International Journal of Psychophysiology 128 (2018) 111–118

Contents lists available at ScienceDirect

International Journal of Psychophysiology

journal homepage: www.elsevier.com/locate/ijpsycho

Reduced pupil dilation during action preparation in schizophrenia

Katharine N. Thakkar[a,b,*], Jan W. Brascamp[a], Livon Ghermezi[a], Kassidy Fifer[a], Jeffrey D. Schall[c,d,e], Sohee Park[c,f]

[a] Department of Psychology, Michigan State University, East Lansing, MI, USA
[b] Division of Psychiatry and Behavioral Medicine, Michigan State University, East Lansing, MI, USA
[c] Department of Psychology, Vanderbilt University, Nashville, TN, USA
[d] Center for Integrative Cognitive Neuroscience, Vanderbilt University, Nashville, TN, USA
[e] Vanderbilt Vision Research Center, Vanderbilt University, Nashville, TN, USA
[f] Kyung Hee University, Seoul, Republic of Korea

ARTICLE INFO

Keywords:
Schizophrenia
Pupillometry
Cognitive control
Eye movements

ABSTRACT

Impairments in cognitive control—the ability to exert control over thoughts and actions and respond flexibly to the environment—are well-documented in schizophrenia. However, the degree to which experimental task performance reflects true cognitive control impairments or more general alterations in effort, arousal and/or task preparedness is unclear. Pupillary responses can provide insight into these latter factors, as the pupil dilates with degree of cognitive effort and response preparation. In the current study, 16 medicated outpatients with schizophrenia (SZP) and 18 healthy controls performed a task that measures the ability to reactively inhibit and modify a planned action—the double-step task. In this task, participants were required to make a saccade to a visual target. Infrequently, the target jumped to a new location and participants were instructed to rapidly inhibit and change their eye movement plan. Applying a race model of performance, we have previously shown that SZP require more time to inhibit a planned action. In the current analysis, we measured pupil dilation associated with task preparation and found that SZP had a shallower increase in pupil size prior to the onset of the trial. Additionally, reduced magnitude of the pupil response was associated with negative symptom severity in patients. Based on primate neurophysiology and cognitive neuroscience work, we suggest that this blunted pupillary response may reflect abnormalities in a general orienting response or reduced motivational significance of a cue signifying the onset of a preparatory period and that these abnormalities might share an autonomic basis with negative symptoms.

1. Introduction

Cognitive control, the ability to control thoughts and actions and respond flexibly to the environment, is impaired in individuals with schizophrenia and those at risk for this condition. These impairments are present before the first psychotic episode and during remission. Given the central role of cognition in functional outcome (Green, 1996), it is of great importance to elucidate the causal mechanisms underlying cognitive control deficits in order to develop targeted interventions.

In recent years, the countermanding, or stop-signal task, has been used to investigate the online recruitment of control processes in response to some external event (Lappin and Eriksen, 1966) in individuals with schizophrenia. This task comprises randomly interleaved GO and STOP trials, in which the participant must make a response to a stimulus (GO trials), unless a signal is presented at some short delay following the GO stimulus (STOP trials). On these STOP trials, participants must reactively suppress (and in a variant of the task, change) their response. Based on a model of task performance, the time needed to inhibit a response, referred to as stop-signal reaction time (SSRT) or target-step reaction time (TSRT), can be estimated. Longer SSRT/TSRT in schizophrenia has been shown in oculomotor (Thakkar et al., 2011; Thakkar et al., 2015a, 2015b) and manual tasks (Bellgrove et al., 2006; Ethridge et al., 2014; Fortgang et al., 2016; Huddy et al., 2009; Hughes et al., 2012; Lipszyc and Schachar, 2010; Matzke et al., 2017; Nolan et al., 2011; Yun et al., 2011). These findings may indicate inefficient reactive control over actions in schizophrenia. However, existing evidence does not disambiguate whether longer SSRT/TSRT indeed arises from a specific impairment in the online inhibition or alteration of a prepared action, or from a more general reduction in task preparation that would be associated with lowered alertness or arousal before any

* Corresponding author at: Department of Psychology, Michigan State University, 316 Physics Road, Room 110C, East Lansing, MI 48824, USA.
E-mail address: kthakkar@msu.edu (K.N. Thakkar).

https://doi.org/10.1016/j.ijpsycho.2018.03.012
Received 29 September 2017; Received in revised form 30 January 2018; Accepted 19 March 2018
Available online 21 March 2018
0167-8760/

task demands are even placed. One way of gauging this latter factor is to measure the pupillary response to a signal that announces the impending onset of task demands, because the extent to which the pupil dilates in response to a given stimulus has been shown to be associated with the degree of cognitive effort and arousal elicited by that stimulus (reviewed in Einhäuser, 2017). In other words, pupil size modulation to a signal that announces the impending task can provide an objective and quantitative window into the general level of cognitive effort put towards task preparation.

There is a rich literature describing reduced pupil dilation during cognitive processing in schizophrenia, particularly as task demands increase (Fish and Granholm, 2008; Granholm et al., 1998; Granholm et al., 2009; Granholm et al., 2000; Granholm et al., 1997; Granholm et al., 2016; Granholm and Verney, 2004; Granholm et al., 2007; Karatekin et al., 2010; Morris et al., 1997). Such abnormal pupillary responses in schizophrenia are correlated with negative symptoms (Granholm et al., 1998; Granholm et al., 2007)—those symptoms that are characterized by interpersonal and affective impairments (e.g., anhedonia and avolition) and contribute to poor social and occupational functioning. However, recent work has additionally revealed pupil dilation during the preparation to exert willful control over actions, and very little is known about potential abnormalities in these preparatory pupil dilations in schizophrenia. Some evidence for preparatory pupil dilation in healthy observers comes from Wang et al. (2015), who measured pupil size changes during an antisaccade task. Here participants were instructed prior to the onset of a visual stimulus whether to generate a saccadic eye movement towards the stimulus (prosaccade) or in the opposite direction to the stimulus (antisaccade). These authors found that pupil dilation in response to this instruction was greater in preparation for making antisaccades, in which a prepotent response must be suppressed, versus prosaccades. In addition, larger pupil dilations were followed by faster saccades.

Here we investigated pupil modulation during the preparatory period of an oculomotor countermanding task variant in individuals with schizophrenia and healthy controls by performing a re-analysis of a dataset from which we have previously published (Thakkar et al., 2015; Thakkar et al., 2015b). In this task, termed the double-step task, participants have to reactively inhibit and change a prepotent saccadic eye movement. We have previously reported performance deficits in people with schizophrenia on this task. Our hypotheses for the current study were as follows. First, we hypothesized that increased pupil dilation in response to a signal that announced the impending onset of a task would be related to an improvement on performance measures both within individuals (inhibition success and performance speed) and between individuals (TSRT) in both groups. Second, we hypothesized that this pupil dilation would be reduced in patients compared to controls, and that this reduction would be related to negative symptom severity. As an exploratory analysis, we also related pupil dilation to social functioning in patients. Findings from the current study have potential implications for understanding whether the well-replicated deficits in reactive control in schizophrenia are specific or instead rooted in a generalized impairment in, for example, arousal, preparedness or effort allocation.

