



## Eye movement abnormalities and their association with cognitive impairments in schizophrenia

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### ABSTRACT

**Background:** Eye movement abnormalities have been identified in schizophrenia; however, their relevance to cognition is still unknown. In this study, we explored the general relationship between eye movements and cognitive function.

**Methods:** The three eye movement measures (scanpath length, horizontal position gain, and duration of fixations) that were previously reported to be useful in distinguishing subjects with schizophrenia from healthy subjects, as well as Wechsler Adult Intelligence Scale-III (WAIS-III) scores, were collected and tested for association in 113 subjects with schizophrenia and 404 healthy subjects.

**Results:** Scanpath length was positively correlated with matrix reasoning and digit symbol coding in subjects with schizophrenia and correlated with vocabulary and symbol search in healthy subjects. Upon testing for interaction effects of diagnosis and scanpath length on correlated WAIS-III scores, a significant interaction effect was only observed for matrix reasoning. The positive correlation between scanpath length and matrix reasoning, which was specific to subjects with schizophrenia, remained significant after controlling for demographic confounders such as medication and negative symptoms. No correlation was observed between the two other eye movement measures and any of the WAIS-III scores.

**Conclusions:** Herein, we reveal novel findings on the association between eye-movement-based measures of visual exploration and cognitive scores requiring visual search in subjects with schizophrenia and in healthy subjects. The association between scanpath length and matrix reasoning, a measure of perceptual organization in subjects with schizophrenia, implies the existence of common cognitive processes, and subjects with longer scanpath length may be advantageous in performance of perceptual organization tasks.

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## 1. Introduction

Schizophrenia is a psychiatric illness with diverse psychopathology that causes impairments relevant to both the affected individual and society in general. Although there have been many genetic, cognitive, neurophysiological, and neuroimaging studies showing differences between subjects with schizophrenia and healthy subjects, the neurobiology behind this disabling syndrome remains to be revealed (Owen et al., 2016).

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Eye movements are an example of a neurophysiological measure that has been studied in depth in the context of schizophrenia pathology. People with schizophrenia are known to have abnormalities in visual exploration during free viewing tasks (Beedie et al., 2011; Kojima et al., 1990), loss of gain during smooth pursuit (Lencer et al., 2015; O'Driscoll and Callahan, 2008), and difficulties in voluntary control of fixations (Radant et al., 2015; Reilly et al., 2014). When compared with healthy subjects, these eye movement measures differ substantially between subjects with schizophrenia and healthy individuals, and there have been multiple studies using eye movement measures to distinguish these groups (Benson et al., 2012; Kojima et al., 2001; Miura et al., 2014; Morita et al., 2017). However, the relevance of these eye movement abnormalities to everyday functioning and cognitive impairments is still unknown.

Schizophrenia was originally characterized by positive symptoms and negative symptoms; however, cognitive impairments are now also considered core features of schizophrenia. Meta-analyses and studies with large sample sizes have shown that these impairments are seen in a wide range of cognitive domains (Fujino et al., 2014; Heinrichs and Zakzanis, 1998). Cognitive impairments are determinant factors of poor functioning in individuals with schizophrenia (Green et al., 2004), and there is also evidence for limited effects of antipsychotics on this impairment (Insel, 2010; Keefe et al., 2007). Therefore, research on factors leading to cognitive impairments will be useful for the recovery of subjects with schizophrenia.

The importance of vision in normal cognition goes without saying, but only a few studies have investigated the association between eye movement and cognitive ability in schizophrenia. Performance of antisaccade tasks have been shown to be related to neurocognitive measures such as working memory and attention, while studies of smooth pursuit tasks have had mixed results (Hutton et al., 2004; Radant et al., 1997; Zanelli et al., 2009). Kurachi directly investigated visual exploration patterns during the WAIS-R (Wechsler Adult Intelligence Scale-Revised) picture completion test in subjects with schizophrenia and revealed that patients showed shorter scanpath lengths than healthy subjects did, with the differences being most prominent during the latter part of exposure to the picture. This study also showed that patients who succeeded in the task showed more efficient visual search strategies than those who failed (Kurachi et al., 1994). In a study by Elahipanah et al. (Elahipanah et al., 2011), similar results showing a poor search strategy were found in a digit symbol coding task. Digit symbol coding has been shown to yield an especially large effect size between healthy subjects and subjects with schizophrenia regardless of study design, medication or symptomatology (Dickinson et al., 2007), and such results show an important connection between eye movement abnormalities and cognitive processing in schizophrenia. However, owing to the small sample sizes and limited measures included in these studies, we have yet to understand the general relationship between eye movement abnormalities and cognitive ability in schizophrenia. In the current study, we will conduct a comprehensive exploratory analysis on the association between eye movements and cognitive measures in subjects with schizophrenia.

