

Effortful Cognitive Resource Allocation and Negative Symptom Severity in Chronic Schizophrenia

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Background: The relationship between negative symptoms, early visual information–processing deficits, and effortful processing resource allocation was investigated. **Methods:** Older patients with chronic schizophrenia ($n = 58$) and healthy controls ($n = 71$) participated. Pupillary responses were recorded during performance of the span of apprehension task (blocks of 3- and 10-letter arrays) as an index of resource allocation or mental effort during the task. **Results:** Patients and controls showed larger pupillary responses in higher relative to lower processing loads both during array processing and just prior to array onset (preparation). Both groups, therefore, invested more cognitive effort preparing for and then processing larger arrays. A subgroup of patients with abnormally small pupillary responses and impaired performance showed greater negative symptom severity relative to a subgroup of patients with normal pupillary responses. Smaller pupillary responses in the patients were also significantly correlated with greater negative symptom severity, independent of positive symptom severity. Patients with reduced effortful resource allocation, therefore, exhibited greater negative symptomatology. A subgroup of patients with normal pupillary responses still showed impaired detection accuracy relative to controls, suggesting that reduced cognitive effort or resource allocation problems cannot account for impairments in early visual information processing in this subgroup. **Conclusions:** The study illustrates important relationships between cognitive effort and performance that can impact conclusions about the nature of cognitive impairments and associations between negative symptoms and neurocognition in schizophrenia.

Key words: schizophrenia/negative symptoms/pupillary responses/resource allocation/information processing

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Introduction

Vulnerability/stress models provide a framework for understanding how neurocognitive impairment might contribute to negative symptom severity in schizophrenia.^{1–3} These models propose that personal enduring vulnerability traits, like “reduced available processing resources,” interact with environmental stressors and coping responses to contribute to symptom formation. In a tentative model for negative symptoms, Nuechterlein⁴ suggested that reduced availability of processing resources leads to impaired early visual information processing under high processing loads and contributes to negative symptom severity.

The personal vulnerability factor of reduced available processing resources describes the pattern of performance impairment commonly found on a number of information-processing tasks under high processing loads, including the partial report span of apprehension (SOA) task.¹ On the SOA task, participants detect which of 2 target letters is among a group of letters flashed very briefly (50–100 milliseconds) in a visual display. In dozens of studies, patients with schizophrenia have shown impaired target detection accuracy in conditions with 8-, 10-, or 12-letter arrays but not with smaller array sizes (for a review, see Asarnow and Granholm¹). Reduced detection accuracy in high processing load conditions of the SOA task has also been reported in first-degree relatives of patients with schizophrenia, suggesting the task may mark genetic vulnerability for schizophrenia.^{5,6} Poor performance only at higher processing loads on tasks like the SOA task may indicate that patients with schizophrenia have insufficient processing resources available to perform tasks under high processing demands (resource-limitations hypothesis).^{2,7}

A reduction in resources available for effortful controlled processing might contribute to negative symptoms of apathy, avolition, affective flattening, anhedonia, asociality, and emotional withdrawal. Patients with diminished resources, eg, would be less able to allocate resources to processing environmental stimuli in complex social situations.⁸ SOA task deficits at high processing loads have been associated with negative, but not positive, symptom severity, and SOA task deficits remain stable through psychotic and remitted states in

longitudinal studies.^{9–11} Impairments on other early visual information-processing tasks have also been linked to negative symptom severity.^{9,11}

Pupil dilation responses evoked by cognitive tasks index the extent of effortful cognitive resources allocated to the task. Greater increase in pupil diameter during a task reflects greater processing resource allocation to the task.^{12,13} Pupillometry methods, therefore, can be used to index resource availability and verify task effort investment.¹⁴ Consistent with the resource-limitations hypothesis, smaller pupillary responses have been found in schizophrenic patients relative to nonpsychiatric controls during orienting and oddball tasks and under higher, but not lower, processing loads on digit span recall tasks, visual backward masking tasks, the SOA task, and serial addition/subtraction tasks.^{15–19}

In the present study, a resource-limitations vulnerability model of negative symptom severity⁴ was examined by recording pupillary responses during the SOA task (3- and 10-letter arrays) in older, very chronic patients with schizophrenia and age-comparable nonpsychiatric controls. Older, chronic patients were studied because stronger links between negative symptoms, cognitive impairment, and autonomic hypo-responsivity have been found in older, more chronic patients.²⁰ These stronger associations in older patients may be due to neurobiological factors associated with normal or accelerated aging processes (eg, age-related processing resource depletion), chronicity, and/or understimulating social and institutional environments. In addition, we previously found accelerated age-related decline in detection accuracy and pupillary dilation responses on the SOA task in older patients with schizophrenia,¹⁶ so sampling older patients provided an opportunity to try to replicate those findings. Based on the resource-limitations hypothesis and our prior study, we predicted that participants with schizophrenia would show poorer detection accuracy and smaller pupillary responses (ie, reduced resource allocation) relative to nonpsychiatric participants, especially in higher (ie, 10-letter arrays) but not lower (ie, 3-letter arrays) processing load conditions. In addition, to examine relationships between effortful cognitive resource allocation, early visual information-processing task performance, and negative symptom severity, we divided the patient sample into high- vs low-pupillary response subgroups. Based on the resource-limitations vulnerability model, we predicted that greater negative symptom severity would be associated with poorer task performance and reduced pupillary responses, especially in the higher processing load condition.