2. Methods and materials

2.1. Participants

Demographic information is presented in Table 1. Individuals who met DSM-IV criteria for schizophrenia (SZP) were recruited from outpatient psychiatric facilities in Nashville, TN. Diagnoses were confirmed using structured clinical interviews (SCID-IV; First et al., 1995). All patients were taking antipsychotic medication, and half of the patient sample was also medicated with antidepressants, anxiolytics, mood stabilizers, or a combination thereof. Detailed medication status of patients is provided in Table 2. Healthy, unmedicated control subjects (HC) without a personal and family history of DSM-IV Axis-I disorders were recruited from the same community by advertisements.

Table 1
Demographic characteristics of the patient and control groups.

	Healthy controls mean (s.d.)	Schizophrenia patients mean (s.d.)	Statistic	p
Age	37.6 (8.3)	39.9 (9.4)	t = 0.8	0.5
Sex	7F/11M	7F/9M	ϕ = 0.08	0.8
IQ	107.7 (2.2)	101.1 (2.3)	t = 2.0	0.05
Education (yrs)	16.1 (2.1)	12.9 (1.9)	t = 2.4	0.0002
Handedness	67.8 (62.5)	54.4 (49.0)	t = 0.7	0.5
SFS				
Withdrawal	119.3 (8.8)	101.2 (12.8)	t = 4.8	< 0.0001
Interpersonal communication	141.5 (8.1)	119.2 (17.5)	t = 4.8	< 0.0001
Independence-performance	112.5 (7.8)	110.4 (10.4)	t = 0.69	0.50
Independence-competence	118.8 (7.1)	115.2 (9.9)	t = 1.2	0.23
Recreation	126.8 (10.8)	113.5 (12.6)	t = 3.3	0.002
Prosocial	124.2 (8.9)	115.7 (12.1)	t = 2.3	0.02
Employment	122.1 (1.5)	102.2(13.9)	t = 6.0	< 0.0001
Years of illness	n/a	19.9 (8.3)		
CPZ equivalent	n/a	486.6 (531.6)		
BPRS	n/a	17.2 (7.0)		
SAPS	n/a	17.0 (7.8)		
SANS	n/a	25.6 (14.3)		

Table 2
Medication status of schizophrenia patients.

Medication group	n
Antipsychotics only	8
Antipsychotics + mood stabilizers only	2
Antipsychotics + antidepressants only	4
Antipsychotics + mood stabilizers + antidepressants	1
Antipsychotics + mood stabilizers + antidepressants + anxiolytics	1

Clinical symptoms were assessed with the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962), Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984), and Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983). We were particularly interested in the relationship between pupil dynamics and negative symptoms, based on previous studies. To examine this construct in greater detail, three scales were derived based on a previous factor analytic study of the SANS (Peralta and Cuesta, 1999): Poverty of Affect and Speech (items 1–5, 7, 9–10), Social Dysfunction (items 15–16, 18–21), and Inattention (items: 11–12, 23–24). We could not derive these subscale scores for one participant as individual item scores were unavailable. Social and occupational functioning was assessed with the Social Functioning Scale (SFS; Birchwood et al., 1990), validated in schizophrenia, that assesses seven areas: social engagement, interpersonal communication, frequency of daily living activities, competence of daily living activities, recreational activities, social activities, and occupational activity. Raw scores were standardized (mean = 100, s.d. = 15) based on normative data from patients with schizophrenia. IQ was measured with the North American Adult Reading Test (NAART; Blair and Spreen, 1989). Handedness was assessed using the Modified Edinburgh Handedness Inventory (Oldfield, 1971). In patients, chlorpromazine (CPZ) equivalent dosages of antipsychotic medication were calculated (Woods, 2003).

Exclusion criteria included meeting DSM-IV criteria for substance abuse or dependence within the previous six months, history of neurological disorder, history of head injury, inability to fixate that

resulted in poor calibration of the eye tracker, and excessive sleepiness that resulted in an inability to track the eyes. All participants were native English speakers and had normal or corrected-to-normal vision. Three patients were excluded based on task performance, as outlined in the Statistical Methods section, and one patient chose to abort the experiment. Analyses were conducted on the remaining 16 SZP and 18 HC. Groups were matched for age, sex, and handedness. All areas of the SFS were reduced in SZP, except the Independence-Performance and Independence-Competence scales, which assess the frequency and competence of daily living activities, respectively (Table 1). All subjects gave written informed consent approved by the Vanderbilt Institutional Review Board and were paid.

2.2. Apparatus and stimuli

Eye position and pupil diameter was monitored using the EyeLink II eyetracker (SR Research, Canada) at a sampling rate of 500 Hz with average gaze position error < 0.5°, noise limited to < 0.01° RMS. Saccades were detected on-line using a velocity criterion (35°/sec) and minimum amplitude criterion (2° visual angle). Subjects were seated 57 cm from the monitor with their head in a chinrest. All participants were tested under the same lighting condition (i.e. no sources of light except for the computer monitor).

2.3. Design and procedure

2.3.1. Double-step task

Subjects performed the saccadic double-step task (Fig. 1), which comprised randomly interleaved *no-step* (60%) and *step* trials (40%). No-step trials required subjects to fixate on a central spot (white square subtending 0.5°) until it disappeared (after a random 500–1000 ms delay) and a target (T1), subtending 1°, flashed for 94 ms at one of eight positions 12° equidistant from fixation. Subjects were instructed to look at the target as quickly as possible. Step trials were initially identical to the no-step trials, but after a variable delay (*target step delay*; TSD) following T1 presentation, a second target (T2) flashed for 94 ms at a new location.[1] T1 and T2 were separated by either 90° or 135°. The target step instructed subjects to inhibit a saccade to T1 and instead look towards T2 as quickly as possible. Saccades that exceeded 2° amplitude and were within 45° polar angle around the vector from the fixation point to the first target were classified as directed towards T1. Likewise, saccades that exceeded an amplitude of 2° visual angle amplitude and were within 45° polar angle around the vector from the fixation point to the second target were classified as directed towards T2. Step trials were labeled *compensated* or *noncompensated* based on whether subjects succeeded or failed to look immediately at T2, respectively. T1 and T2 were different isoluminant colors (cyan and magenta, 2.06 cd/m^2), facilitating detection of target order. Color mapping was counterbalanced across subjects. Targets were presented on a black background and a three-stop neutral density filter covered the monitor to reduce stray light.

Response inhibition and redirection become more difficult with increasing TSDs. TSDs were dynamically adjusted using two independent, interleaved tracking procedures, 2-up/1-down (converging near 71% successful inhibition) and 1-up/2-down (converging near 29% successful inhibition). This procedure ensures successful inhibition on approximately 50% of the step trials, but makes the TSD on any given trial less contingent on the previous trial than a 1-up/1-down procedure. Initial TSD was 94 ms. If a particular step trial was part of the 2-up/1-down staircase, TSD increased by 47 ms if the previous two step trials that were part of that staircase were compensated and decreased by 47 ms if the previous step trial in that staircase was noncompensated. Otherwise, the TSD was held constant. Likewise, for trials that were part of the 1-up/2-down staircase, TSD increased by 47 ms if the previous step trial was compensated, decreased by 47 ms if the two previous step trials were noncompensated, and was otherwise held constant.

