unique mechanisms of these symptoms.

2. Methods

2.1 Overview

Pupil dilation in preparation to make an eye movement was measured in participants with schizophrenia or schizoaffective disorder (SZ), bipolar disorder with a history of psychotic features (BPP), and demographically matched healthy controls (HC) using the saccadic double-step task. The pupil light reflex (PLR) was measured in individuals with schizophrenia or schizoaffective disorder and demographically matched healthy controls only, using a light stimulation protocol. Preparatory dilation and PLR were measured during separate sessions that may or may not have occurred on the same day. The samples of HC and SZ in these two studies were largely overlapping.

2.2 Participants

Eighty-four individuals with schizophrenia spectrum disorders (SZ), thirty-nine individuals with bipolar disorder with psychotic features (BPP), and sixty-nine healthy controls (HC) completed the saccadic double-step task and/or the pupil light reflex. Participants were recruited from outpatient mental health facilities, existing research registries and subject pools, and community advertisements in the greater Lansing, MI area and were between the ages of 19 – 59. Diagnoses for all groups were based upon interviews conducted utilizing the electronic version of the Structured Clinical Interview for DSM-5 (SCID-5), medical records, and collateral informants. Groups were matched on age, race, ethnicity, and gender (see Table 1). Years of education ($F(2,155) = 29.45$, $p < .001$) and IQ ($F(2,149) = 3.29$, $p = .04$) did differ across the three groups. Post-hoc comparisons revealed that SZ had fewer years of education than both HC ($t(121) = -7.24$, $p < .001$) and BPP ($t(110) = - 3.23$, $p = .002$), and lower IQ scores than BPP ($t(105) = -3.22$, $p < .001$) but not HC ($t(116) = -1.65$, $p = 0.51$). In terms of clinical variables, SZ

had higher scores for SAPS total ($t(107) = 2.69$, $p = .01$), SANS total ($t(106) = 2.35$, $p = .02$), SANS EXP $t(106) = 3.77$, $p < .001$, Alogia $t(106) = 2.94$, $p < .005$, Flat Affect $t(106) = 3.63$, $p < .001$, and BPRS Total $t(107) = 2.72$, $p = .01$. Finally, normalized antipsychotic dose was higher in SZ ($t(109) = 2.98$, $p = <.005$. See Table 1 for descriptive statistics and group comparisons.

2.3 Exclusion Criteria

Exclusion criteria for all participants included age <18 or >60, a history of head injury with loss of consciousness > 1-hour, diagnosed neurological disorder, moderate or severe substance use disorder within the past 6 months, estimated premorbid IQ < 70 using the Wechsler Test of Adult Reading (Crawford et. al., 1992), and vision that was not normal or corrected to normal. Healthy controls were additionally excluded for current history of mental illness or psychotropic use, and first-degree relatives with a history of schizophrenia spectrum or bipolar disorder. All participants gave written informed consent and were reimbursed for participation. The study was approved by the Michigan State University Institutional Review Board.

2.4 Clinical Assessments

Positive and negative symptoms of schizophrenia were assessed using the following measures: the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1986), and the Scale for Assessment of Negative Symptoms (SANS; Andreasen, 1983). General psychiatric symptoms were evaluated with the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962). To specifically explore motivational negative symptoms, two subscales were derived based on a previous factor analytic study of the SANS (Strauss et. al., 2018): the expressive subscale (EXP) comprising blunted affect and alogia, and the motivation and pleasure subscale (MAP) comprising anhedonia, asociality, and avolition. As only the MAP subscale was our

measure of interest, all additional symptom analyses were exploratory, including the primary exploratory aim investigating avolition.

In further exploratory analyses, manic and depressive symptoms were assessed using the Young Mania Rating Scale (YMRS; Young et. al., 1978) and the Hamilton Rating Scale for Depression (HRSD; Hamilton et. al., 1960). Working memory was assessed through the Digit Span task, as it is the most frequently used paradigm in studies looking at effort-related dilation (Fish and Granholm, 2008; Granholm et. al., 2016).

2.5 Additional Measures

To account for potential medication confounds (e.g. the effects of medication on pupil size (Loga, Curry & Lader, 1981)), chlorpromazine (CPZ) equivalent dosages were calculated for each patient (Andreasen et. al., 2010). Illness duration was calculated as the difference between the date of assessment and the date of first diagnosis. Premorbid IQ was assessed using the Wechsler Test of Adult Reading (Wechsler, 2001), and years of education were provided through participant self-report.

2.6 Experimental Paradigms and Procedures

2.6.1 Double-Step Task

Eye position and pupil diameter were measured using the EyeLink 1000 (SR Research) eye tracker, at a sampling rate of 500Hz with average gaze position error < 0.5^{O}, noise limited to < 0.01^{O} and minimum amplitude criterion (2^{O} visual angle). Participants were seated 59 cm from a 22-inch CRT monitor (1280 x 960 resolution; 85 Hz refresh rate), with head position stabilized using a chinrest. All participants were tested in a fully dark room with no source of light except the computer monitor, which was kept at a consistent brightness (set to '0'). In addition, a three-stop neutral density filter was used to reduce stray light emitted from the monitor.

MATLAB Psychophysics and EyeLink toolboxes (MathWorks, Portola Valley, CA) were used to present stimuli and collect responses on the double-step task. Individuals were first asked to initiate a calibration procedure by pressing the space bar. After calibration was completed and prior to starting each trial, a drift check procedure required participants to fixate on a central white ring and press the space bar. If the eye position exceeded a maximum distance from the white ring, the procedure was repeated. If the procedure failed a second time, the experimenter re-performed the calibration procedure.

After calibration, participants were asked to complete a total of 28 practice trials (8 easy, 20 hard). Trials began with a fixation period of a random duration between 2 to 3 seconds. Then, two visual targets were presented, and subjects were instructed to look at these two visual targets presented 12 degrees of visual angle from fixation in succession, as quickly as possible. On easy trials, the first target (T_1) stayed on the screen for 1000ms. On hard trials, T_1 was presented for 120ms. The second target (T_2) always flashed for 50ms. A visual representation of the task is available in Figure 1.

Figure 1: Visual representation of easy and hard trials on the saccadic double-step. Participants were asked to make a visual saccade to T_1 first followed by T_2.

Following practice, participants completed 4 to 8 experimental blocks, with each block consisting of 96 (easy and hard randomized) trials. Participants were given no a priori indication

as to upcoming trial difficulty. If participants visual saccade to the first target (to T_1) was below 60% across all trials within the same block, additional blocks were performed until a total of four valid blocks were achieved. As performance and saccade engagement on the saccadic double-step was not a measure of interest, and fixation did not vary across blocks, all completed blocks across all participants were included in my analyses.

2.6.2 Light Stimulation Protocol

Per previous study procedures (Fattal et. al., 2022), participants were seated in a dark room (0.2Lux of ambient light). A handheld NeurOptics PLR 3000 pupillometer (30 Hz sampling rate, accuracy +/- 0.03mm) controlled light presentation and measured pupil diameter. Participants were instructed to keep their eyes open, look straight ahead, and blink minimally throughout the 5-second light protocol. Upon the start of the measurement, a 451-lux pulse of light was flashed for 1s. The light remained off for the remaining 4s. For most participants, this procedure was repeated twice per eye, resulting in four total measurements. If the pupillometer flagged the data as unusable, the measurement was repeated.

2.7 Data Analysis

2.7.1 Double-Step Task

Analysis of pupil dynamics was conducted using MATLAB 2022b. As described above, each trial was initiated by the participant's key press that formed the end of a successful drift correction procedure and that instantly triggered an on-screen change from the drift-correction annulus to the task's initial central fixation spot, which indicated to the participant that they would soon be presented with visual targets to which they should make an eye movement. This fixation window varied randomly between 2-3 seconds on each trial to control for anticipatory effects. The change in pupil size during the first 2 seconds of the fixation window was my

measure of interest. In addition, due to the lack of a priori signaling of upcoming trial difficulty, no differences in preparatory pupil between easy and hard trials were anticipated. As such, trial difficulty was not subsequently considered as a variable of interest.

Prior to any statistical analysis, pupillary measurements were smoothed using a low-pass Butterworth filter with a cutoff frequency of 100Hz and down sampled using a bin size of 20ms. Pupil dilation was then quantified on each trial as the difference in mean pupil diameter between the last 100ms of the fixation period and baseline (mean diameter in the first 100ms after the start of central fixation). As pupil diameter is significantly influenced by both blinks (Knapen et. al., 2016) and gaze position (Gagl et. al., 2011), trials in which the subjects blinked (full or partial blink) or made a deviation from fixation of $>2^{o}$ (a visual saccade) were excluded from all analyses. Full blinks were identified using the automated Eyelink procedure. Partial blinks not captured by the built-in blink detection algorithm were identified by computing velocity traces for all remaining trials across all participants. Trials showing abnormally large positive or negative velocities in subsequent bins (5 standard deviations above or below the mean average velocity between two bins for all trials across all participants) were then removed. In addition, trials in which baseline pupil values fell above or below 4 standard deviations from mean baseline pupil values at the subject level were also removed to control for blinks occurring during the transition from the drift correction to the central fixation cross). Participants were then removed from analyses if they had fewer than 10 usable trials. As a result, data from 15 SZ, 7 BPP and 7 HC were removed from all analyses. Information about excluded participants can be found in Table 2. There were no significant differences in individuals included or excluded from the study for all three groups (SZ, BPP or HC).