Materials and Methods

Participants

This research protocol was approved by the human subjects committees of the University of California,

Table 1. Participant Characteristics

Variable	Group	
	Schizophrenia	Nonpsychiatric
<i>n</i>	58	71
Age, M (SD)	54.0 (7.9)	56.6 (9.7)
Gender, % male	63.8	50.7
Race, % Caucasian	77.6	77.5
ANART, M (SD)	106.1 (10.8)	111.1 (8.8)
SAPS total, M (SD)	3.90 (2.78)	—
SANS total, M (SD)	6.62 (3.36)	—

Note: ANART, American National Adult Reading Test⁶⁹ was missing for one patient and one control; SAPS, Scale for Assessment of Positive Symptoms²⁶; SANS, Scale for Assessment of Negative Symptoms.²⁶ SANS total, sum of global ratings for affective flattening, avolition–apathy, anhedonia–Asociality, and attention. SAPS total, sum of global ratings for hallucinations, delusions, bizarre behavior, and positive formal thought disorder. Groups did not differ significantly on any variable, except for ANART: nonpsychiatric > schizophrenia, $t_{125} = 2.87$, $P < .01$.

San Diego, and the Veterans Affairs San Diego Healthcare System institutional review boards, and informed consent was obtained from all participants (and their legal representatives, when appropriate). Outpatients ($n = 58$, age 40–75 years) with schizophrenia or schizoaffective disorder were recruited from the San Diego Veterans Affairs Healthcare System; San Diego County Mental Health Services; University of California, San Diego, Outpatient Psychiatric Services; and San Diego County–assisted living (board and care) facilities and private psychiatrists. The Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*—Patient Version²¹ was used to determine *DSM-IV* diagnoses.²² All but 3 patients were receiving antipsychotic medications at the time of testing (11 typical, 31 atypical, 10 both typical and atypical, and 3 unknown), 27 were taking anticholinergic medications (28 none, 3 unknown), and 31 were taking antidepressant or mood medications (24 none, 3 unknown). For patients receiving antipsychotic medications, the chlorpromazine equivalent dosage (CPZE)^{23–25} was calculated if the dosage could be verified through medical records or information from psychiatrists ($M = 320.1$, $SD = 262.8$, $n = 42$). For patients receiving anticholinergic medications, clinically recommended benztropine equivalent scores (ACHE)^{23,24} were calculated if the dosage could be verified through medical records or information from psychiatrists ($M = 0.65$, $SD = 1.12$, $n = 27$). Positive and negative symptom severity was rated (table 1) using the Scale for Assessment of Positive Symptoms (SAPS)²⁶ and the Scale for Assessment of

Negative Symptoms (SANS).²⁶ SAPS and SANS ratings of symptom severity during the past 2 weeks were carried out by trained technicians using the SAPS and SANS clinical interviews, after the Structured Clinical Interview for *DSM-IV* was administered. Interrater reliability (mean kappa) across raters was .87 for total SAPS and .83 for total SANS. SAPS and SANS ratings (table 1) indicated mild-to-moderate symptom severity.

Newspaper advertisements were used to recruit non-psychiatric controls ($n = 71$) from the general community to be comparable in age to the patients with schizophrenia. Control participants had no lifetime diagnosis of mood or psychotic disorders based on the Structured Clinical Interview for *DSM-IV*—Nonpatient Version.²¹ All participants were screened using a brief background interview to exclude for factors that may affect pupil dilation or cognitive functioning, including neurological disorders (eg, seizures) or head injury with loss of consciousness (>30 minute), substance-dependence disorder (*DSM-IV* criteria) other than nicotine or caffeine in the past 6 months, visual acuity worse than 20/40 based on a Snellen eye examination (corrected or uncorrected), ocular damage or disease, eye surgery or ocular medications that may alter pupil function, or insulin-dependent diabetes. Participant characteristics are shown in table 1.

Apparatus

Participants were seated comfortably in a lighted room (85 lux) facing a 50-cm flat screen color monitor with their chin and forehead stabilized in chin/head rest. The apparatus maintained a standard distance of 77 cm between the eye and the computer monitor and minimized movement artifact. A PC-compatible micro-computer was used to administer the SOA task, and a 2-button box was used to gather the responses. A Micromeasurements System 1200 corneal reflection–pupil center infrared pupillometer system with associated software was used to record pupillary responses from the left eye. A video camera sensitive to infrared light and an infrared light source were positioned 24 cm from the participant's eye below the line of sight. Analog pupil area was digitized at a 60-Hz sampling rate and saved for offline analysis. Pupil area was later transformed to diameter for comparison with typical pupillometric studies. The resolution of the pupillometer was .05-mm diameter, but with signal averaging, differences on the order of .01–.02 mm can be reliably detected.

Procedure

On the SOA task, participants were instructed to press 1 of the 2 buttons corresponding to 1 of the 2 target letters (“T” or “F”) presented on the computer screen within a group of other letters. Participants were informed that 1, but never both, of the 2 target letters would be presented on every trial. Both detection accuracy and

speed were stressed in the instructions. The target was embedded in arrays containing 2 (3-letter condition) or 9 other letters (10-letter condition) randomly selected from the remaining letters of the English alphabet. Array letters were arbitrarily assigned to locations in a 5×5 matrix, with an equal number of each target presented within each array-size condition. The visual angle for the 5×5 matrix was $18.4^\circ \times 23.5^\circ$ (height \times width) and for each letter was $3.4^\circ \times 3.4^\circ$.