Prior to the onset of each trial, a drift correct procedure was performed. A white annulus was presented centrally and participants were required to fixate the stimulus and press the space bar. If the eye position exceeded a maximum distance from the central annulus, the drift correct procedure was repeated. If the drift correct procedure failed a second time, the experimenter was prompted to perform the calibration routine. Groups did not differ on the number of repetitions of the drift correct procedure across the experiment (HC: mean = 23.2, s.d. = 22.1; SZ: mean = 28.3, s.d. = 30.3; $t(32) = 0.56$, $p = 0.58$). With regard to recalibration, there was only one participant that required recalibration during the course of the run, and this only occurred during one run. Participants performed a practice block of 60 trials, and 4 experimental blocks of 120 trials each. Adjustments of the pupil threshold could be made between, but not within, experimental blocks.

2.3.2. Double-step task performance evaluation

Performance was evaluated through measurements of reaction times (RTs) on no-step, compensated, and noncompensated trials, and TSDs to arrive at two main outcome measures relevant to the current analysis: 1) the speed of response execution; and 2) the speed of response inhibition; Performance in this task can be accounted for by a mathematical model that assumes a race between independent processes that generate a response to T1 (GO1 process) and inhibit (STOP process) the T1 response (Boucher et al., 2007; Camalier et al., 2007; Logan and Cowan, 1984; Logan et al., 2014; Ramakrishnan et al., 2012). The saccade to T1 is executed or inhibited if GO1 or STOP wins the race, respectively. The speed of response execution can be measured directly from observable RTs. RTs on no-step and non-compensated trials were defined as the time between T1 onset and the onset of the first saccade. RTs on compensated trials were defined as the time between the onset of T2 and the first saccade.

On the other hand, the speed of response inhibition must be estimated. The independent race model provides an estimate of the time needed to respond to T2 and cancel the initially planned movement, referred to as the *target step reaction time* (TSRT). This measure is analogous to stop signal reaction time (SSRT) in the countermanding task. TSRT was calculated using the integration method (Verbruggen et al., 2013) by sorting no-step RTs and finding the RT corresponding to the proportion of noncompensated trials. Then the mean TSD was subtracted from this RT.

2.3.3. Pupillary response analysis

As described above, each trial was preceded 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 spot, which indicated to the participant that the next trial had started. We observed reliable pupil dilations associated with this event. Because pupil size is confounded with eye position when using video based eye tracker, we were only interested in the initial 500–1000 ms of this dilation, which preceded the appearance of any target. Trials in which subjects blinked or made a saccade during this interval were excluded from further analysis. The percentage of excluded trials did not differ across groups (HC: mean = 12.6%, s.d. = 15.6%; SZP: mean = 15.6%, s.d. = 20.3%; $t(32) = 0.49$, $p = 0.63$).

In other words, our measure of interest was the change in pupil size during the fixation period that immediately followed an event that indicated a new target would soon appear, but before the target was actually presented. The duration of event-triggered pupil dilation is such that their peak lies outside of the 500–1000 ms fixation window reliably measured by our procedure, so we do not report dilation

[1] If the TSD was less than 94 ms, T1 was only presented for the length of the TSD. At TSDs of 47 or 94 ms, T1 offset and T2 onset were simultaneous.

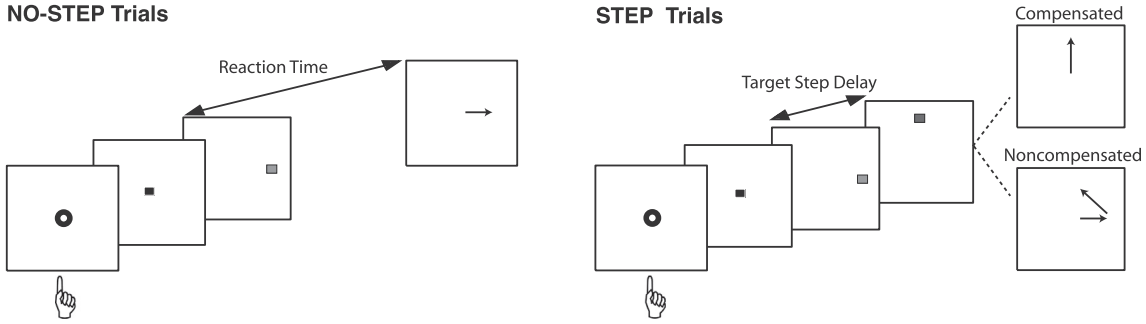

Fig. 1. Modified double-step task. Each trial began with a drift correct procedure. Subjects fixated an annulus and pressed the space bar. Successful drift correction initiated the onset of a variable fixation period between 500 and 1000 ms. The pupil response was measured during this period. Following fixation offset, a target (T1) flashed at a non-central location, and subjects were instructed to saccade to the target as quickly as possible. On step trials, a second target (T2) was flashed at an alternate location at some delay following T1 (target step delay; TSD). On these trials, subjects were instructed to inhibit the planned saccade to T1 and instead redirect gaze towards T2. Trials in which subjects were successful in looking immediately at T2 were referred to as compensated, and trials in which participants erroneously looked first towards T1 were referred to as noncompensated. On the majority of noncompensated trials, subjects made a second corrective saccade to T2. The probability of correctly compensating becomes more difficult with longer TSD; thus, TSD was dynamically altered using a staircase procedure to ensure approximately 50% accuracy on redirect trials.

amplitude itself. Instead, we relied on the fact that event-triggered pupil dilations are stereotyped, such that responses of various amplitudes can be closely approximated by applying various y-axis scalings of the same basic shape (de Gee et al., 2014; Hoeks and Levelt, 1993; Knapen et al., 2016). Accordingly, the steepness of the slope over a given time window early during the response is highly indicative of eventual response amplitude, and will serve as our index of the size of the pupil response. Specifically, we characterized the pupil response for each trial in terms of the proportion pupil size change per unit time (i.e. pupil proportion change scores), as measured across the 500–1000 ms fixation window. To obtain this rate of proportional pupil change, for each sample, we subtracted the mean pupil measure across the first 100 ms of the fixation period and then divided by that same baseline pupil measure. Fixation windows for each trial were divided into 10 ms bins, and the pupil proportion change scores were averaged across each bin. Then, for each bin, we averaged the mean pupil proportion change score across different trial types, arriving at an average time course of pupil size over the fixation window for each subject for a given trial type. For each subject, a line was fit to this time course for each trial type, and the slope parameter was extracted. This measure represented the change in pupil size for each subject for a particular trial type. This slope measure, then, served as our measure of the pupil response for each subject for a particular trial type.