## 2. Materials and methods

### 2.1. Subjects

Data were obtained from 113 subjects with schizophrenia and 404 healthy subjects as part of a large-scale cohort recruited at Osaka University (Fujimoto et al., 2016; Fujino et al., 2017; Isomura et al., 2017; Koshiyama et al., 2018a; Koshiyama D et al., 2018b; Miura et al., 2014; Morita et al., 2017; Ohi et al., 2015; Sumiyoshi et al., 2016). Two hundred and forty nine healthy subjects and 68 subjects with schizophrenia were overlapped with a previous study on eye movement abnormalities in schizophrenia (Morita et al., 2017). The subjects were biologically unrelated, were of Japanese descent, and had no history of neurological/

medical conditions that could influence the central nervous system. The specific exclusion criteria included atypical headaches, head trauma with loss of consciousness, chronic lung disease, kidney disease, chronic hepatic disease, thyroid disease, active cancer, cerebrovascular disease, epilepsy, seizures, substance-related disorders and mental retardation. All subjects had no history of ophthalmological disease and had normal or corrected-to-normal vision. Subjects with schizophrenia were recruited from Osaka University Hospital and had been diagnosed by two or more trained psychiatrists according to criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) using the Structured Clinical Interview for DSM-IV (SCID). Healthy subjects between age eighteen and 75 years old were recruited through regional advertisements at Osaka University and were evaluated for psychiatric, medical, and neurological concerns using the non-patient version of the SCID to exclude individuals with current or past contact with psychiatric services or a history of receiving psychiatric medication. Healthy subjects were also excluded if they had first-degree relatives with a history of psychiatric disorders. We collected data of the twenty-five question Japanese version of the National Adult Reading Test (JART-25) (Matsuoka et al., 2006) which was also used as an estimation of premorbid IQ in subjects with schizophrenia. Estimated cognitive decline was calculated by the methods described by Fujino (Fujino et al., 2017). The current symptoms of the subjects with schizophrenia were evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and daily antipsychotic use was calculated in chlorpromazine (CPZ) equivalents (mg/day) (Inada and Inagaki, 2015).

This study was performed in accordance with the World Medical Association's Declaration of Helsinki and was approved by the Research Ethical Committees. All participants provided written consent to the study after full explanation of the study procedures. Anonymity was preserved for all participants.

### 2.2. Eye movement recordings and processing of eye movement data

The subjects faced a 19-inch liquid crystal display monitor placed 70 cm from their eyes. Visual stimuli were presented using MATLAB (MathWorks, Natick, MA, USA) via the Psychophysics Toolbox extension (Brainard, 1997). Eye movements and pupil areas of the left eye were measured at 1 kHz using either the EyeLink 1000 or the EyeLink 1000 Plus system (SR Research, Ontario, Canada). The data were analyzed using computer programs based on MATLAB.

On the basis of a previous study (Morita et al., 2017), we administered three eye movement examinations to extract three eye movement measures. These three measures were used to calculate an integrated score of schizophrenia eye movement pathology (the eye movement score). We have found that this score was associated with work hours in subjects with schizophrenia (Morita et al., 2018). In the present study, we studied whether this score and the three measures comprising the score were correlated with cognitive measures. The free viewing test was performed using 20 original images of pictures, geometric patterns, and noises. The subjects were instructed to freely view each presented image for 8 s. We calculated mean scanpath length over the 20 images. We also calculated the number of saccades and the amplitude of saccades for supplementary analysis. In the smooth pursuit test, subjects were required to track a target moving along a Lissajous trajectory for 20 s. The trial was repeated twice. We estimated the horizontal position gain for each trial and then obtained the average when data from two trials were available. In the fixation stability test, subjects were required to maintain their gaze on a fixation target presented at the center of the monitor for 5 s in the presence of a distractor stimulus that suddenly appeared the left or right of the fixation target. Each condition was repeated twice and a total of four trials were conducted in random order. We calculated the median duration of the fixation periods (duration of fixations) for each trial. Data were averaged for each distractor position when two trials were available and then averaged

over the positions. The eye movement score ( $y$ ) was calculated using the following equation:

$$y = 0.0312 \times \{\text{Scanpath length}\} + 5.614 \times \{\text{Horizontal position gain}\} + 0.000203 \times \{\text{Duration of fixations}\} - 9.637$$