2.7.2 Light Stimulation Protocol

Analyses of pupil dynamics were conducted using MATLAB 2022b. In line with Fattal et. al., 2022, baseline pupil size was calculated as the mean diameter during the first 150ms of the measurement, which is prior to the onset of the pupil response to even an intense light stimulus (Ellis, 1981). Constriction amplitude was quantified as the absolute value of the difference between the maximally constricted pupil diameter and initial diameter. Pupillary measurements were smoothed using a low-pass Butterworth filter with a cutoff frequency of 4Hz. Velocity and acceleration traces were then calculated to identify blinks (successive >3x interquartile range negative-then-positive outliers in the velocity trace occurring within 0.5 seconds of one another). If blinks occurred before initial constriction to light, the entire trial was removed. If blinks occurred after redilation onset, dilation metrics were removed but constriction metrics were kept. Then, pupil size time courses were averaged across each measurement trial for each subject. Information about excluded participants can be found in Table 3. There were no significant differences in individuals included or excluded from the study for all three groups (SZ, BPP, HC).

2.8 Statistical Analysis

Prior to my main analyses, independent samples t-tests and Chi Square Goodness of Fit tests were conducted to compare demographic and clinical characteristics of the BPP and HC groups to the SZ group. All analyses were conducted using SPSS Statistics Version 28.0 (IBM, Armonk, NY).

2.8.1 Relating Preparatory Pupil Dilation and Pupil Light Reflex in HC and SZ

All analyses were conducted using SPSS Statistics Version 28.0. First, independent samples t-tests were conducted to investigate differences between SZ and HC in mean

preparatory pupil dilation (averaged across trials for each subject) on the double-step task and constriction amplitude on the pupil light reflex. Then, Spearman correlations between these two pupil parameters and motivational negative symptom severity were evaluated using Spearman's rho (r_s) for SZ. Exploratory Spearman's correlations were conducted replacing motivational negative symptom severity with avolition. Finally, correlations between constriction amplitude on the light stimulation protocol and mean preparatory pupil dilation (averaged across trials for each subject) on the double-step task were evaluated using Spearman's rho (r_s) for SZ and HC separately. Fisher's R to Z test was subsequently performed to determine the significance of the difference between these two correlations.

2.8.2 Preparatory Pupil Dilation in SZ, BPP, and HC: Differences and Symptom Correlates

Multilevel modeling (MLM) was utilized to examine group differences in preparatory pupil dilation using the nlme package (version 3.1-162) in R Studio. MLM is well suited for analyzing nested data, which was the case in this study, as trials (level 1) were nested within participants (level 2). In my first model, I tested the effect of diagnostic group on pupil dilation using maximum likelihood (ML) estimation to account for missing data and provide an unbiased estimate of model parameters. When interpreting the multilevel model results, I focused on one main parameter: the slope of the change in pupillary dilation. The slope indexes how much the estimated value of pupillary dilation is expected to change when moving from our reference category (HC) to our other categories (SZ and BPP). A positive value indicates that, on average, individuals in either the SZ or BPP group show greater pupil dilations relative to the HC group. A negative value would instead mean reduced pupillary dilation relative to the HC group. To account for individual differences in performance generally, random effects included variance

for the intercepts. In sum, the first model can be expressed in the following regression equations, where i stands for the trial, and j stands for the participant:

Lower level (i.e. trial-level) equation:

$Y_{ij} = \beta_{0j} + \beta_{1j} (Diagnosis_{ij}) + e_{ij}$

Higher level (i.e. subject level) equation:

$\beta_{0j} = \gamma_{00} + \gamma_{01} (Diagnosis_{ij}) + u_{0j}$

Grand mean centered CPZ dosages were then entered into the model to control for the effects of medication when comparing SZ to BPP. When there were significant interactions, I computed simple slopes. In other words, I investigated the effect of predictor A on my predicted variable within different levels of predictor B, by computing simple regression slopes for selected values of B. As predictor B was continuous (CPZ dosages), I derived simple slopes for high (i.e. 1SD above the mean) and low (i.e. 1SD below the mean) values of B and conducted post-hoc tests to break down all interactions.

Using MLM, I next investigated whether pupillary dilation varied as a function of motivational negative symptom severity in individuals with SZ or BPP only. All main effects and interactions were included in this model, and motivational negative symptom severity was grand mean centered. Much like my first model, random effects included variance for the intercepts. When a significant interaction was found, I computed simple slopes. As predictor B was continuous (motivational negative symptom severity), I derived simple slopes for high (i.e. 1SD above the mean) and low (i.e. 1SD below the mean) values of B and conducted post-hoc tests to break down all interactions. In sum, the second model can be expressed in the following regression equations, where i stands for the trial, and j stands for the participant:

Lower level (i.e. trial-level) equation:

$Y_{ij} = \beta_{0j} + \beta_{1j}$ (*Diagnosis*$_{ij}$) + β_{2j} (Motivational Negative Symptom Severity$_{ij}$) + β_{3j} (Motivational Negative Symptom Severity$_{ij}$) + e_{ij}

Higher level (i.e. subject level) equation:

For $k = 0 – 3$:

$\beta_{0j} = \gamma_{00} + \gamma_{01}$ (*Diagnosis*$_{ij}$) + u_{0j}

Grand mean centered CPZ dosages were then entered into a separate model to control for the effects of medication. I ran additional exploratory models by entering avolition scores into the model, replacing motivational negative symptom severity and repeated the process with the other symptom measures.

3. Results

3.1 Relating Preparatory Pupil Dilation and Pupil Light Reflex in HC and SZ

Individuals with schizophrenia (SZ) showed significantly blunted preparatory dilation ($t(89) = 4.04$, $p < .001$; Figure 2) and constriction amplitude ($t(90) = 2.21$, $p = .03$; Figure 3) when compared to healthy controls (HC).

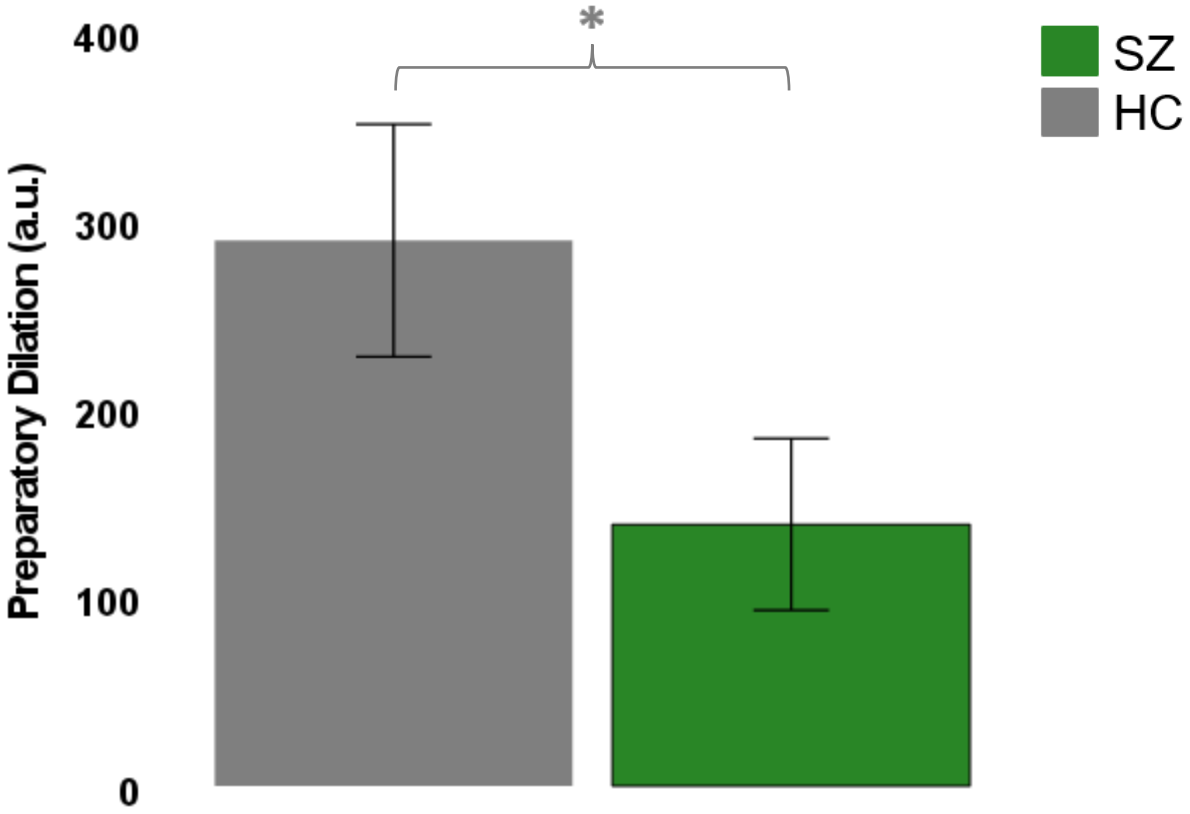

Figure 2: Differences in preparatory dilation (in arbitrary units) for both diagnostic groups (HC and SZ). Error bars represent 95% confidence intervals. SZ show blunted preparatory dilation. * indicates a significant difference between groups at $p < .005$.