Trials were separated in three ways. First, we separated trials into no-step, compensated, and non-compensated trials to examine whether pupil modulation differed across trial types. Second, we separated trials into noncompensated and compensated trials that were matched on TSDs. Because compensated and noncompensated trials differ in their difficulty (i.e. subjects are more often successfully able to compensate for the initial saccade when TSDs are short), the average TSD for compensated trials will typically be shorter than for noncompensated trials. Thus, to make a more valid assessment of whether pupil modulation is different on trials when subjects successfully inhibit versus those when they do not, we derived a subset of compensated and noncompensated trials that were matched for difficulty (i.e. TSD) and derived the slope of the pupil response for each of these trial types. To do this, we sorted compensated and noncompensated trials by TSDs. Then, using an iterative procedure, we made subsets of compensated and noncompensated trials based on TSD. Specifically, we took the noncompensated trial with the shortest TSD and the compensated trial with the longest TSD and added them to those matched subsets of trials. If the average TSD on the subset of matched compensated trials was longer than the TSD on the subset of matched noncompensated trials, the process continued until the mean TSD for the subset of matched noncompensated trials was greater than the mean TSD for the subset of matched compensated trials. Finally, to examine the relationship between pupil modulation and response speed, we performed a median split on no-step latencies and separated no-step trials into fast and slow responses and computed the slope of the pupil response for each of these two trial types.

Because the slopes of the pupil responses were non-normally distributed, slopes were log-transformed prior to statistical analyses. To accommodate negative slopes a constant value was added to the slope prior to transformation.

2.4. Statistical methods

Fisher's exact tests, independent *t*-tests, and repeated measures ANOVAs were used where appropriate. Spearman rank-correlation coefficients were used to evaluate the association between clinical symptoms, social functioning, and pupil measures in SZP patients. All tests were two-tailed except where noted. Subjects were excluded if the adaptive tracking procedure in the double-step task was ineffective, defined by a proportion of successfully inhibited responses lying outside a 95% binomial confidence interval around $p = 0.5$.

3. Results

3.1. Double-step task performance

Double-step task performance was reported in Thakkar et al. (2015b). Descriptive statistics are presented in Table 3 and analyses are re-presented below.

3.1.1. Probability of inhibition

The dynamic tracking procedure was successful. The mean percentage of noncompensated trials was 48%, and results from an independent samples *t*-test indicated that there was no group difference ($t(32) = 0.01$, $p = 0.99$).

Table 3
Performance measures of the patient and control groups.

	Controls mean (s.d.)	SZP patients mean (s.d.)
Probability of inhibition (%)	47.8 (2.7)	47.8 (4.0)
No-step RT (ms)	289 (46)	311 (80)
Noncompensated RT(ms)	256 (36)	269 (88)
Compensated RT (ms)	284 (58)	349 (86)
TSRT (ms)	131 (37)	163 (57)

3.1.2. Speed of response execution

The effect of trial type (no-step, noncompensated, compensated) on median RT of the first saccade was assessed using a repeated measures ANOVA with diagnostic group as a between-subjects variable and trial type as a within-subjects variable. There was a significant effect of trial type ($F(2,64) = 11.67$, $p < 0.0001$). Noncompensated RTs were faster than no-step RTs ($t(33) = 8.2$, $p < 0.0001$), consistent with race model predictions (Logan and Cowan, 1984), and compensated RTs ($t(33) = 4.8$, $p < 0.0001$). There was no difference between compensated and no-step RTs ($t(33) = 1.6$, $p = 0.11$). There was no main effect of group ($F(1,32) = 2.5$, $p = 0.13$); however, there was a significant group-by-trial type interaction ($F(1,32) = 6.0$, $p = 0.004$). Planned comparisons indicated longer compensated RTs in SZP patients ($t(32) = 2.6$, $p = 0.01$) but no significant group differences in no-step ($t(32) = 1.0$, $p = 0.31$) or noncompensated ($t(32) = 1.48$, $p = 0.59$) RTs. RTs in SZP were only slowed when required to first inhibit a saccade and then redirect gaze.

3.1.3. TSRT

Given previous findings of longer SSRT in schizophrenia using an oculomotor countermanding task (Thakkar et al., 2011), TSRT was compared across groups using a one-tailed independent samples *t*-test. SZP had significantly longer TSRT than HC ($t(32) = 1.96$, $p = 0.03$).

3.2. Pupil modulation

The effects of trial type (no-step, noncompensated, compensated) and group on the slope of the pupil response were assessed using a repeated measures ANOVA. There was a significant effect of group, with the slope of the pupil response being shallower in SZP (Fig. 2; $F(1,32) = 4.74$, $p = 0.04$). There was no significant effect of trial type ($F(2,64) = 0.12$, $p = 0.89$) or trial type-by-group interaction ($F(2,64) = 0.62$, $p = 0.53$).

The effects of trial outcome and group on the pupil response were assessed using a second repeated measures ANOVA, by including trial outcome (TSD-matched compensated and noncompensated trials) as a within-subjects variable. There was no effect of trial outcome ($F(1,32) = 0.003$, $p = 0.96$), nor a group-by-trial outcome interaction effect ($F(1,32) = 0.31$, $p = 0.59$).

Finally, the effect of saccade latency and group on the slope of the pupil response was assessed using a third repeated measures ANOVA, by including no-stop trial latency type (slow, fast) as a within-subjects variable. There was no effect of latency type ($F(1,32) = 0.20$, $p = 0.66$), nor a group-by-latency type interaction effect ($F(1,32) = 2.87$, $p = 0.10$).

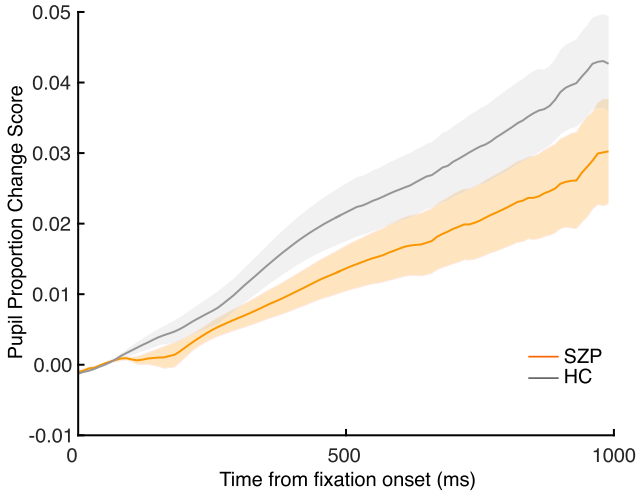

Fig. 2. Normalized pupil responses during the inter-trial interval in SZP (black dotted line) and controls (grey line). Error bars represent standard error of the mean.

We conducted two control analyses to help disambiguate the cause of group differences in pupil dilation. First, the observed dilation of the pupil size locked to the onset of the inter-trial interval could reflect changes in visual input caused by the appearance of the fixation cue. Indeed, both reduced diameter of the dark-adapted pupil and a reduced pupil luminary response have been shown in an older body of psychophysiology studies in schizophrenia (reviewed in Buchsbaum, 1977). Since the onset delay of the pupillary light response is approximately 200 ms (Barbur, 2004), we would expect that group differences in the rate of pupil dilation would emerge only after 200 ms if the pupil light response were driving the effect. To address this issue, we divided the fixation window into five 200 ms intervals and calculated the slope of the pupil size change within each of these intervals for each subject. We then conducted a mixed model ANOVA on these log-transformed slope parameters, using interval as a within-subject factor and group as a between-subject factor and performing a Greenhouse-Geisser adjustment of degrees of freedom. Importantly, there was no significant group-by-interval interaction ($F(2.2,69.7) = 0.39$, $p = 0.70$), indicating that group differences in the rate of pupil dilation did not vary significantly across time.