Participants were given 10 practice trials (5 consecutive 3-letter, 5 consecutive 10-letter) with accuracy feedback. A total of 64 test trials were then administered without feedback in blocks of 8 trials per condition (sequence: 3-letter, 3-letter, 10-letter, 10-letter, 10-letter, 10-letter, 3-letter, 3-letter) with a 1-minute rest between blocks, for a total of 32 test trials per array-size condition. At the start of each trial, a dark screen was replaced by a white fixation square (1.0×1.0 cm, 0.4° of visual angle) that was displayed for 250 milliseconds in the center of the monitor on a dark screen background and a tone was sounded. These stimuli oriented the participant to prepare to attend to the letter arrays, which were displayed 250 milliseconds after fixation square offset (500 milliseconds after trial onset, see figure 1). The letter arrays were displayed for 100 milliseconds as white letters on a black screen background. A 5-second interval was maintained from onset of fixation on one trial to onset of fixation on the next. Participants were asked to refrain from blinking during trials and encouraged to blink during a 1-minute rest between trial blocks. The entire task was completed in 20–25 minutes.

Data Analyses

A computer algorithm was used to remove blinks and artifacts (identified as large changes in dilation outside the possible rate of change in pupil area) from digitized pupillary response trial waveforms (4 seconds), and discarded data were replaced using linear interpolation. Trials were discarded if over 50% of the waveform comprised blinks and artifacts. A 2-pass 5-point digital smoothing filter (3.7 Hz) was then applied to the data, and valid trials were averaged for each condition. All valid trials were averaged, regardless of whether the participant's response to the trial was correct or incorrect. Participants who did not have at least 5 valid trials in each array-size condition were excluded because visual inspection of averaged waveforms indicated instability with fewer than 5 trials averaged. Originally, 99 controls and 86 patients with schizophrenia were included in this study, but 24 controls and 26 patients were excluded for having fewer than 5 valid trials per condition. Four additional controls and 2 patients were excluded due to mechanical failure or examiner error that resulted in loss of pupil data. Participants excluded for excessive pupil data artifact did not differ significantly from participants included on any of

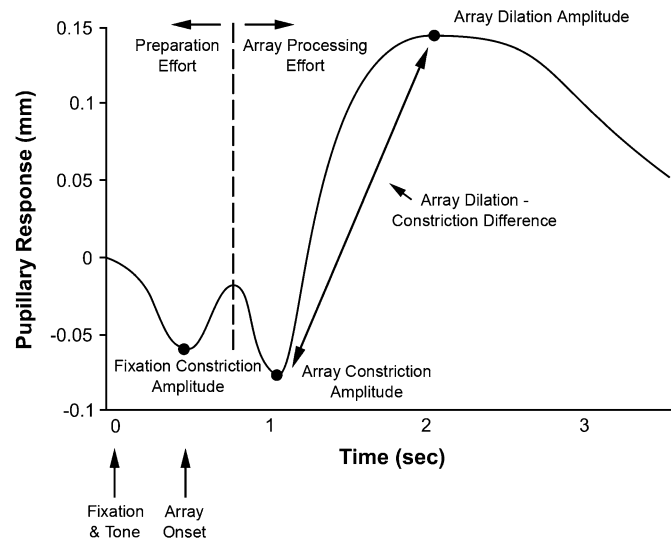


Fig. 1. Pupillary response waveform (change in pupil diameter relative to baseline) evoked by the span of apprehension task and pupillary response variables derived from the waveform. At the start of each trial, a dark screen was replaced by a white fixation square in the center of the monitor and a tone was sounded. An initial small light reflex constriction response to the increased luminance of the fixation square was observed prior to array exposure (preparation effort). Three- or 10-letter arrays were displayed 500 milliseconds after trial onset as white letters on a black screen for 100 milliseconds. The arrays evoked a larger light reflex and a subsequent dilation response (array-processing effort).

the following variables: SOA detection accuracy, SAPS total, SANS total, American National Adult Reading Test intelligence quotient (ANART IQ) estimates, gender, or race, but older participants in both groups were more likely to be excluded (included vs excluded: $F_{1,181} = 4.51$, $P = .035$; group \times included/excluded: $F_{1,181} = 0.00$, $P = .953$). For the final sample of included participants with valid pupil data (schizophrenia: $n = 58$, nonpsychiatric: $n = 71$), cleaning procedures resulted in a mean (SD) of 22.3 (7.2) and 20.0 (7.4) trials for the controls and 20.4 (7.3) and 18.2 (7.3) trials for the patients with schizophrenia in 3-letter and 10-letter array conditions, respectively.

Pupillary responses to cognitive tasks with visual displays that increase in luminance are typically bimodal waveforms, with an initial light reflex constriction elicited by the increased array luminance followed by a peak dilation response. In response to the SOA task in this study, 2 such bimodal waveforms were observed (figure 1). An initial small light reflex to the increased luminance of the fixation square (white pixels on dark screen) was observed prior to array exposure (preparation phase), and this was followed by a larger light reflex to the brighter stimulus arrays and a subsequent dilation response evoked by array processing (figure 1). The following pupillary response variables were derived: baseline pupil diameter (average of 5 samples recorded immediately prior to fixation on each trial), fixation constriction amplitude (difference between baseline and the smallest diameter between 0 and 800 milliseconds), latency to fixation constriction amplitude, array constriction amplitude (difference between baseline and the smallest

diameter between 800 and 1500 milliseconds), latency to array constriction amplitude, array dilation amplitude (difference between baseline and the largest pupil diameter occurring between 1000 and 4000 milliseconds), latency to array dilation amplitude, and array dilation–array constriction difference score, which was the primary pupillary response measure (see figure 1). The 2 array sizes differed in both luminance and processing load (more letters produced more light), so greater array constriction amplitude was expected for larger arrays. The array dilation–constriction difference score accounted for this by computing dilation responses relative to peak array constriction.