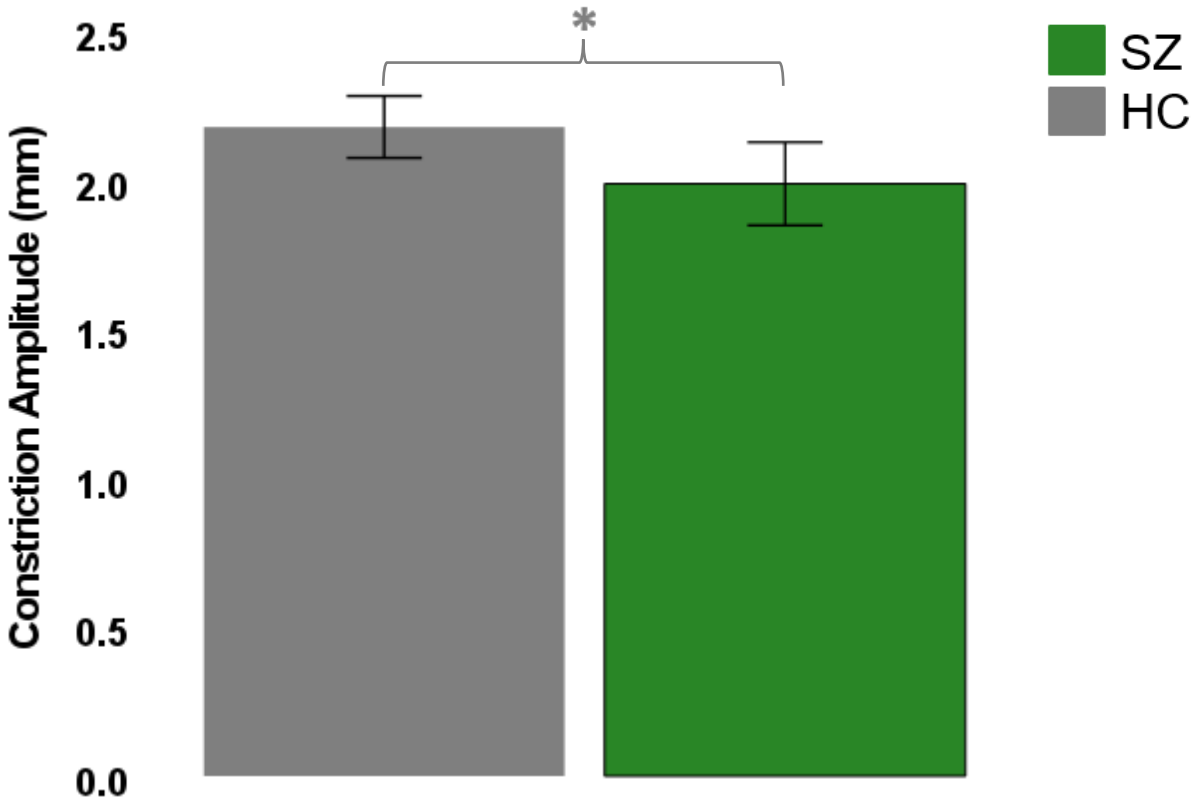

Figure 3: Differences in constriction amplitude (in mm) for both diagnostic groups (HC and SZ). Error bars represent 95% confidence intervals. SZ show blunted constriction amplitude. * indicates a significant difference between groups at $p < .005$.

Constriction amplitude ($r_s(54) = -.32$, $p = .02$; Figure 4) but not preparatory pupil dilation ($r_s(55) = -.02$, $p = .91$; Figure 5) was negatively associated with motivational negative symptom severity suggesting that as individuals with schizophrenia showed increased motivational negative symptom severity, these same individuals showed reductions in constriction amplitude. Exploratory analyses revealed no significant correlation between avolition, specifically, and either constriction amplitude ($r_s(54) = -.25$, $p = .07$) or preparatory pupil dilation ($r_s(55) = .104$, $p = .45$).

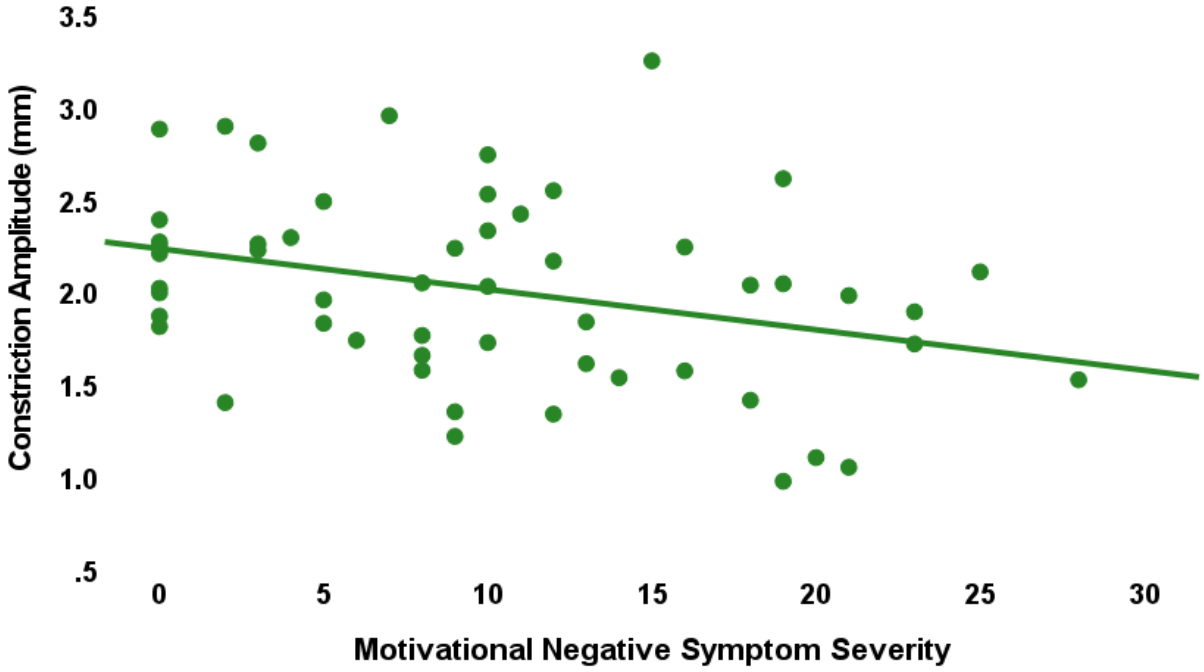

Figure 4: Correlation between constriction amplitude (in mm) and motivational negative symptom severity for SZ. SZ showed a significant negative correlation between amplitude and symptom severity.

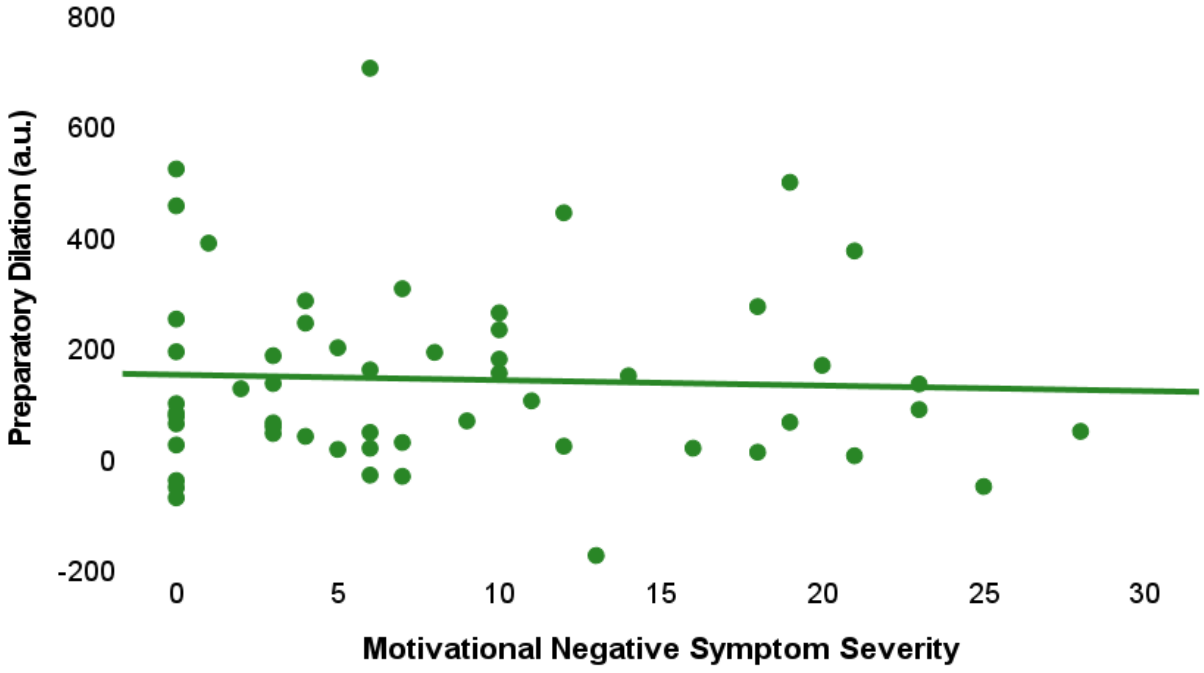

Figure 5: Correlation between preparatory dilation (in arbitrary units) and motivational negative symptom severity for SZ. SZ showed no correlation between preparatory dilation and motivational negative symptom severity.