3.3. Correlations between symptoms, social functioning, performance, medication, and change in pupil size

First, we examined the relationship between the pupil response and symptom severity (SAPS, SANS, and BPRS scores) using Pearson correlation coefficients. Since pupil modulation did not significantly differ across trial types, all correlations were performed using the slope of the pupil response collapsed across all trials. Pupil modulation was significantly correlated with total SANS score, once a bivariate outlier who fell outside a 99% density ellipse was removed from the analysis (without outlier: $r_s = -0.76$, $p = 0.001$; with outlier: $r_s = -0.45$, $p = 0.08$); patients with more severe negative symptoms showed a shallower increase in the pupil response during fixation (Fig. 3). We additionally examined correlations between the three SANS scales and pupil modulation. Pupil dilation rate was significantly negatively related to scores on the Social Dysfunction scale, which assesses anhedonia, apathy, asociality, and asociality (without outlier: $r_s = -0.71$, $p = 0.004$; with outlier: $r_s = -0.52$, $p = 0.05$). There was no relationship between pupil dilation rate and either the Poverty of Speech and Affect (without outlier: $r_s = -0.21$, $p = 0.47$; with outlier: $r_s = 0.02$, $p = 0.95$) or Inattention (without outlier: $r_s = -0.44$, $p = 0.11$; with outlier: $r_s = -0.18$, $p = 0.51$) subscales. Additionally, there was no relationship between pupil modulation and either SAPS ($r_s = -0.03$, $p = 0.91$) or BPRS scores ($r_s = -0.36$, $p = 0.17$). Second, we examined the relationship between pupil modulation and social functioning. Greater increase in the pupil response was associated with significantly higher scores on the Independence-Performance scale of the SFS, which assesses the frequency of daily living activities ($r_s = 0.65$, $p = 0.007$) and, at a trend level, higher scores on the Recreation scale ($r_s = 0.48$, $p = 0.06$). There were no significant correlations between the slope of the pupil response any of the other SFS subscales (all p's > 0.1). Third, we examined the relationship between pupil modulation and task performance across subjects, as indexed by TSRT. There were no significant correlations between the slope of the pupil response and TSRT in either SZP ($r = 0.05$, $p = 0.85$) or HC ($r = 0.19$, $p = 0.44$). Finally, to address potential medication confounds, we also correlated pupil modulation with CPZ dosages. There was no significant relationship between normalized medication dose and the slope of the pupil response ($r = 0.15$, $p = 0.63$).

4. Discussion

Within the context of cognitive-based pupil motility, the bulk of the

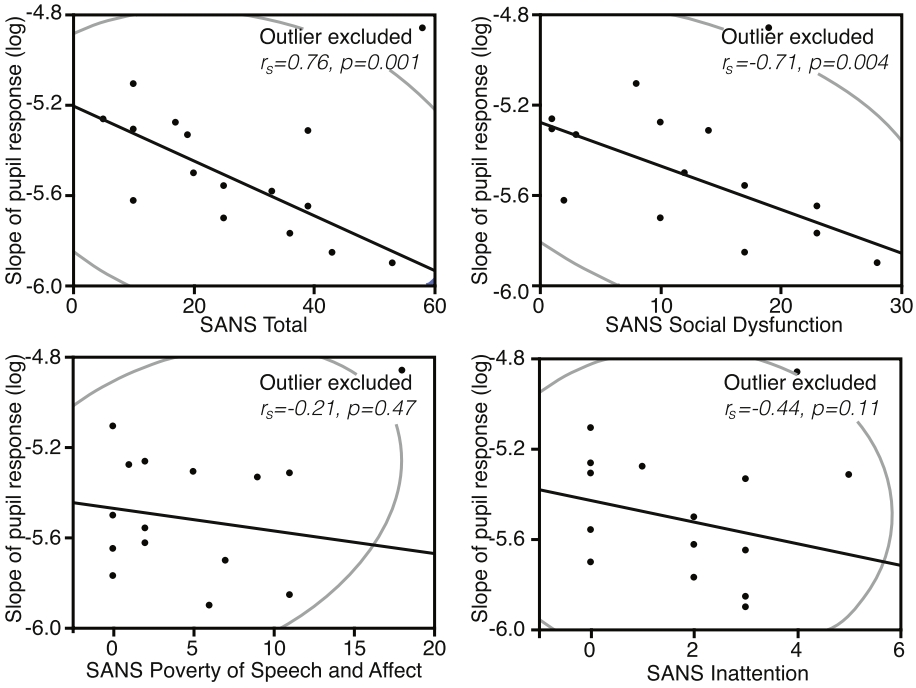

Fig. 3. Relationship between the pupil response and severity of negative symptoms, indexed by SANS total score and three subscale scores: Social Dysfunction, Poverty of Speech and Affect, and Inattention.

existing literature in schizophrenia has focused on periods of effortful cognitive performance across various different experimental paradigms. This rich body of literature shows reduced pupil dilations in schizophrenia, particularly as processing demands increase (Fish and Granholm, 2008; Granholm et al., 1998; Granholm et al., 2009; Granholm et al., 2000; Granholm et al., 1997; Granholm et al., 2016; Granholm and Verney, 2004; Granholm et al., 2007; Karatekin et al., 2010; Morris et al., 1997). These findings have been interpreted as reflecting abnormalities in cognitive processing due to insufficient information processing resources or inappropriate allocation of attention and/or effort. The relationship between reduced pupil dilation and clinical status is inconsistent; although a handful of studies have reported correlations between negative symptom severity and defeatist beliefs and reduced pupil dilation (Granholm et al., 1998; Granholm et al., 2016; Granholm et al., 2007). The results of the current study replicate and extend existing findings by showing that reduced pupil dilations are evident in schizophrenia even as the participant prepares to engage in a cognitively demanding task and are correlated with negative symptoms, specifically those related to apathy, anhedonia, and asociality, and with social functioning.

Consistent with predictions, we observed that pupil size increased across the inter-trial interval of a countermanding task variant in both HC and SZP. However, SZP had a shallower increase in pupil size, which was related to negative symptom severity and some aspects of social functioning. Despite these clinically relevant observations, we did not observe any significant relationships between pupil modulation and behavior, as pupil modulation did not predict speed of inhibiting and redirecting an eye movement.

In interpreting the current findings, we consider two possible causes of pupil dilation during the fixation interval. First, dilation could be related to the preparation for the upcoming eye movement task. Second, dilation could be related to the key press that immediately preceded the pupil measurement interval on each trial. We discuss both of these options in turn.