To control for possible confounding factors in the eye movement variables, we calculated the residual values by fitting a multiple linear regression model to healthy subject data. Age, a dummy variable for gender, and a dummy variable for the EyeLink machine version used (EyeLink 1000 or EyeLink 1000 Plus) were included as possible confounding variables. A stepwise approach with the entry criteria ( $p < 0.05$ ) and the removal criteria ( $p > 0.1$ ) was used to create the final linear regression model for each eye movement measure. EyeLink machine version was the only significant confounding variable for horizontal position gain and eye movement score, and age was the only significant confounding variable for duration of fixations. For number of saccades and saccade amplitude, which were used for supplementary analysis, EyeLink machine and age were significant. Models including significant confounders were applied to each eye movement measure to calculate a residual value for use in further analyses in all subjects. There were no significant confounding variables for scanpath length; therefore, the raw value was used in the subsequent analyses.

### 2.3. Cognitive measures

Age-referenced scores from the Japanese version of the WAIS-III (Wechsler Adult Intelligence Scale-II) (Japanese WAIS-III Publication Committee, 2006) were used to measure the cognitive ability of the subjects. The WAIS-III was used because the Japanese version of the WAIS-IV (Wechsler Adult Intelligence Scale-IV) has not yet been released. The measures included were full-scale IQ, the four index scores (verbal comprehension index score, working memory index score, perceptual organization index score, and processing speed index score), and the scaled scores for all 13 subtests (vocabulary, similarity, information, comprehension, arithmetic, digit span, letter-number sequencing, picture completion, block design, matrix reasoning, picture arrangement, digit symbol coding, and symbol search).

### 2.4. Statistical analysis

Statistical analyses were performed using SPSS Statistics 24.0 software (IBM Corp., Armonk, NY, USA). We analyzed group differences using independent  $t$ -tests or the  $\chi^2$  test when appropriate. Pearson's correlation coefficients ( $R$ ) and hierarchical linear regression analysis were used to examine the association between individual eye

movement measures and cognitive measures. For all statistical analyses, the significance level was set at  $p < 0.05$ , and the Bonferroni correction was applied when appropriate.

## 3. Results

### 3.1. Demographics

The demographics of both groups are shown in Table 1. There were significant differences in age, education years, JART-25, and WAIS full-scale IQ ( $p = 1.25 \times 10^{-4}$ ,  $p = 1.18 \times 10^{-4}$ ,  $p = 2.05 \times 10^{-14}$ , and  $p = 9.43 \times 10^{-33}$ , respectively). On the other hand, there was no difference in gender ratio between the two groups ( $p = 0.478$ ).

### 3.2. Group comparison of eye movement measures and cognitive measures

All three individual eye movement measures, the integrated eye movement score, and the eighteen WAIS-III scores significantly differed between healthy subjects and subjects with schizophrenia (Table 2). The mean for healthy subjects equaled zero because residual values from the multiple regression analysis were used for the eye movement measures, with the exception of scanpath length, which had no significant confounders. Among the three individual eye movement measures, scanpath length was the most different between groups ( $p = 6.33 \times 10^{-33}$ , Cohen's  $d = -1.38$ ). We also compared the saccade amplitude and the number of saccades during the free viewing task, and healthy subjects had both longer saccades ( $p = 2.02 \times 10^{-6}$ , Cohen's  $d = -0.51$ ) and more number of saccades ( $p = 7.75 \times 10^{-17}$ , Cohen's  $d = -1.13$ ). Correlation analysis between eye movement measures and demographical measures of age, education years, JART-25, and estimated cognitive decline was also conducted. These results are summarized in Table 3. We also found broad deficits in WAIS-III scores, with digit symbol coding being the subtest with the largest difference between groups ( $p = 3.00 \times 10^{-52}$ , Cohen's  $d = -1.85$ ).