Preparatory pupil dilation was positively associated with mean constriction amplitude in SZ ($r_s(33) = .48$, $p = .01$; Figure 6) but not HC ($r_s(24) = .13$, $p = .55$; Figure 6), indicating that individuals with schizophrenia who showed greater constriction to light also showed greater preparatory pupil dilation. Using partial correlation, this relationship in SZ persisted when controlling for normalized antipsychotic dose ($r(30) = .53$, $p < .005$). Fisher's R to Z indicated that the relationship between constriction to light and preparatory dilation were not significantly different between HC and SZ.

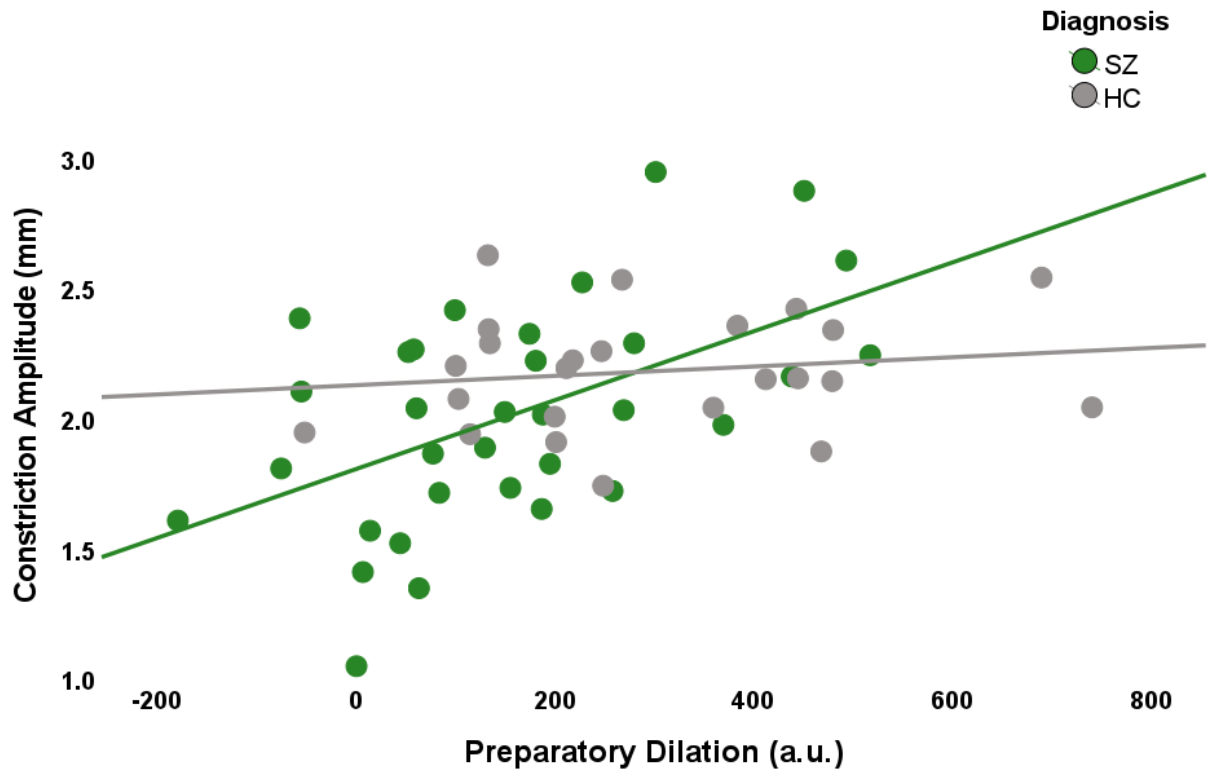

Figure 6: Correlation between preparatory dilation (in arbitrary units) and constriction amplitude (in mm) for SZ and HC separately. SZ showed a significant negative correlation between amplitude and preparatory dilation that was not present in HC.

3.2 Preparatory Pupil Dilation in SZ, BPP, and HC: Differences and Symptom Correlates

Results indicate a significant main effect of diagnosis $F(2, 118) = 8.06$, $p < .001$ (Figure 7). To follow up the significant main effect, I calculated simple slopes for our three diagnostic

groups and used a Bonferroni correction for multiple comparisons (results are reported with corrected p-values). SZ showed significantly smaller preparatory dilation than HC $t(118) = 3.99$, $p < .001$. BPP did not differ from either HC $t(118) = 1.80$, $p = .22$ nor SZ $t(118) = -1.84$, $p = .20$.

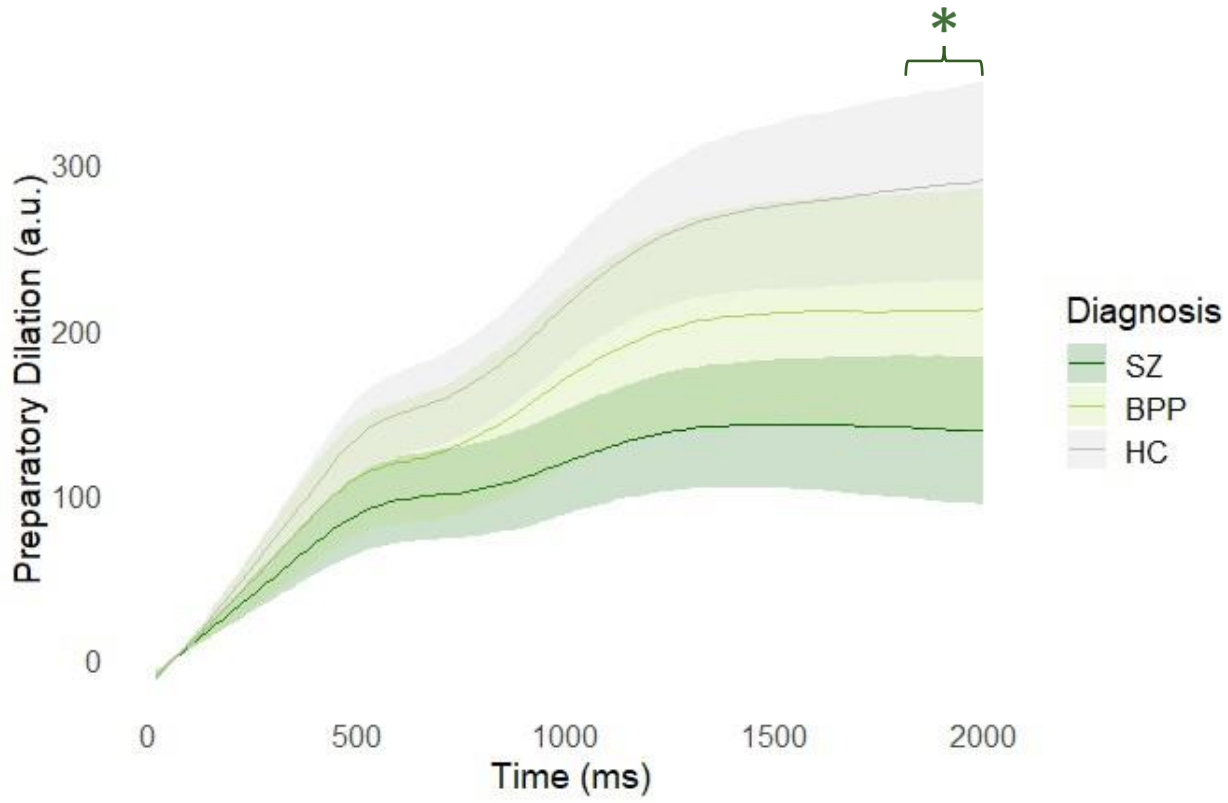

Figure 7: Pupil dilation during the fixation period of the double-step task for SZ, BPP, and HC. Shaded error bars represent 95% confidence intervals. SZ showed significantly blunted pupil dilation during the last 100ms of measurement when compared to HC.