A split-plot 2×2 analysis of variance (ANOVA), with diagnostic group (schizophrenia vs nonpsychiatric) as a between-subjects factor and array size (3- and 10-letter arrays) as a repeated-measures factor, was computed for each dependent variable. To examine relationships between pupil dilation, performance, and negative symptoms in the patients with schizophrenia, they were divided into high-dilation ($n = 29$) and low-dilation ($n = 29$) subgroups based on a median split on the array dilation–constriction difference score in the high-load (10-letter) condition. Split-plot 3×2 ANOVAs, with group (high-dilation patients, low-dilation patients, nonpsychiatric) as a between-subjects factor and array size as a repeated-measures factor, were computed for the array dilation–constriction difference score and detection accuracy variables. Tukey tests were used for all post hoc comparisons. Subgroups were compared on positive (SAPS total) and negative (SANS total) symptom severity using 2-tailed t tests. Pearson correlations (r) and

Table 2. Performance and Pupillary Response Variables on the Span of Apprehension Task for Each Participant Group

	Schizophrenia		Nonpsychiatric		Group			Array			Group × Array Interaction		
	3-Letter	10-Letter	3-Letter	10-Letter	<i>F</i>	<i>P</i>	η^2	<i>F</i>	<i>P</i>	η^2	<i>F</i>	<i>P</i>	η^2
Detection accuracy (%)	89.3 (10.4)	66.8 (13.0)	96.2 (4.7)	77.0 (9.2)	37.54	<.001	.23	478.16	<.001	.79	3.14	.079	.02
Baseline pupil diameter (mm)	3.78 (0.87)	3.81 (0.88)	3.91 (0.84)	3.93 (0.91)	0.69	.409	.01	4.59	.034	.03	0.01	.919	.00
Fixation constriction amplitude (mm)	-0.07 (0.06)	-0.06 (0.05)	-0.08 (0.07)	-0.07 (0.06)	0.69	.408	.01	4.40	.038	.03	0.35	.557	.00
Fixation constriction latency (s)	0.50 (0.21)	0.48 (0.22)	0.46 (0.18)	0.46 (0.17)	0.98	.323	.01	0.65	.423	.01	0.77	.382	.01
Array constriction amplitude (mm)	-0.05 (0.08)	-0.09 (0.10)	-0.01 (0.10)	-0.10 (0.14)	0.91	.342	.01	90.27	<.001	.42	12.03	.001	.09
Array constriction latency (s)	1.13 (0.14)	1.19 (0.12)	1.12 (0.14)	1.16 (0.09)	1.53	.218	.01	18.10	<.001	.13	0.29	.589	.00
Array dilation amplitude (mm)	0.08 (0.07)	0.09 (0.08)	0.17 (0.10)	0.17 (0.12)	27.73	<.001	.18	0.58	.446	.01	0.03	.865	.00
Array dilation latency (s)	2.44 (0.74)	2.72 (0.80)	2.11 (0.52)	2.43 (0.55)	9.00	.003	.07	32.11	<.001	.20	0.15	.699	.00
Array dilation-constriction difference (mm)	0.13 (0.08)	0.18 (0.10)	0.18 (0.10)	0.27 (0.14)	13.03	<.001	.09	74.67	<.001	.37	7.41	.007	.06

Note: All variables are M (SD). For all *F* tests, *df* = 1, 127.

partial correlations (r_p) were used to examine relationships between pupillary responses and detection accuracy and specific demographic, medication, and symptom variables. To examine age-related effects, separate linear regression analyses similar to those used in our previous study¹⁶ were computed for overall (average of 3- and 10-letter) SOA detection accuracy and overall pupillary responses (array dilation-constriction difference) as dependent variables and age, diagnostic group (coded 0 = nonpsychiatric, 1 = schizophrenia), and the interaction between age and diagnostic group (transformed to *z* scores before computing their product) entered simultaneously as independent variables.

Results

Performance

Detection accuracy for both groups is shown in table 2 with results of the 2 (groups) × 2 (array sizes) ANOVA. A significant group effect indicated poorer performance in the patients, and a significant array-size effect indicated poorer performance in larger array-size conditions. A trend ($P = .079$) was found for the group × array size interaction, indicating marginally greater impairment in detection accuracy in the higher load condition in the patients with schizophrenia.

Pupillary Responses

Figure 2 shows the pupillary response waveforms for each group in each array-size condition. Pupillary response variables derived from these waveforms are shown for each group in each array-size condition in table 2 with the results of the 2 (groups) × 2 (array sizes)

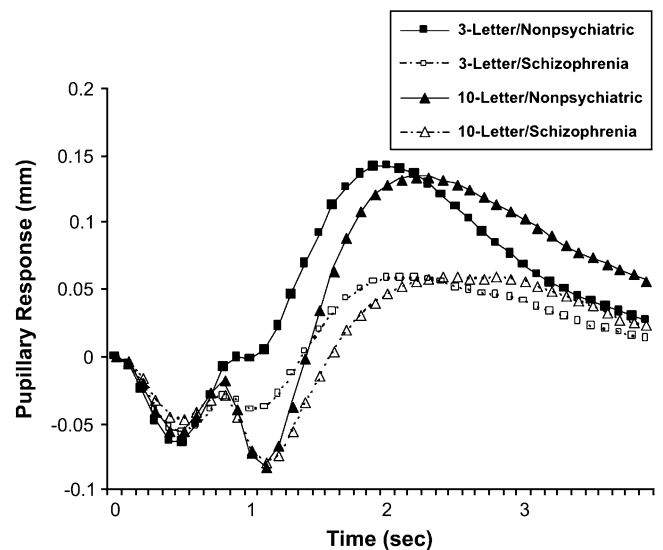


Fig. 2. Pupillary response waveforms (change in pupil diameter relative to baseline) for each group in each array-size condition.