With regard to the first interpretation, pupil dilation has been found to reflect preparatory activity related to the preparation of a saccadic eye movement, preparation to exert control over a prepotent saccade, or both—an idea that has received support from a study using the antisaccade task in healthy human subjects (Wang et al., 2015). These preparatory pupil dilations are argued to be a correlate of the known preparatory responses, and general orienting and attentional control functions, of neurons in the superior colliculus (SC) and frontal eye fields (FEF). These SC and FEF neurons play a crucial role in the execution and control of eye movements and are also nodes in a pupil control circuit (Ebitz and Moore, 2017; Gandhi and Katnani, 2011; Lehmann and Corneil, 2016; Wang et al., 2014; Wang et al., 2012; Wang and Munoz, 2014, 2015). An argument against an interpretation of pupil dilations in this context in the present study, is that we found no relationship between pupil dilation and measures of gaze control. A previous study also found no such relationship between countermanding task performance and pupil dilations prior to onset of the GO signal, although these results are unpublished (see Fig. 6 in Chambers et al., 2006). One possible explanation for this lack of a relationship is that participants in these paradigms have no way to know whether or not they will have to exert cognitive control in order to alter a prepared eye movement. Accordingly, the reduced pupil dilation in schizophrenia that we observed may correspond to a more general reduction of preparation, to move the eyes, exert voluntary control over the eyes, or both. Within this conceptualization of the current findings, the correlation between pupil dilation and negative symptoms would suggest that these symptoms may reflect a general disturbance in the preparation to act—consistent with the longstanding notion that they reflect a disorder of willed activity, which reflects in part the inability to link goals with the actions required for their initiation (Frith, 1992).

With regard to the second interpretation, the pupil dilation could be related to the key press that validates fixation and initiates the trial. There is widespread evidence for pupil dilations associated with stimulus-driven motor responses (Aston-Jones and Cohen, 2005; Richer and Beatty, 1987). In these cases, transient pupil responses and phasic activity of the locus coeruleus (LC) are used interchangeably due to their tight relationship (Aston-Jones and Cohen, 2005; Murphy et al., 2014). One interpretation of the pupil response accompanying these stimulus-driven motor responses is that it has to do with the decision process leading up to the action (de Gee et al., 2014). Indeed, negative

symptoms have been associated with abnormal effort-based decision-making. Schizophrenia patients—particularly those with more severe negative symptoms—are less willing to expend effort (Barch et al., 2014; Docx et al., 2015; Fervaha et al., 2013; Gold et al., 2013; McCarthy et al., 2016; Treadway et al., 2015). These findings suggest that they may overestimate the cost of effortful actions, which leads to avolition. One caveat regarding an interpretation of pupil dilations in our experiment in the context of the associated key presses is that these key presses did not lead to any reward. In many cases, whether a key press is associated with pupil dilation and phasic LC activity depends on whether the key press leads to a reward. We do not wish to altogether rule out an interpretation in terms of key presses, however, because phasic LC activity has been observed even in the absence of reward (e.g. Clayton, 2004). In those cases, it has been suggested that the promise of potential future reward, rather than immediate reinforcement, can explain the phasic LC activity.

The findings of the current study should be interpreted in light of several limitations. Most importantly, all patients were using antipsychotic medications, which have anticholinergic properties that can influence pupil size. Indeed, haloperidol and chlorpromazine lead to smaller pupil diameter in both healthy individuals and patients with schizophrenia (Sakalis et al., 1972; Smolen et al., 1975b; Smolen et al., 1975a). However, we did not observe any relationship between the rate of pupil dilation and normalized medication dose. Nevertheless, future studies should investigate pupil motility in a population of unmedicated patients. Second, we cannot temporally dissociate pupil dilations associated with the key press to confirm calibration validity, preparation to engage in the task, and the change in visual input, which obscures a more precise interpretation. Third, this study comprises a relative small sample size. Although we did observe group differences in pupil dilation rate that correlated with symptom severity, we may have been underpowered to detect relationships between pupil dynamics and task performance.

In conclusion, the results of the current study indicate a reduced pupil response in schizophrenia patients during the preparation to act, which is strongly associated with negative symptoms. This reduced response may reflect abnormalities in a general orienting response or reduced motivational significance of the cue signifying the onset of a preparatory period thought to be driven by LC activity. These findings additionally suggest that dysfunction in these processes, and their underlying neural mechanisms, may underlie the debilitating negative symptoms of the illness. Given the relative ease of measuring pupil responses, as opposed to more direct brain measures (e.g. EEG and fMRI), pupillometry may have real and immediate clinical utility (Graur and Siegle, 2013) as an illness biomarker.

Acknowledgements

We would like to thank Lindsay Gilling McIntosh and Heathman Nichols for their assistance with clinical interviews, Dr. Gordon Logan for contributions to study design and data analysis, and Dr. Stefan Heckers for his contributions to subject recruitment. This work was supported in part by the National Institute of Health (grant numbers R01MH112644 (KNT), F31-MH085405-01 (KNT), R01MH073028 (SP)), a NARSAD Young Investigator Award from the Brain and Behavior Foundation (KNT), and the E. Bronson Ingram Chair in Neuroscience (JDS).

References

Andreasen, N.C., 1983. The scale for the assessment of negative symptoms (SANS). University of Iowa, Iowa City, IA.

Andreasen, N.C., 1984. The scale for the assessment of positive symptoms (SAPS). University of Iowa, Iowa City, IA.

Aston-Jones, G., Cohen, J.D., 2005. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu. Rev. Neurosci. 28, 403–450. http://dx.doi.org/10.1146/annurev.neuro.28.061604.135709.

Barbur, J.L., 2004. Learning from the pupil: studies of basic mechanisms and clinical applications. In: Chalupa, L.M., Werner, J.S. (Eds.), The Visual Neurosciences. MIT Press, pp. 641–656.

Barch, D.M., Treadway, M.T., Schoen, N., 2014. Effort, anhedonia, and function in schizophrenia: reduced effort allocation predicts amotivation and functional impairment. J. Abnorm. Psychol. 123 (2), 387–397. http://dx.doi.org/10.1037/a0036299.

Bellgrove, M.A., Chambers, C.D., Vance, A., Hall, N., Karamitsios, M., Bradshaw, J.L., 2006. Lateralized deficit of response inhibition in early-onset schizophrenia. Psychol. Med. 36 (4), 495–505.

Birchwood, M., Smith, J., Cochrane, R., Wetton, S., Copestake, S., 1990. The social functioning scale: the development and validation of a new scale of social adjustment for use in family intervention programmes with schizophrenic patients. Br. J. Psychiatry 157, 853–859.

Blair, J.R., Spreen, O., 1989. Predicting premorbid IQ: a revision of the na- tional adult reading test. Clin. Neuropsychol. 3, 129–136.

Boucher, L., Palmeri, T.J., Logan, G.D., Schall, J.D., 2007. Inhibitory control in mind and brain: An interactive race model of countermanding saccades. Psychol. Rev. 114, 376–397.

Buchsbaum, M.S., 1977. Psychophysiology and schizophrenia. Schizophr. Bull. 3 (1), 7–14.

Camalier, C.R., Gotler, A., Murthy, A., Thompson, K.G., Logan, G.D., Palmeri, T.J., et al., 2007. Dynamics of saccade target selection: Race model analysis of double step and search step saccade production in human and macaque. Vis. Res. 47, 2187–2211.

Chambers, C.D., Bellgrove, M.A., Stokes, M.G., Henderson, T.R., Garavan, H., Robertson, I.H., ... Mattingley, J.B., 2006. Executive "brake failure" following deactivation of human frontal lobe. J. Cogn. Neurosci. 18 (3), 444–455. http://dx.doi.org/10.1162/089892906775990606.