Despite not replicating the correlation between motivational negative symptom severity and preparatory pupil dilation in individuals with schizophrenia, we nevertheless ran an MLM. Motivational negative symptom severity did not significantly predict preparatory pupil dilation $F(1, 79) = .06$ $p = .81$. There was furthermore no main effect of diagnosis $F(1, 79) = 3.09$, $p = .08$, nor an interaction between diagnosis and motivational negative symptoms $F(79) = .04$, $p = .82$. When adding CPZ dosage into the model, effects of motivational negative symptoms

($F(1,75) = .04$, $p = .84$) and diagnosis were largely unchanged ($F(1, 75) = .52$, $p = .47$), and there was no main effect of CPZ dosage ($F(1, 75) = .70$, $p = .41$), nor any significant two-way or three-way interaction involving CPZ dosage, diagnosis and/or motivational negative symptom severity.

Next, I examined the specific effects of avolition on preparatory dilation. There was no significant main effect of either avolition ($F(1, 79) = .15$, $p = .69$) nor diagnosis ($F(1,79) = 2.89$, $p = .09$) and no interaction between diagnosis and avolition ($F(1,79) = .39$, $p = .54$). When adding CPZ into the model, I once again observed a non-significant main effect of avolition $F(1,75) = .01$, $p = .92$ and a non-significant main effect of diagnosis $F(1,75) = 3.63$, $p = .06$. I also observed a non-significant main effect of CPZ dosage $F(1, 75) = 1.48$, $p = .23$, and no significant two-way interactions nor three-way interaction involving CPZ dosage. Additional exploratory analyses with the other SANS subfactors as well as the other symptom measures revealed no significant main effects of symptom measure nor interaction with diagnosis.

4. Discussion

The purpose of the current study was two-fold. First, I aimed to replicate two pupillary findings observed in individuals with schizophrenia (blunted constriction to light and blunted dilation in preparation to act) and their relationship to motivational negative symptoms. I then explored whether both findings were related to each other across individuals, which may suggest a common mechanism underlying motivational negative symptoms. Next, I examined the transdiagnostic relevance of blunted pupillary dilation in preparation to act in individuals with a vulnerability to psychosis. Here, I aimed to replicate findings of blunted preparatory dilation in individuals with bipolar disorder with psychotic features and extend these findings by investigating whether motivational deficits are also related to blunted preparatory dilation in bipolar disorder with psychotic features, and not just schizophrenia.

4.1 Relating Preparatory Pupil Dilation and Pupil Light Reflex in HC and SZ

With regards to my first aim, I replicated previous findings of blunted pupil dilation during the preparation to act and blunted pupillary constriction in response to light for individuals with schizophrenia compared to healthy controls. However, while I replicated previous findings of blunted constriction correlating to motivational negative symptom severity, the same was not true for the association with blunted dilation. Potential reasons for this failed replication are outlined in the following section. Additional exploratory analysis did not reveal a significant correlation between avolition and pupillary indices (constriction amplitude and preparatory pupil dilation).

Critically, I found a statistically significant correlation between these two pupillary indices, which was only present in individuals with schizophrenia. This relationship was such that individuals with schizophrenia showing less dilation in preparation to act also showed less

constriction to light. This is the first study, to my knowledge, to show a significant association between these two sets of previously independently established findings.

While blunted preparatory dilation has typically been interpreted as reflecting insufficient information processing or reduced effort allocation in individuals with schizophrenia, blunted pupillary constriction has typically been interpreted within the context of autonomic imbalance. Light innervates the parasympathetic Edinger-Westphal (EW) nucleus, which projects onto the sphincter muscles that constrict the pupil. This circuit is modulated by sympathetic activity such that signals from the noradrenergic locus coeruleus can inhibit the EW, thus reducing the PLR. Thus, reduced constriction may be interpreted as reflecting autonomic imbalance due to reduced parasympathetic outflow. Indeed, prior research has demonstrated that individuals with schizophrenia exhibit blunting of the parasympathetic branch of the autonomic nervous system as indicated by reduced vagal activity (Montaquilla et. al., 2015; Clamor et. al., 2016; Quintana et. al., 2016) in comparison to healthy controls. These changes have been observed in first degree relatives of individuals with schizophrenia (Bär et. al., 2010; Bär et. al., 2015), suggesting that deficits in parasympathetic function are related to genetic predisposition towards the illness and thus not fully explained by long-term effects of medication, illness-stigma, co-morbid health conditions or any other major changes that come with a diagnosis of a severe mental illness (e.g. unemployment). As such, individuals with schizophrenia show deficits in their ability to return to homeostasis following stressful events while engagement of the sympathetic nervous system, responsible for the stress response itself, remains unaltered (Ieda et. al., 2014).

Blunted constriction to light observed at the level of the pupil may instead reflect an increase in sympathetic outflow to the pupil counteracting constriction. Indeed, research has shown that the autonomic nervous system may regulate output to various organs differently

(Jänig, 2022). Therefore, it is possible that parasympathetic deficits in schizophrenia are unique to outflow to the heart, and blunted pupil constriction instead reflects an overactive sympathetic response. However, this explanation seems unlikely, as pupillary metrics predominantly associated with sympathetic activity (e.g., baseline pupil size and later redilation processes) were unaltered in individuals with schizophrenia in the current study (Appendix). In addition, prior studies have found that constriction amplitude is significantly correlated with indices of vagal parasympathetic activity in individuals with schizophrenia (Bär et. al., 2008), further reinforcing an interpretation of the current findings in terms of reductions in parasympathetic activity. Therefore, blunted pupillary light reflex for individuals with schizophrenia observed in the current study may reasonably be interpreted as reflecting a deficit in the return to homeostasis after exposure to external (in this case light) stimulation, which is consistent with other well established autonomic indices of parasympathetic deficit in schizophrenia such as decreases in vagal tone (Montaquila et. al., 2015).

While decreases in parasympathetic activity leading to increased sympathetic drive may best explain blunted pupillary constriction to light, it does not provide a straightforward explanation for blunted pupillary preparatory dilation, nor for the relationship between blunted pupil-light reflex and blunted task-related dilation. Task-related pupil dilation is likely due to both increased sympathetic outflow to the dilator muscle and sympathetic inhibition of the EW. Indeed, research has shown that the locus coeruleus – norepinephrine (LC-NE) system primarily involved in the modulation of attention, arousal (Samuels & Szabadi, 2008), and the stress response characterizing autonomic function (Benarroch, 2018) also plays a role in cognitive control (Grueschow, Kleim & Ruff, 2020). In addition, sustained processing and performance during difficult cognitive tasks is thought to be modulated by inhibition of the parasympathetic

pathway (Steinhauer et. al., 2004), with deficits in inhibition of parasympathetic activity being related to worse performance on tasks of central executive function (Matthewson et. al., 2012). As such, decreased pupillary dilation in preparation to act may represent an inability of individuals with schizophrenia to inhibit parasympathetic activity during effortful processing or increase sympathetic outflow given current demands.

Thus, while a blunted PLR suggests a dominant sympathetic system, blunted task-related pupil dilation suggests a dominant parasympathetic system. So, what might explain reduced pupillary dilation in the preparation to act within the context of increased sympathetic drive to external stimuli? One potential explanation is a reduction in attentional resource allocation to internal versus external goals. Individuals with schizophrenia displaying deficits in the return to homeostasis (blunted parasympathetic response) following stress response to the external environment may be simultaneously experiencing difficulties in disengaging from homeostasis in order to engage in internally driven goal-directed behavior. It may be the case that increased *duration* of the stress response to the external environment results in sustained activation of the LC-NE system to external, rather than internal goal-directed behavior. As such, a greater degree of cognitive resources and attention may be spent on the external environment, significantly reducing the proportion of resources available for internal goal-directed behavior. Indeed, this idea seems to coincide with prior research linking deficits in autonomic nervous system function with impaired cognition (Stogios et. al., 2021) in individuals with schizophrenia. With reference to pupil dynamics more specifically, disordered reactivity of the LC would manifest as a bigger inhibitory influence of the LC on the EW during light stimulation and a decreased inhibitory effect on the LC during internal challenges and demands (Fattal et al., 2022). Such an explanation would account for the larger body of pupillary findings in schizophrenia as well as

the specific association between blunted constriction and blunted task-related dilation observed in the current study.

However, there are other more trivial explanations for the observed correlation that should be ruled out. More specifically, part of the "preparatory" dilation may be attributed to a pupil dark reflex—redilation upon light stimulus offset. In the double-step task, central fixation was preceded by a drift-check procedure consisting of a central white annulus. This central annulus, representing 2.5% of screen size, was larger than the subsequent fixation cross, representing 1.5% of screen size. As both the annulus and fixation cross were white, it is plausible that the on-screen luminance change from drift-correction to central fixation resulted in a pupil dark reflex (Lowenstein, 1943), initiating increases in pupillary dilation. The duration of the pupillary dark reflex, although not currently established in the literature, can be estimated to last between ~1 to ~1.5 seconds, with initial latency to dilation lasting around .5 seconds. As the on-screen change to the fixation cross occurred 150ms after drift correction, and we observed pupillary dilation through about 1200ms into the fixation period, it is possible that pupillary dilation in the preparation to act observed in the current study was driven in part by a pupil dark reflex. Therefore, the association between dilation during the demand to act and constriction during exposure to light in individuals with schizophrenia may both be driven by processes related to the response to light. However, given the dilation latency described above, this interpretation does not fully account for dilation occurring immediately from the start of the on-screen change to the fixation cross which was observed in the current study. Cognitive processes may account for the first "bump" in pupil dilation across diagnostic groups while a pupil dark reflex may instead account for the second "bump" in pupil dilation occurring across diagnostic group later in the preparatory period (Figure 7). I am currently working on control experiments

to rule out the influence of the pupil dark reflex. A final explanation for the observed correlation may be linked to the impact of antipsychotic medications on pupil size. As stated above, pupil size is affected by antipsychotic medication use (Loga, Curry & Lader, 1981). Therefore, the observed correlation in individuals with schizophrenia may be driven by the combined effect of antipsychotic medications on pupil size. This may also explain the lack of a significant correlation in healthy controls, who do not utilize antipsychotic medication. However, despite my inability to account for long-term effects of antipsychotic use, analyses including CPZ dosage replicated all findings, reducing the strength of such an explanation.