ANOVA for each variable. Baseline pupil diameter was significantly greater in the 10-letter relative to 3-letter condition, but the group and interaction effects were not significant. Similarly, fixation constriction amplitude was significantly smaller (ie, pupil size was greater just prior to array onset) in the 10-letter relative to 3-letter condition, but the group and interaction effects were not significant. Both groups, therefore, showed comparable significant increase in pupil diameter in the higher, relative to lower, processing load condition both between trials (baseline) and in the interval between the warning tone/fixation square and array onset (preparation phase).

As expected, array constriction amplitude (light reflex) to larger arrays was significantly greater than to smaller arrays. A significant interaction was also found, where nonpsychiatric participants showed significantly less constriction than patients with schizophrenia in the 3-letter ($P < .05$), but not 10-letter, condition. Array dilation amplitude was significantly greater in nonpsychiatric participants relative to patients with schizophrenia, but the array-size and interaction effects were not significant.

For the primary pupillary response variable, array dilation-constriction difference, significant effects were found for group, array size, and the group \times array size interaction. The significant array-size effect indicated that pupil dilation was significantly greater in the 10-letter, relative to 3-letter, condition. As predicted, the significant group \times array size interaction indicated that pupillary responses of patients with schizophrenia were significantly smaller than those of nonpsychiatric participants, especially in the higher load condition. Correlations between detection accuracy and pupillary response (array dilation-constriction difference) were not significant for either group in the 3-letter (nonpsychiatric: $r = -.10$, schizophrenia: $r = -.19$) or 10-letter condition (nonpsychiatric: $r = -.01$, schizophrenia: $r = .04$).

Latency to fixation constriction showed no significant effects. Latency to array constriction was significantly longer in larger arrays, but the group and group \times array size interaction effects were not significant. Latency to array dilation was also significantly longer in larger arrays, and people with schizophrenia showed significantly longer latency to peak dilation than nonpsychiatric participants, but the group \times array size interaction was not significant.

High/Low-Pupil Dilation Subgroups

Figure 3 shows pupillary responses (top) and SOA task performance (bottom) for patients with schizophrenia who showed high and low pupil dilation (median split on 10-letter array dilation-constriction difference score) and nonpsychiatric controls. The figure shows that pupillary responses were abnormally small and performance was impaired in the low-dilation subgroup, but performance was still impaired, despite normal pupillary

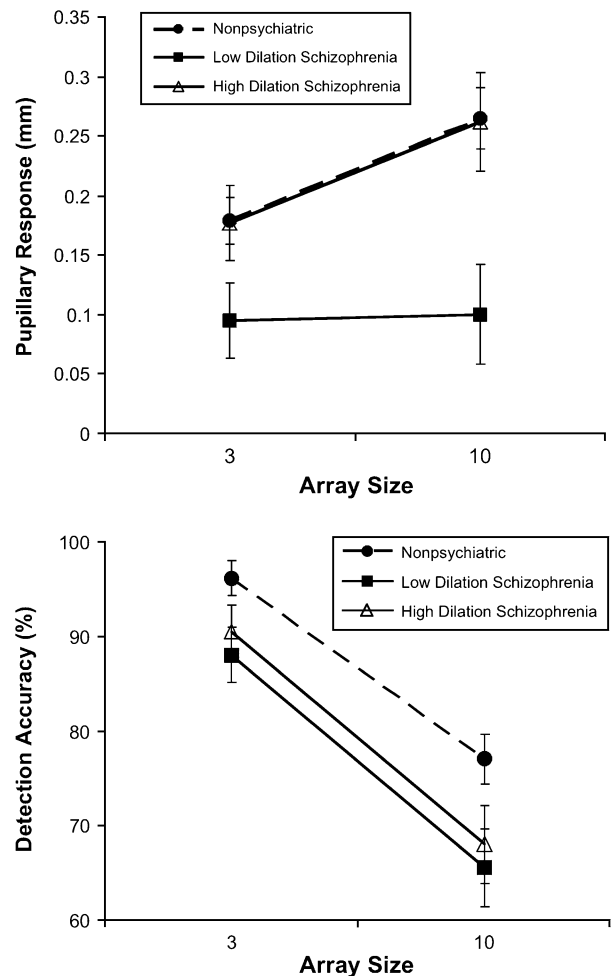


Fig. 3. Array dilation-constriction difference score pupillary responses (top) and span of apprehension task detection accuracy (bottom) in 3- and 10-letter array-size conditions for patients with schizophrenia who showed high and low pupil dilation (median split on 10-letter array dilation-constriction difference score) and nonpsychiatric controls.