Clayton, E.C., 2004. Phasic activation of monkey locus coeruleus neurons by simple decisions in a forced-choice task. J. Neurosci. 24 (44), 9914–9920. http://dx.doi.org/10.1523/JNEUROSCI.2446-04.2004.

de Gee, J.W., Knapen, T., Donner, T.H., 2014. Decision-related pupil dilation reflects upcoming choice and individual bias. Proc. Natl. Acad. Sci. U. S. A. 111 (5), E618–625. http://dx.doi.org/10.1073/pnas.1317557111.

Docx, L., de la Asuncion, J., Sabbe, B., Hoste, L., Baeten, R., Warnaerts, N., Morrens, M., 2015. Effort discounting and its association with negative symptoms in schizophrenia. Cogn. Neuropsychiatry 20 (2), 172–185. http://dx.doi.org/10.1080/13546805.2014.993463.

Ebitz, R.B., Moore, T., 2017. Selective modulation of the pupil light reflex by microstimulation of prefrontal cortex. J. Neurosci. 37 (19), 5008–5018. http://dx.doi.org/10.1523/JNEUROSCI.2433-16.2017.

Einhäuser, W., 2017. The pupil as a marker of cognitive processes. In: Zhao, Q. (Ed.), Comuptational and Cognitive Neuroscience of Vision. Springer, Singapore, pp. 141–169.

Ethridge, L.E., Soilleux, M., Nakonezny, P.A., Reilly, J.L., Hill, S.K., Keefe, R.S., ... Sweeney, J.A., 2014. Behavioral response inhibition in psychotic disorders: diagnostic specificity, familiality and relation to generalized cognitive deficit. Schizophr. Res. 159 (2–3), 491–498. http://dx.doi.org/10.1016/j.schres.2014.08.025.

Fervaha, G., Graff-Guerrero, A., Zakzanis, K.K., Foussias, G., Agid, O., Remington, G., 2013. Incentive motivation deficits in schizophrenia reflect effort computation impairments during cost-benefit decision-making. J. Psychiatr. Res. 47 (11), 1590–1596. http://dx.doi.org/10.1016/j.jpsychires.2013.08.003.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1995. Structured clinica l interview for DSM-IV Axis I disorders. Biometrics Research, New York.

Fish, S.C., Granholm, E., 2008. Easier tasks can have higher processing loads: task difficulty and cognitive resource limitations in schizophrenia. J. Abnorm. Psychol. 117 (2), 355–363. http://dx.doi.org/10.1037/0021-843X.117.2.355.

Frith, C., 1992. The Cognitive Neuropsychology of Schizophrenia. Lawrence Erlbaum, Hove, UK.

Fortgang, R.G., Hultman, C.M., van Erp, T.G., Cannon, T.D., 2016. Multidimensional assessment of impulsivity in schizophrenia, bipolar disorder, and major depressive disorder: testing for shared endophenotypes. Psychol. Med. 46 (7), 1497–1507. http://dx.doi.org/10.1017/S0033291716000131.

Gandhi, N.J., Katnani, H.A., 2011. Motor functions of the superior colliculus. Annu. Rev. Neurosci. 34, 205–231. http://dx.doi.org/10.1146/annurev-neuro-061010-113728.

Gold, J.M., Strauss, G.P., Waltz, J.A., Robinson, B.M., Brown, J.K., Frank, M.J., 2013. Negative symptoms of schizophrenia are associated with abnormal effort-cost computations. Biol. Psychiatry 74 (2), 130–136. http://dx.doi.org/10.1016/j.biopsych.2012.12.022.

Granholm, E., Verney, S.P., 2004. Pupillary responses and attentional allocation problems on the backward masking task in schizophrenia. Int. J. Psychophysiol. 52 (1), 37–51. http://dx.doi.org/10.1016/j.ijpsycho.2003.12.004.

Granholm, E., Morris, S.K., Sarkin, A.J., Asarnow, R.F., Jeste, D.V., 1997. Pupillary responses index overload of working memory resources in schizophrenia. J. Abnorm. Psychol. 106 (3), 458–467.

Granholm, E., Chock, D., Morris, S., 1998. Pupillary responses evoked during verbal fluency tasks indicate semantic network dysfunction in schizophrenia. J. Clin. Exp. Neuropsychol. 20 (6), 856–872. http://dx.doi.org/10.1076/jcen.20.6.856.1107.

Granholm, E., Morris, S., Asarnow, R.F., Chock, D., Jeste, D.V., 2000. Accelerated age-related decline in processing resources in schizophrenia: evidence from pupillary responses recorded during the span of apprehension task. J. Int. Neuropsychol. Soc. 6 (1), 30–43.

Granholm, E., Verney, S.P., Perivoliotis, D., Miura, T., 2007. Effortful cognitive resource allocation and negative symptom severity in chronic schizophrenia. Schizophr. Bull. 33 (3), 831–842. http://dx.doi.org/10.1093/schbul/sbl040.

Granholm, E., Fish, S.C., Verney, S.P., 2009. Pupillometric measures of attentional