4.2 Preparatory Pupil Dilation in SZ, BPP, and HC: Differences and Symptom Correlates

With regards to my second aim, I found significantly reduced preparatory pupil dilation in the preparation to act for individuals with schizophrenia compared to healthy controls. However, contrary to prior findings (Karpouzian-Rogers et. al., 2022), individuals with bipolar disorder with psychotic features did not differ from healthy controls. Consistent with Karpouzian- Rogers et. al. (2022), I did not find significant differences between the two clinical samples. Moreover, I did not replicate prior findings that preparatory pupil dilation was related to motivational negative symptoms in individuals with schizophrenia (Thakkar et. al., 2018), nor was such a relationship observed in people with bipolar disorder with psychotic features. Additional exploratory analyses demonstrated that blunted preparatory dilation was not explained by avolition (nor the other subfactors), expressive negative symptoms, positive symptoms, working memory, sex, race, ethnicity, nor medication dosage.

Findings of reduced pupillary dilation *in preparation* to act in schizophrenia may best be interpreted through the lens of cognitive effort and motivation. Indeed, prior research has demonstrated that blunted pupillary dilation *during* cognitive tasks observed in individuals with

schizophrenia is associated with both deficits in effort and motivation (McGovern et. al., 2020). In addition, deficits in effortful processing in individuals with schizophrenia have been hypothesized as reflecting overestimation of the subjective cost of effort paired with an underestimation of reward associated with effort (Gold, Waltz & Frank, 2015). Individuals with schizophrenia may therefore feel less motivated to recruit effort in preparation for cognitively demanding tasks due to deficits in reward-cost prediction, resulting in blunted preparatory dilation.

Deficits in reward-cost prediction are also present transdiagnostically in bipolar disorder with psychotic features. Indeed, prior research has demonstrated deficits in reward magnitude, reward probability and expected value in schizophrenia, bipolar disorder, and major depressive disorder (Zou et. al., 2020) when compared to healthy controls. It is somewhat surprising then that I did not observe the same preparatory pupil blunting in individuals with bipolar disorder with psychotic features that I did in individuals with schizophrenia relative to healthy controls.

There are a multitude of reasons as to why this may be the case. First, I may have been underpowered to detect true differences between the BPP and control group: the current sample size was smaller than the previous study which did observe blunted preparatory dilation in BPP (Karpouzian-Rogers et. al., 2022). Indeed, the results were such that individuals with bipolar disorder with psychotic features fell midway between people with schizophrenia spectrum disorders and healthy controls.

Next, differences observed between the current study and Karpouzian-Rogers et. al., 2022 may relate to methodological differences. Karpouzian-Rogers et. al., 2022 used a longer preparatory period. Pupillary changes in preparation to act may have continued past our 2000ms cutoff, resulting in a significant difference between healthy controls and bipolar disorder with

psychotic features. However, this explanation seems unlikely, as pupillary dilation plateaued at around 1200ms into fixation (See Figure 7). As noted above, preparatory dilation and a pupil dark reflex may have been confounded in the current study, thereby complicating the interpretation of group differences. Finally, differences between the task itself may have resulted in differences in preparatory dilation. The anti-saccade task utilized by Karpouzian-Rogers et. al., 2022, which involved inhibiting a pre-potent response, was more cognitively demanding than the simpler reaction time task in the current study. Indeed, prior research has demonstrated that task-related pupil dilation scales with task difficulty (Minassian et. al., 2004). While upcoming trial difficulty was not indicated to participants a priori in the current task suggesting that preparatory pupil dilation was unaffected by upcoming trial difficulty, reduced pupil modulation in the comparatively easier double-step *task* may have made it more challenging to resolve group differences.

I also failed to replicate an association between reduced preparatory pupil dilation and the severity of negative symptoms, generally, and avolition specifically, in individuals with schizophrenia, and furthermore did not observe a relationship in bipolar disorder with psychotic features.

Within the context of the existing literature and our predictions, these results are surprising. Indeed, prior studies have shown that blunted task-related dilation is significantly correlated with increased motivational negative symptom severity (Thakkar et. al., 2018; Granholm et. al. 2016; McGovern et. al., 2020; Reddy et. al., 2018) in individuals with schizophrenia. One potential explanation for these results is that negative symptoms may serve as a proxy for a measure that is more closely aligned with blunted preparatory dilation: defeatist attitudes. Prior research has demonstrated that blunted dilation during effortful processing is

associated with defeatist attitudes (Granholm et. al., 2016), or the idea that individuals with schizophrenia engage in negative thinking patterns (e.g. “I should just give up, I will never get this right”). These defeatist beliefs are significantly correlated to motivational negative symptoms (Granholm et. al., 2016; Campellone, Sanchez & King, 2016) and are associated with deficits in pupillary effort such that, as individuals with schizophrenia exhibit greater defeatist beliefs, they show simultaneous decreases in pupillary dilation (Granholm et. al., 2016) as task demands increase. In addition, individuals with schizophrenia with greater defeatist beliefs also show greater motivational negative symptom severity when compared to individuals with lower defeatist beliefs (Granholm et. al., 2016). Therefore, the motivational negative symptom blunted preparatory dilation relationship observed in Thakkar et. al., 2018 may be moderated by the level of defeatist attitudes. Further separating individuals in level of defeatist attitudes may have yielded a significant preparatory pupil dilation motivational negative symptom severity relationship for our schizophrenia sample.

Another explanation for our lack of significant associations between pupillary dilation and negative symptoms are sample characteristics. The current sample had relatively low levels of positive and negative symptoms. Recruiting individuals who are higher in motivational negative symptom severity may have resulted in a greater ability for us to detect an effect of motivational negative symptoms on preparatory dilation. However, this explanation seems unlikely as our sample had comparable levels of symptoms to the sample described in Thakkar et. al. (2018), who did observe a relationship between blunted preparatory dilation and negative symptoms in schizophrenia.

A final explanation may be related to external factors associated with having a severe mental illness. Higher dosages (Iwamoto et. al., 2012) and differences in antipsychotic

medication affinity for neurotransmitter receptors (Hattori et. al., 2018) have been associated with greater alterations of autonomic function in individuals with schizophrenia. Lower antipsychotic dosages for individuals with bipolar disorder with psychotic features (Yu et. al., 2023; Table 1) compared to individuals with schizophrenia may explain the "middling" effect for individuals with bipolar disorder with psychotic features and the significant difference between individuals with schizophrenia and healthy controls. As such, pupillary differences in preparatory dilation when compared to healthy controls may be driven by antipsychotic medication response, and not motivational negative symptoms. However, like above, analyses including CPZ dosage replicated all findings, reducing the strength of an antipsychotic medication driven explanation for blunted preparatory dilation.

Individuals with schizophrenia also experience high levels of illness stigma (Valery & Prouteau, 2020; Colizzi, Ruggeri & Lasalvia, 2020) lower levels of socio-economic status (Werner et. al., 2007), and high rates of comorbid medical conditions (Jeste et. al., 1996). While similar rates of these factors also exist in bipolar disorder with psychotic features (Perich et. al., 2022; Kumar et. al., 2020), individuals with schizophrenia may show unique vulnerability to these stressors due to the over-prioritization of external factors described above. However, this explanation remains implausible given findings of blunted dilation in first-degree relatives of individuals with schizophrenia (Bär et. al., 2010; Bär et. al., 2015) who do not experience these same stressors.

Future studies may expand on the results of the current study in two meaningful ways. First, my inability to establish the blunted preparatory pupil dilation constriction amplitude association in individuals with schizophrenia as a mechanism of motivational negative symptoms suggests that this association may instead be a mechanism for other schizophrenia-specific

alterations. Researchers may focus on investigating the impact of defeatist attitudes, disorganized symptoms, or cognitive deficits as initial avenues. Second, current findings may be replicated at the within-person level. Establishing a clear within-person relationship between over-prioritization of external goals paired with under-prioritization of internal goals gives rise to the possibility of an objective metric for tracking treatment response or clinical status over time in the same individual.