responses in the high-dilation subgroup. These impressions were confirmed by 3 (groups) \times 2 (array sizes) ANOVAs computed for pupillary responses (array dilation-constriction difference) and detection accuracy. For pupillary responses, significant effects were found for group ($F_{2,126} = 20.86$, $P < .001$, $\eta^2 = .25$) and the group \times array size interaction ($F_{2,126} = 11.00$, $P < .001$, $\eta^2 = .15$). The high-dilation subgroup did not differ significantly from nonpsychiatric participants in either array-size condition. In contrast, the low-dilation group differed significantly from both the other groups in both array-size conditions ($P < .05$), and larger group differences were found in the larger array-size condition. For detection accuracy, a significant effect was found for group ($F_{2,126} = 19.55$, $P < .001$, $\eta^2 = .24$) but not for the group \times array size interaction ($F_{2,126} = 1.56$, $P = .215$, $\eta^2 = .02$). The nonpsychiatric participants showed significantly greater detection accuracy overall relative to

those in both the high- and low-dilation subgroups ($P < .05$), who did not differ significantly from each other. (A similar pattern of results was found when the participants with schizophrenia were divided according to a median split on array dilation amplitude, with high- and low-dilation groups showing comparably impaired performance, despite normal array dilation amplitude in the high-dilation patients. The partial correlation between array dilation amplitude and negative symptom severity (SANS total), controlling for positive symptoms (SAPS total), was $r_p = -.25$, $P = .058$.) High- and low-dilation groups did not differ significantly in age, ANART, gender, or race.

Symptoms

Negative symptom severity was significantly greater in the low-dilation ($M = 7.6$, $SD = 3.6$) relative to high-dilation subgroup ($M = 5.7$, $SD = 2.9$) ($t_{56} = 2.18$, $P = .033$, $d = 0.59$), but positive symptom severity did not differ significantly between the subgroups (low dilation: $M = 4.0$, $SD = 3.0$; high dilation: $M = 3.8$, $SD = 2.6$) ($t_{56} = 0.28$, $P = .780$, $d = 0.07$). The correlation between pupillary response (array dilation-constriction difference) in the 10-letter condition and negative symptom severity was significant ($r = -.32$, $P = .015$) even with both positive symptom severity and SOA detection accuracy controlled ($r_p = -.31$, $P = .021$). In contrast, correlations were not significant between pupillary response and positive symptom severity ($r = -.14$, $P = .282$), detection accuracy and negative ($r = -.14$, $P = .306$), or positive ($r = -.02$, $P = .894$) symptom severity. Correlations were also not significant between pupil dilation and reality distortion ($r = -.15$, $P = .272$) or disorganization ($r = -.08$, $P = .572$) symptom domains of the SAPS.

Demographics and Medications

Age was not significantly correlated with overall pupillary response (average array dilation-constriction difference for 3- and 10-letter arrays) for either group (nonpsychiatric: $r = .01$, schizophrenia: $r = -.07$). In contrast, the correlation between age and overall detection accuracy (average percent correct for 3- and 10-letter arrays) was significant for nonpsychiatric participants ($r = -.28$, $P = .020$) but not for patients with schizophrenia ($r = -.10$). The combined model for the regression of age, group, and the group \times age interaction onto overall SOA detection accuracy explained a significant amount of variance ($R^2 = .25$, $F_{3,125} = 13.63$, $P < .001$). Significant variance was accounted for by group ($\beta = -.50$, $t = 6.29$, $P < .001$), and age was marginally significant ($\beta = -.15$, $t = 1.80$, $P = .074$), but the group \times age interaction was not significant ($\beta = .01$, $t = 0.15$, $P = .883$). The combined model for the regression on overall pupillary responses also explained a significant amount of variance ($R^2 = .09$, $F_{3,125} = 4.35$, $P = .006$). Significant variance was

accounted for by group ($\beta = -.31$, $t = 3.59$, $P < .001$) but not age ($\beta = -.02$, $t = 0.26$, $P = .792$) or the group \times age interaction ($\beta = -.03$, $t = 0.39$, $P = .695$). We explored similar regression analyses for detection accuracy and pupillary responses within each array-size condition and for all other pupillary response variables but did not find any significant age \times group interactions. When all participants with span task data were included ($n = 185$), regardless of whether they had valid pupillary response data, the pattern of results was similar (for the group \times age interaction for overall detection accuracy, $\beta = .11$, $t = 0.24$, $P = .809$). The present study, therefore, did not replicate our prior findings.¹⁶

Because ANART IQ estimates were significantly higher in nonpsychiatric relative to schizophrenia participants (table 1), all analyses were repeated using an ANART-matched control group (controls with ANART scores over 120 were excluded; $M = 108.9$, $SD = 7.9$, $n = 59$) and the same pattern of results was found. Overall detection accuracy was not significantly correlated with CPZE ($r = -.10$) or ACHE ($r = -.06$) scores. None of the pupillary response variables in table 2 were significantly correlated with CPZE (r values ranged from $-.30$ to $.15$) or ACHE (r values ranged from $-.06$ to $.13$). Comparisons between participants taking and not taking anticholinergic medications and between participants taking and not taking mood medications showed no significant group differences for detection accuracy or array dilation-constriction difference score.

Discussion

The results offered some support for the resource-limitations vulnerability model⁴ that reduced availability of processing resources and impairments in early visual information processing are associated with negative symptom severity. Individuals with schizophrenia with more severe negative symptoms showed impaired detection accuracy and abnormally small pupillary responses (resource allocation) and did not increase their resource allocation when challenged by increased processing loads. Smaller pupillary responses were associated with greater negative symptom severity, independent of positive symptom severity.