allocation to target and mask processing on the backward masking task in schizophrenia. Psychophysiology 46 (3), 510–520.
Granholm, E., Ruiz, I., Gallegos-Rodriguez, Y., Holden, J., Link, P.C., 2016. Pupillary responses as a biomarker of diminished effort associated with defeatist attitudes and negative symptoms in schizophrenia. Biol. Psychiatry 80 (8), 581–588. http://dx.doi.org/10.1016/j.biopsych.2015.08.037.
Graur, S., Siegle, G., 2013. Pupillary motility: bringing neuroscience to the psychiatry clinic of the future. Curr. Neurol. Neurosci. Rep. 13 (8), 365. http://dx.doi.org/10.1007/s11910-013-0365-0.
Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am. J. Psychiatr. 153 (3), 321–330.
Hoeks, B., Levelt, W.J.M., 1993. Pupillary dilation as a measure of attention: a quantitative system analysis. Behav. Res. Methods Instrum. Comput. 25 (1), 16–26.
Huddy, V.C., Aron, A.R., Harrison, M., Barnes, T.R., Robbins, T.W., Joyce, E.M., 2009. Impaired conscious and preserved unconscious inhibitory processing in recent onset schizophrenia. Psychol. Med. 39 (6), 907–916.
Hughes, M.E., Fulham, W.R., Johnston, P.J., Michie, P.T., 2012. Stop-signal response inhibition in schizophrenia: behavioural, event-related potential and functional neuroimaging data. Biol. Psychol. 89 (1), 220–231. http://dx.doi.org/10.1016/j.biopsycho.2011.10.013.
Karatekin, C., Bingham, C., White, T., 2010. Oculomotor and pupillometric indices of pro- and antisaccade performance in youth-onset psychosis and attention deficit/hyperactivity disorder. Schizophr. Bull. 36 (6), 1167–1186. http://dx.doi.org/10.1093/schbul/sbp035.
Knapen, T., de Gee, J.W., Brascamp, J., Nuiten, S., Hoppenbrouwers, S., Theeuwes, J., 2016. Cognitive and ocular factors jointly determine pupil responses under equiluminance. PLoS ONE 11 (5), e0155574. http://dx.doi.org/10.1371/journal.pone.0155574.
Lappin, J., Eriksen, C.W., 1966. Use of a delayed signal to stop a visual reaction-time response. J. Exp. Psychol. Gen. 72 (6), 805–811.
Lehmann, S.J., Corneil, B.D., 2016. Transient pupil dilation after subsaccadic microstimulation of primate frontal eye fields. J. Neurosci. 36 (13), 3765–3776. http://dx.doi.org/10.1523/JNEUROSCI.4264-15.2016.
Lipszyc, J., Schachar, R., 2010. Inhibitory control and psychopathology: a meta-analysis of studies using the stop signal task. J. Int. Neuropsychol. Soc. 16 (6), 1064–1076. http://dx.doi.org/10.1017/S1355617710000895.
Logan, G.D., Cowan, W.B., 1984. On the ability to inhibit thought and action: a theory of an act of control. Psychol. Rev. 91, 295–327.
Logan, G.D., Van Zandt, T., Verbruggen, F., Wagenmakers, E.J., 2014. On the ability to inhibit thought and action: general and special theories of an act of control. Psychol. Rev. 121, 66–95.
Matzke, D., Hughes, M., Badcock, J.C., Michie, P., Heathcote, A., 2017. Failures of cognitive control or attention? The case of stop-signal deficits in schizophrenia. Atten. Percept. Psychophys. 79 (4), 1078–1086. http://dx.doi.org/10.3758/s13414-017-1287-8.
McCarthy, J.M., Treadway, M.T., Bennett, M.E., Blanchard, J.J., 2016. Inefficient effort allocation and negative symptoms in individuals with schizophrenia. Schizophr. Res. 170 (2–3), 278–284. http://dx.doi.org/10.1016/j.schres.2015.12.017.
Morris, S.K., Granholm, E., Sarkin, A.J., Jeste, D.V., 1997. Effects of schizophrenia and aging on pupillographic measures of working memory. Schizophr. Res. 27 (2–3), 119–128. http://dx.doi.org/10.1016/S0920-9964(97)00065-0.
Murphy, P.R., O'Connell, R.G., O'Sullivan, M., Robertson, I.H., Balsters, J.H., 2014. Pupil diameter covaries with BOLD activity in human locus coeruleus. Hum. Brain Mapp. 35 (8), 4140–4154. http://dx.doi.org/10.1002/hbm.22466.
Nolan, K.A., D'Angelo, D., Hoptman, M.J., 2011. Self-report and laboratory measures of impulsivity in patients with schizophrenia or schizoaffective disorder and healthy controls. Psychiatry Res. 187 (1–2), 301–303. http://dx.doi.org/10.1016/j.psychres.2010.10.032.
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97–113.
Overall, J.E., Gorham, D.R., 1962. The brief psychiatric rating scale. Psychol. Rep. 10, 799–812.
Peralta, V., Cuesta, M.J., 1999. Dimensional structure of psychotic symptoms: an item-level analysis of SAPS and SANS symptoms in psychotic disorders. Schizophr. Res. 38 (1), 13–26.
Ramakrishnan, A., Sureshbabu, R., Murthy, A., 2012. Understanding how the brain changes its mind: Microstimulation in the macaque frontal eye field reveals how saccade plans are changed. J. Neurosci. 32, 4457–4472.
Richer, F., Beatty, J., 1987. Contrasting effects of response uncertainty on the task-evoked pupillary response and reaction time. Psychophysiology 24 (3), 258–262.
Sakalis, G., Curry, S.H., Mould, G.P., Lader, M.H., 1972. Physiologic and clinical effects of chlorpromazine and their relationship to plasma level. Clin. Pharmacol. Ther. 13 (6), 931–946.
Smolen, V.F., Murdock Jr., H.R., Williams, E.J., 1975a. Bioavailability analysis of chlorpromazine in humans from pupilometric data. J. Pharmacol. Exp. Ther. 195 (3), 404–415.
Smolen, V.F., Murdock Jr., H.R., Stoltman, W.P., Clevenger, J.W., Combs, L.W., Williams, E.J., 1975b. Pharmacological response data for comparative bioavailability studies of chlorpromazine oral dosage forms in humans: I. Pupilometry. J. Clin. Pharmacol. 15 (11 − 12), 734–751.
Thakkar, K.N., Schall, J.D., Boucher, L., Logan, G., Park, S., 2011. Response inhibition and response monitoring in a saccadic countermanding task in schizophrenia. Biol. Psychiatry 69 (1), 55–62.
Thakkar, K.N., Schall, J.D., Heckers, S., Park, S., 2015. Disrupted saccadic corollary discharge in schizophrenia. J. Neurosci. 35 (27), 9935–9942.
Thakkar, K.N., Schall, J.D., Logan, G.D., Park, S., 2015a. Cognitive control of gaze in bipolar disorder and schizophrenia. Psychiatry Res. 225 (3), 254–262. http://dx.doi.org/10.1016/j.psychres.2014.12.033.
Thakkar, K.N., Schall, J.D., Logan, G.D., Park, S., 2015b. Response inhibition and response monitoring in a saccadic double-step task in schizophrenia. Brain Cogn. 95, 90–98. http://dx.doi.org/10.1016/j.bandc.2015.01.007.
Treadway, M.T., Peterman, J.S., Zald, D.H., Park, S., 2015. Impaired effort allocation in patients with schizophrenia. Schizophr. Res. 161 (2–3), 382–385. http://dx.doi.org/10.1016/j.schres.2014.11.024.
Verbruggen, F., Chambers, C.D., Logan, G.D., 2013. Fictitious inhibitory differences: How skewness and slowing distort the estimation of stopping latencies. Psychol. Sci. 24, 352–362.
Wang, C.A., Munoz, D.P., 2014. Modulation of stimulus contrast on the human pupil orienting response. Eur. J. Neurosci. 40 (5), 2822–2832. http://dx.doi.org/10.1111/ejn.12641.
Wang, C.A., Munoz, D.P., 2015. A circuit for pupil orienting responses: implications for cognitive modulation of pupil size. Curr. Opin. Neurobiol. 33, 134–140. http://dx.doi.org/10.1016/j.conb.2015.03.018.
Wang, C.A., Boehnke, S.E., White, B.J., Munoz, D.P., 2012. Microstimulation of the monkey superior colliculus induces pupil dilation without evoking saccades. J. Neurosci. 32 (11), 3629–3636. http://dx.doi.org/10.1523/JNEUROSCI.5512-11.2012.
Wang, C.A., Boehnke, S.E., Itti, L., Munoz, D.P., 2014. Transient pupil response is modulated by contrast-based saliency. J. Neurosci. 34 (2), 408–417. http://dx.doi.org/10.1523/JNEUROSCI.3550-13.2014.
Wang, C.A., Brien, D.C., Munoz, D.P., 2015. Pupil size reveals preparatory processes in the generation of pro-saccades and anti-saccades. Eur. J. Neurosci. 41 (8), 1102–1110. http://dx.doi.org/10.1111/ejn.12883.
Woods, S.W., 2003. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J. Clin. Psychiatry 64 (6), 663–667.
Yun, D.Y., Hwang, S.S., Kim, Y., Lee, Y.H., Kim, Y.S., Jung, H.Y., 2011. Impairments in executive functioning in patients with remitted and non-remitted schizophrenia. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 35 (4), 1148–1154. http://dx.doi.org/10.1016/j.pnpbp.2011.03.018.