In conclusion, my findings establish a significant relationship between blunted constriction to light and blunted cognitively related preparatory dilation in individuals with schizophrenia for the first time. Interpretation of my findings within the context of autonomic function suggest that schizophrenia is characterized by a pattern of increased duration of arousal to externally generated stimulus potentially resulting in under-activation and under-prioritization of internal goal-directed behavior. These findings have substantial clinical implications, as they provide one potential mechanism to be acted upon during psychotherapeutic intervention. Improvements in internal/external prioritization may result in improvements in functioning, without necessarily targeting symptomology. In addition, our findings point towards the increased utility of pupillometry as a tool capable of indexing internal functioning by leveraging knowledge of the well-established pupillary motility to autonomic response pathway. As such, implementation of pupillary methods in future research as well as clinical settings is needed to better study symptomatic etiology, functional outcome, and transdiagnostic mechanisms. Notably, however, my inability to replicate the motivational negative symptom preparatory dilation relationship observed in other studies may point to the difficulty in identifying reliable mechanisms of clinical symptoms.

TABLES

Table 1: Demographics information for all participants who completed the saccadic double-step and/or the pupil light reflex.

	Diagnostic Category			Analysis		
	SZ	**BP**	**HC**	**Test**	***p***	***Post Hoc***
Sample Size						
Usable PLR and/or DS (n = 160)	77	35	48			
DS Only Usable (n = 121)	55	30	36			
PLR Only Usable (n = 118)	55	27	36			
Age						
Usable PLR and/or DS	35.04 (11.36)	36.63 (10.84)	36.00 (10.48)	$F(2,157) = .28$	.76	
DS Only Usable	34.18 (11.06)	36.50 (10.69)	37.06 (9.92)	$F(2,118) = .93$	.39	
PLR Only Usable	36.62 (11.34)	35.93 (11.25)	36.11 (10.72)	$F(1,115) = .04$	.96	
Gender (Female/Male/Non-Binary/Other)						
Usable PLR and/or DS	47/27/3/0	17/18/0/0	28/19/0/1	$X^2(6, 159) = 7.84$	.25	
DS Only Usable	34/19/2/0	15/15/0/0	20/16/0/0	$X^2(4, 121) = 4.14$	.39	
PLR Only Usable	33/19/3/0	12/15/0/0	23/12/0/1	$X^2(6, 118) = 9.3$	.16	
Hispanic/Latino (Y/N)						
Usable PLR and/or DS	7/70	2/33	2/46	$X^2(2, 160) = 1.21$	.55	
DS Only Usable	5/50	2/28	1/35	$X^2(2, 121) = 1.41$	.49	
PLR Only Usable	5/50	2/25	2/34	$X^2(2, 118) = .39$	.82	
Race						

Table 1 (cont'd)

Usable PLR and/or DS				$X^2(10, 161) = 17.54$	.06	
DS Only Usable				$X^2(10, 121) = 15.79$	.11	
PLR Only Usable				$X^2(10, 118) = 15.48$	.12	
Native American						
Usable PLR and/or DS	1	0	0			
DS Only Usable	1	0	0			
PLR Only Usable	1	0	0			
Asian						
Usable PLR and/or DS	0	1	4			
DS Only Usable	0	1	2			
PLR Only Usable	0	1	4			
Black						
Usable PLR and/or DS	23	4	10			
DS Only Usable	19	3	5			
PLR Only Usable	15	4	8			
White						
Usable PLR and/or DS	45	26	30			
DS Only Usable	30	23	26			
PLR Only Usable	34	19	22			
Multiracial						
Usable PLR and/or DS	4	0	3			
DS Only Usable	2	0	2			
PLR Only Usable	4	0	1			
Other						
Usable PLR and/or DS	4	4	1			
DS Only Usable	3	3	1			
PLR Only Usable	1	3	1			

Table 1 (cont'd)

Years of Education						
Usable PLR and/or DS	13.29 (2.41)	14.76 (1.78)	16.64 (2.62)	$F(2,155) = 29.45$	<.001	SZ < BPP < HC
DS Only Usable	13.36 (2.45)	14.78 (1.87)	17.00 (2.54)	$F(2,118) = 26.01$	<.001	SZ < BPP < HC
PLR Only Usable	13.26 (2.28)	14.83 (1.62)	16.34 (2.68)	$F(2,113) = 19.59$	<.001	SZ < BPP < HC
Years of Illness						
Usable PLR and/or DS	11.06 (9.21)	13.14 (9.46)		$F(1,106) = 1.19$	.28	
DS Only Usable	9.79 (8.79)	13.20 (9.78)		$F(1,81) = 2.65$	.11	
PLR Only Usable	12.22 (9.33)	11.33 (8.54)		$F(1,76) = .17$	.68	
IQ						
Usable PLR and/or DS	96.66 (23.27)	106.88 (9.54)	104.00 (23.82)	$F(2,149) = 3.29$	.04	SZ < BP
DS Only Usable	95.74 (26.07)	106.77 (9.79)	103.97 (26.18)	$F(2,117) = 2.62$	.08	
PLR Only Usable	98.10 (18.18)	106.27 (9.64)	104.33 (20.23)	$F(2,108) = 2.42$	.09	
CPZ Dosage						
Usable PLR and/or DS	366.45 (594.56)	142.51 (187.26)		$t(109) = 2.98$	<.005	
DS Only Usable	330.19 (406.54)	138.58 (150.84)		$t(83) = 3.12$	<.005	
PLR Only Usable	375.42 (657.16)	143.57 (287.82)		$t(79) = 1.75$	.09	

Table 1 (cont'd)

SANS Total						
Usable PLR and/or DS	27.30 (19.39)	18.08 (16.73)		*t*(106) = 2.35	.02	
DS Only Usable	26.53 (20.75)	16.41 (15.22)		*t*(80) = 2.25	.03	
PLR Only Usable	30.33 (19.82)	19.85 (17.04)		*t*(79) = 2.35	.02	
SANS MAP						
Usable PLR and/or DS	8.72 (7.22)	8.20 (8.30)		*t*(106) = .33	.74	
DS Only Usable	10.55 (7.65)	7.48 (7.24)		*t*(80) = .50	.62	
PLR Only Usable	10.37 (7.43)	9.00 (8.74)		*t*(79) = .74	.46	
Avolition Total						
Usable PLR and/or DS	1.51 (1.29)	1.21 (1.23)		*t*(106) = 1.12	.27	
DS Only Usable	1.45 (1.39)	1.11 (1.09)		*t*(80) = 1.13	.26	
PLR Only Usable	1.80 (1.35)	1.27 (1.28)		*t*(79) = 1.69	.09	
Anhedonia Total						
Usable PLR and/or DS	1.05 (1.42)	0.95 (1.30)		*t*(106) = .34	.73	
DS Only Usable	0.96 (1.47)	0.89 (1.39)		*t*(80) = .41	.83	
PLR Only Usable	1.22 (1.49)	1.19 (1.42)		*t*(79) = .11	.92	
Asociality Total						
Usable PLR and/or DS	1.05 (1.10)	1.21 (1.38)		*t*(106) = -.64	.53	
DS Only Usable	1.02 (1.14)	1.09 (1.21)		*t*(80) = -.25	.80	
PLR Only Usable	1.25 (1.18)	1.33 (1.46)		*t*(79) = -.29	.78	

Table 1 (cont'd)

SANS EXP						
Usable PLR and/or DS	9.35 (8.65)	4.09 (5.55)		*t*(106) = 3.77	<.001	
DS Only Usable	9.16 (8.72)	3.52 (5.57)		*t*(80) = 3.55	<.001	
PLR Only Usable	9.70 (9.12)	4.44 (5.75)		*t*(79) = 3.16	<.005	
Alogia Total						
Usable PLR and/or DS	0.68 (0.75)	0.34 (0.43)		*t*(106) = 2.94	<.005	
DS Only Usable	0.71 (0.79)	0.27 (0.38)		*t*(80) = 3.39	<.001	
PLR Only Usable	0.73 (0.75)	0.37 (0.48)		*t*(79) = 2.63	<.005	
Flat Affect Total						
Usable PLR and/or DS	1.22 (1.21)	0.51 (0.78)		*t*(106) = 3.63	<.001	
DS Only Usable	1.17 (1.19)	0.45 (0.81)		*t*(80) = 3.22	<.005	
PLR Only Usable	1.25 (1.28)	0.56 (0.76)		*t*(79) = 3.04	<.005	
BPRS Total						
Usable PLR and/or DS	42.72 (12.28)	36.61 (10.03)		*t*(107) = 2.72	.01	
DS Only Usable	43.16 (13.29)	35.29 (9.04)		*t*(81) = 2.82	.01	
PLR Only Usable	43.48 (12.79)	36.37 (10.45)		*t*(79) = 2.5	.02	
SAPS Total						
Usable PLR and/or DS	19.64 (17.57)	10.42 (12.64)		*t*(107) = 2.69	.01	
DS Only Usable	19.78 (16.13)	8.70 (10.79)		*t*(80) = 3.68	<.001	
PLR Only Usable	19.56 (18.05)	10.26 (12.49)		*t*(80) = 2.41	.02	
YMRS Total						
Usable PLR and/or DS	9.29 (6.87)	6.85 (8.21)		*t*(90) = 1.52	.13	

Table 1 (cont'd)

DS Only Usable	9.25 (6.77)	6.07 (6.84)		$t(74) = 1.97$	.05	
PLR Only Usable	9.86 (7.54)	6.33 (8.13)		$t(67) = 1.84$	.07	
HRSD Total						
Usable PLR and/or DS	10.44 (7.34)	9.52 (8.01)		$t(88) = .56$	.58	
DS Only Usable	10.61 (7.89)	8.71 (6.51)		$t(72) = 1.07$	.29	
PLR Only Usable	11.21 (7.53)	9.48 (8.36)		$t(67) = .89$	.38	
Digit-Span Total						
Usable PLR and/or DS	24.49 (7.16)	26.06 (9.04)		$t(110) = -.99$	.33	
DS Only Usable	25.84 (7.66)	27.17 (7.62)		$t(83) = -.77$	.45	
PLR Only Usable	23.95 (7.47)	24.67 (9.58)		$t(80) = -.37$	.71	

Table 2: Demographics information for included/excluded participants who completed the saccadic double-step task.