In contrast, patients with less severe negative symptoms showed normal pupillary responses but still showed impaired detection accuracy. The normal pupillary responses shown by this subgroup confirmed that resources were available and invested according to task demands. The performance impairment found in this subgroup, therefore, can be attributed to dysfunction in one or more of the cognitive operations that contribute to data processing (data limitations) rather than to insufficient effort or resource limitations.²⁷ Candidate deficits in specific cognitive operations that could impair processing on the SOA task include search initiation, serial

and/or parallel scanning processes used to detect targets in iconic and/or visual working memory, rate of iconic and/or visual working memory decay, and transfer/interactions between iconic and working memory systems.¹ An important question about schizophrenia that remains unanswered despite decades of neurocognitive research is whether cognitive impairments in these individuals are due to (1) deficits in specific cognitive functions or (2) generalized deficits related to insufficient effort and reduced general processing capacity. The difficulty distinguishing between these sources of impairment is a classic problem in schizophrenia research that can be addressed by recording pupillary responses or other psychophysiological measures of effortful resource allocation during cognitive tasks.^{28,29} The present finding of impaired SOA task performance in a subgroup of people with normal pupillary responses and less severe negative symptoms suggests a specific early visual information-processing deficit that cannot be attributed to a generalized deficit involving resource limitations and is not linked to negative symptoms.

At least 2 factors (or their interaction) might explain the link found between smaller pupillary responses and negative symptom severity. One possibility is that hypofrontality contributes to associations between autonomic hyporesponsivity, reduced processing capacity, cognitive deficits, negative symptoms, and poor functional outcome, especially in older chronic patients with schizophrenia (for a review, see Kelly and Nuechterlein²⁰). Frontal anterior cingulate activity and the anterior attention system may modulate energetical aspects of attention and effortful resource allocation,^{30,31} and reduced activation in these systems has been associated with negative symptom severity.³² Greater impairment on neuropsychological tests of frontal executive functions has also been associated with negative symptom severity.^{33–37} Frontal systems are known to contribute to reactivity in the pupil and other autonomic systems,^{8,38–40} so autonomic hyporeactivity during cognition tasks may reflect frontal hypoactivation-associated energetical aspects of attention and negative symptoms. The hypothesis (eg, Bryson *et al.*⁴¹) that frontal system deficits involving working memory, hypothesis testing, abstraction, planning, and attention can influence behavioral output, especially in complex social situations, is intuitively appealing.

Activation abnormalities associated with frontal functions and negative symptoms, however, are not likely reducible to simply too much or too little activation. For example, electrodermal overreactivity has been associated with greater severity of negative symptoms in the early phases of schizophrenia.⁴² In addition, hypoactivation in some areas of the prefrontal cortex is sometimes accompanied by hyperactivation in other frontal areas in patients with schizophrenia.⁴³ Several studies of patients with schizophrenia have also found normal or exagger-

ated frontal activation (inefficiency) in response to working memory tasks at lower processing loads and reduced activation only at higher loads.^{44–48} We previously found this same dynamic relationship between task load and activation in the pupil, whereby patients with schizophrenia showed normal pupil dilation under low loads but abnormally reduced dilation when working memory capacity was exceeded.¹⁷ Cortical activation may not reflect a passive response to changing task difficulty; rather greater activation (eg, in the anterior cingulate) has been found to reflect the extent of active voluntary increases in mental effort to tasks under a constant load.³¹ Taken together, these findings point more to a compromised strategy for handling information under different processing loads, rather than simple hyper- or hypoactivation.^{43,44,49,50}

In research on energetical aspects of cognition, complex, nonlinear relationships between resource allocation (brain activation) and performance under different processing loads are not surprising, because relationships between performance, effortful resource investment, task difficulty, and individual differences in processing capacity/ability are complex.^{51–53} Consistent with this, the present study did not find a simple linear correlation between magnitude of pupillary response and task performance level. The amount of effortful resources invested in a task to meet perceived difficulty challenges has been found to vary according to a number of factors, including performance standards, mood states, ability beliefs, whether success is perceived as possible and worthwhile, and level of depletion/fatigue.^{51–54} People with low perceived ability find tasks more difficult than people with high perceived ability.⁵² These low-ability individuals will allocate more resources to a task to meet increasing difficulty challenges (active compensatory coping),⁵¹ as long as they view success as possible and worthwhile.⁵⁴ For example, Ahern and Beatty⁵⁵ found that healthy individuals with low math ability had greater pupil dilation (resource allocation) than individuals with high math ability when solving arithmetic problems. Some people with low ability, however, accept lower performance standards and allocate fewer resources (passive coping),⁵¹ especially if success is not perceived as possible or worthwhile.⁵⁴

These factors identified in cognitive-energetics studies as determinants of cognitive effort investment might also be determinants of negative symptom severity. In particular, a passive coping response to perceived reduced processing capacity may contribute to negative symptoms. Beck and colleagues^{56–58} recently suggested that, in addition to neurobiological factors, specific cognitive appraisals and beliefs may play a role in the expression and persistence of negative symptoms. Their cognitive model proposes that predisposing factors, including perceived limited cognitive resources, interact with negative performance attitudes and low expectancies for success to produce a compensatory pattern of disengagement and

motivational and behavioral inertia. People with more severe cognitive impairments and more chronic illness may be more likely to have multiple failure experiences and demoralization leading to dysfunctional achievement attitudes (eg, “Taking even small risks is foolish because the loss is likely to be a disaster”). As in cognitive-energetics models, this model proposes that negative symptoms stem, at least in part, from a passive coping style of conserving energy by minimizing investment in effortful activities and disengagement (safety behaviors) when perceived ability is low and success is not believed possible or worthwhile. Minimized effortful engagement, especially as task difficulty increases, would be reflected in smaller pupil responses in patients with more severe negative symptoms.

If negative performance attitudes, expectancies, and ability beliefs contribute to effort investment and negative symptoms, then cognitive-behavioral therapy (CBT) interventions that modify such beliefs might be useful treatments for negative symptoms. In fact, randomized controlled trials have found that CBT improves negative symptom outcomes in patients with schizophrenia.^{59–62} Other CBT trials have also found improvement in social anxiety and social functioning.⁶³ The fact that negative symptoms and functional outcomes can change in response to CBT suggests that beliefs about competence and fear of failure play some role in withdrawal, passivity, and other negative symptoms. As adjunctive interventions to pharmacologic treatments, further development and testing of CBT interventions for negative symptoms is a promising new area of research. Pupillary response measures may prove useful as an outcome measure of changes in effortful task engagement in CBT studies. If reduced pupillary responses are due in part to negative performance beliefs and expectancies, then change in attribution variables should be associated with change in cognitive task-evoked pupillary responses following CBT.

Pupil dilation, but not SOA task performance, was associated with negative symptom severity in this study. This suggests a stronger link between negative symptoms and autonomic reactivity/effort investment than with cognitive impairment, *per se*. Several, but not all, studies have found significant associations between early visual processing task performance and negative symptom severity.^{1,9–11} Inconsistent findings may be related, at least in part, to the complex relationships between effortful resource allocation and task performance discussed above. Associations between performance and negative symptom severity may be stronger when reduced resource allocation contributes to poor performance.

Latency to peak dilation amplitude was significantly longer in people with schizophrenia relative to nonpsychiatric participants. The meaning of longer latencies is not clear in the pupillometry literature. Latency to peak dilation is, in part, a function of peak dilation am-

plitude because the muscles controlling pupil dilation take time to constrict (dilator) and relax (sphincter), so it takes longer to dilate more.³⁸ This cannot account for the longer latencies in the patients in this study, however, because the patients dilated less than controls. Longer latency to peak dilation may indicate longer latency to initiate a stage of processing or more sustained neural response in the patients than in controls. Further research is needed on the meaning of increased latency to peak dilation.

Patients with schizophrenia and controls showed greater pupil size in 10-letter relative to 3-letter arrays between trials (larger baseline diameter) and just prior to array onset (less fixation constriction). Cognitive effort inhibits pupillary light reflex constriction,^{64,65} so the smaller fixation constriction amplitude in the 10-letter condition indicates greater cognitive effort prior to processing higher relative to lower load arrays. Participants were not informed which array size would be presented on each trial, but this information could be derived from the stimulus context (blocked trial administration). Based on the stimulus context, therefore, both groups were able to anticipate when higher load arrays were going to be presented and invested additional effort preparing for processing higher loads. Some studies have found that patients with schizophrenia are not able to derive expectancies or efficient top-down attentional allocation strategies through repeated exposure to a particular stimulus context, unless the salience of the stimulus context is heightened by task manipulations or explicit instructions.^{66–68} Consistent with this, the between-trial pupil size and fixation constriction findings suggested patients with schizophrenia were able to use salient cues about trial-by-trial array size to appropriately modulate their effort for the next trial.

Our prior study of middle-aged and older outpatients with chronic schizophrenia found abnormally accelerated rates of age-related decline in both detection accuracy and pupillary responses on the SOA task.¹⁶ Accelerated age-related decline in detection accuracy on a similar version of the SOA task has also been found in first-degree relatives of patients with schizophrenia.⁶ The present study, however, did not find any evidence of accelerated age-related decline for detection accuracy or pupillary responses. The demographic and symptom characteristics of the participant groups were similar between our 2 studies, but the present sample size was about twice that of our prior study, so the present findings may be more reliable. Different processing load conditions were also used (1, 6, and 12 letter arrays in our prior study; 3 and 10 letter arrays in this study). Longitudinal studies can more reliably answer questions about age-related rates of progression of neurocognitive impairment.

This study had several limitations. Patients were receiving medications that might impact task performance

and pupillary responses, although no clear medication effects were found. A large number of participants were excluded due to excessive artifacts in pupillary response data, and older participants were more likely to have data discarded. Several factors likely contributed to greater pupil data loss with aging, including reduction in resting pupil size (smaller pupils are more difficult to image), greater use of bifocal glasses (multiple lens glasses can compromise the image), loss of muscle tone leading to eyelids drooping over the pupil, and increased blinking due to drier eyes and older people can become more easily fatigued by testing. Older participants are also more likely to be excluded for problems with visual acuity, cataracts, and eye disease. No significant differences were found between included and excluded participants for symptoms, demographics, or performance variables, but the amount of data loss might impact the generalizability of the findings and compromise the utility of pupillometric methods in older populations. The patients with schizophrenia had significantly lower estimated IQ, but the pattern of results did not change when an IQ-matched subgroup of controls was used.

In conclusion, this study found that reduced effortful cognitive resource allocation during early visual information processing was associated with greater negative symptom severity in chronic schizophrenia. Further research is needed to determine whether the link between smaller pupillary responses and negative symptoms is related to frontal neural circuit hypoactivation or negative performance beliefs and passive coping strategy or the interaction of these factors.

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