	Performance Exclusion Criteria		Analysis		
	Included	**Excluded**	**Test**	***p***	**Effect Size (*d*)**
Sample Size					
SZ	55	15			
BPP	30	7			
HC	36	7			
Age					
SZ	34.18 (11.06)	38.73 (11.32)	$t(68) = -1.41$	.16	-.13
BPP	36.50 (10.69)	35.00 (13.32)	$t(35) = .32$	.75	.04
HC	37.06 (9.92)	29.29 (5.74)	$t(41) = 1.99$	.053	.22
IQ					
SZ	95.74 (26.07)	102.21 (9.38)	$t(66) = -.91$	.37	-.07
BPP	106.77 (9.79)	104.71 (8.83)	$t(35) = .51$	.62	.02
HC	103.97 (26.18)	111.14 (6.91)	$t(41) = -.71$	.48	-.07
SANS Total					
SZ	26.53 (20.75)	30.40 (19.58)	$t(68) = -.65$	.52	-.14
BPP	16.41 (15.22)	12.71 (16.54)	$t(32) = .56$	.58	.23
HC					
SANS MAP					
SZ	10.55 (7.65)	8.75 (8.68)	$t(68) = -.91$	.37	-.23
BPP	7.48 (7.24)	5.86 (9.10)	$t(32) = .50$	.62	.22
HC					
Avolition Total					
SZ	1.45 (1.39)	1.87 (1.08)	$t(68) = -1.07$	.29	-.27
BPP	1.11 (1.09)	1.05 (1.38)	$t(32) = .13$	.89	.06
HC					
Anhedonia Total					
SZ	0.96 (1.47)	1.00 (1.19)	$t(68) = -.09$	.93	-.04
BPP	0.89 (1.39)	0.29 (0.76)	$t(32) = 1.09$	.28	.74
HC					
Asociality Total					
SZ	1.02 (1.14)	1.27 (1.22)	$t(68) = -.74$	.46	-.23
BPP	1.09 (1.21)	0.81 (1.46)	$t(32) = .52$	.61	.27
HC					

Table 2 (cont'd)

SANS EXP					
SZ	9.16 (8.72)	8.87 (8.32)	*t*(68) = .12	.91	.03
BPP	3.52 (5.57)	3.00 (3.79)	*t*(32) = .23	.82	.15
HC					
Alogia Total					
SZ	0.71 (0.79)	0.80 (0.94)	*t*(68) = -.38	.71	-.12
BPP	0.27 (0.38)	0.14 (0.26)	*t*(32) = .84	.41	.51
HC					
Flat Affect Total					
SZ	1.17 (1.19)	1.08 (1.08)	*t*(68) = .28	.78	.08
BPP	0.45 (0.81)	0.43 (0.53)	*t*(32) = .07	.95	.05
HC					
BPRS Total					
SZ	43.16 (13.29)	47.27 (12.76)	*t*(68) = -1.07	.29	- .09
BPP	35.29 (9.04)	38.43 (10.63)	*t*(33) = -.79	.43	-.09
HC					
SAPS Total					
SZ	19.78 (16.13)	24.27 (19.72)	*t*(66) = -.91	.37	-.22
BPP	8.70 (10.79)	14.57 (17.25)	*t*(32) = -.86	.42	-.58
HC					
YMRS Total					
SZ	9.25 (6.77)	11.93 (8.23)	*t*(61) = -1.27	.21	-.27
BPP	6.07 (6.84)	7.43 (11.99)	*t*(33) = -.40	.69	-.21
HC					
HRSD Total					
SZ	10.61 (7.89)	11.00 (5.81)	*t*(59) = -.18	.86	-.04
BPP	8.71 (6.51)	10.20 (8.64)	*t*(31) = -.45	.66	-.17
HC					
Digit-Span Total					
SZ	25.84 (7.66)	24.67 (3.85)	*t*(68) = .57	.57	.05
BPP	27.17 (7.62)	24.71 (8.04)	*t*(35) = .76	.45	.09
HC					

Table 3: Demographics information for included/excluded participants who completed the pupil light reflex.

	Performance Exclusion Criteria		Analysis		
	Included	**Excluded**	**Test**	***p***	**Effect Size (*d*)**
Sample Size					
SZ	55	11			
BPP	27	1			
HC	36	19			
Age					
SZ	36.62 (11.34)	33.18 (10.46)	*t*(64) = .93	.36	.09
BPP	35.93 (11.25)	28			
HC	37.06 (9.92)	36.11 (10.72)	*t*(53) = .03	.97	-.02
IQ					
SZ	98.10 (18.18)	92.27 (33.06)	*t*(61) = .82	.41	.06
BPP	106.27 (9.64)	115			
HC	103.97 (26.18)	104.33 (20.23)	*t*(50) = - 1.16	.25	-.05
SANS Total					
SZ	30.33 (19.82)	33.09 (24.48)	*t*(63) = -.40	.69	-.09
BPP	19.85 (17.04)	2			
HC					
SANS MAP					
SZ	10.37 (7.43)	11.45 (8.98)	*t*(63) = -.43	.67	-.10
BPP	9.00 (8.74)	2			
HC					
Avolition Total					
SZ	1.80 (1.35)	2.06 (1.57)	*t*(63) = -.56	.58	-.14
BPP	1.27 (1.28)	.33			
HC					
Anhedonia Total					
SZ	1.22 (1.49)	1.27 (1.42)	*t*(63) = -.10	.92	-.04
BPP	1.19 (1.42)	0			
HC					
Asociality Total					
SZ	1.25 (1.18)	1.33 (1.20)	*t*(63) = -.22	.83	-.07
BPP	1.33 (1.46)	.33			

Table 3 (cont'd)

HC					
SANS EXP					
SZ	9.70 (9.12)	11.91 (10.02)	*t*(63) = -.72	.47	-.22
BPP	4.44 (5.75)	0			
HC					
Alogia Total					
SZ	0.73 (0.75)	1.03 (1.12)	*t*(63) = -.84	.42	-.37
BPP	0.37 (0.48)	0			
HC					
Flat Affect Total					
SZ	1.25 (1.28)	1.46 (1.31)	*t*(63) = -.52	.61	-.17
BPP	0.56 (0.76)	0			
HC					
BPRS Total					
SZ	43.48 (12.79)	43.10 (13.99)	*t*(62) = .09	.93	.01
BPP	36.37 (10.45)	33			
HC					
SAPS Total					
SZ	19.56 (18.05)	25.82 (20.65)	*t*(64) = -1.03	.31	-.30
BPP	10.26 (12.49)	9			
HC					
YMRS Total					
SZ	9.86 (7.54)	6.14 (5.73)	*t*(47) = 1.24	.22	.39
BPP	6.33 (8.13)	2			
HC					
HRSD Total					
SZ	11.21 (7.53)	6.14 (6.72)	*t*(47) = 1.67	.10	.47
BPP	9.48 (8.36)	5			
HC					
Digit-Span Total					
SZ	23.95 (7.47)	24.55 (6.85)	*t*(64) = -.25	.81	-.02
BPP	24.67 (9.58)	26			
HC					

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APPENDIX

Table 4: Comparison of pupillary metrics associated with sympathetic activity in SZ and HC.

	Diagnostic Category		Analysis		
	SZ Mean (SD)	HC Mean (SD)	Test	p	Effect Size (*d*)
Initial Diameter	5.23 (1.04)	5.29 (.66)	$t(90) = .36$	.72	.01
End Diameter	3.24 (.75)	3.11 (.53)	$t(90) = -.89$	.38	-.04
Dilation Latency	.25 (.14)	.29 (.12)	$t(89) = 1.68$	.09	.18
Dilation Velocity	.46 (.12)	.51 (.09)	$t(89) = 1.94$	.06	.10
Max Dilation Velocity	1.81 (.39)	1.91 (.53)	$t(89) = .99$	.32	.05
T50	2.29 (.40)	2.38 (.39)	$t(89) = 1.09$	.28	.04