### 3.3. Exploratory analysis of associations between eye movement measures and cognitive measures within subject groups

The results of correlation between eye movement measures and WAIS scores are given in Tables 4 and S1-S3. Scanpath length was significantly correlated with WAIS scores. In subjects with schizophrenia, correlations between scanpath length and matrix reasoning score ( $R = 0.39$ ,  $p = 2.25 \times 10^{-3}$ ) and between scanpath length and digit symbol coding score ( $R = 0.33$ ,  $p = 4.72 \times 10^{-2}$ ) were significant (Table 4). For healthy subjects, the correlations between scanpath length and verbal comprehension index score ( $R = 0.20$ ,  $p = 1.02 \times 10^{-2}$ ), between

**Table 1**  
Demographical and clinical characteristics of subjects.

	Subjects with schizophrenia (N = 113)		Healthy subjects (N = 404)		Statistics	
	Mean	SD	Mean	SD	$t$ value or $\chi^2$	$p$ value
Age (years)	35.54	12.31	30.32	12.80	-3.9	<b><math>1.25 \times 10^{-4}</math></b>
Gender (male/female)	57/56		219/185		0.4	<b><math>4.78 \times 10^{-1}</math></b>
Education years	13.93	2.36	14.88	1.79	4.0	<b><math>1.18 \times 10^{-4}</math></b>
JART-25	102.07	9.56	110.23	6.64	8.5	<b><math>2.05 \times 10^{-14}</math></b>
Estimated cognitive decline	-12.94	12.53	NA	NA	NA	NA
Onset age (years)	23.19	10.83	NA	NA	NA	NA
Duration of illness (years)	12.28	9.95	NA	NA	NA	NA
PANSS positive symptoms	18.96	5.39	NA	NA	NA	NA
PANSS negative symptoms	20.78	5.01	NA	NA	NA	NA
PANSS general psychopathology	43.36	9.69	NA	NA	NA	NA
PANSS total	83.10	19.06	NA	NA	NA	NA
Daily antipsychotic dose (mg/day)	544.67	515.99	NA	NA	NA	NA

Daily antipsychotic dosages were converted to chlorpromazine equivalents (mg/day). Group differences in gender were tested using the  $\chi^2$  test and  $t$ -tests were used elsewhere. The bold and underlined  $p$  values represent  $p < 0.05$ .

Abbreviations N: number of subjects; SD: standard deviation; PANSS: Positive and Negative Syndrome Scale; NA: Not applicable.

**Table 2**  
Group differences in eye movement measures and WAIS-III scores.

		SZ		HS		Statistics		
		Mean	SD	Mean	SD	Cohen's <i>d</i>	<i>t</i> value	<i>p</i> value
Eye movement measures	Eye movement score	−1.65	1.14	0.0	0.93	−1.68	16	<b><u>1.13 × 10<sup>−45</sup></u></b>
	Scanpath length	78	27	114	26	−1.38	13	<b><u>6.33 × 10<sup>−33</sup></u></b>
	Horizontal position gain	−0.06	0.10	0.0	0.06	−0.91	7	<b><u>5.47 × 10<sup>−9</sup></u></b>
	Duration of fixations	−783	1021	0.0	1508	−0.55	6	<b><u>2.55 × 10<sup>−9</sup></u></b>
WAIS scores	FIQ	88	17	114	12	−2.04	16	<b><u>1.70 × 10<sup>−31</sup></u></b>
	VCI	95	16	113	13	−1.38	11	<b><u>3.25 × 10<sup>−21</sup></u></b>
	Vocabulary	9	3	13	3	−1.40	13	<b><u>6.89 × 10<sup>−33</sup></u></b>
	Similarities	9	3	12	2	−1.12	9	<b><u>1.26 × 10<sup>−14</sup></u></b>
	Information	9	3	12	3	−0.98	8	<b><u>8.71 × 10<sup>−13</sup></u></b>
	Comprehension	8	4	13	3	−1.71	13	<b><u>1.23 × 10<sup>−25</sup></u></b>
	WMI	90	17	113	15	−1.53	14	<b><u>2.87 × 10<sup>−38</sup></u></b>
	Arithmetic	8	3	13	3	−1.69	16	<b><u>4.80 × 10<sup>−45</sup></u></b>
	Digit Span	9	3	12	3	−0.71	7	<b><u>1.03 × 10<sup>−9</sup></u></b>
	Letter–number sequencing	8	3	12	3	−1.30	12	<b><u>3.50 × 10<sup>−29</sup></u></b>
	POI	89	17	108	13	−1.36	11	<b><u>2.92 × 10<sup>−20</sup></u></b>
	Picture completion	8	3	10	3	−0.88	8	<b><u>3.89 × 10<sup>−11</sup></u></b>
	Block design	8	4	12	3	−1.06	9	<b><u>4.23 × 10<sup>−15</sup></u></b>
	Matrix reasoning	8	4	12	3	−1.10	9	<b><u>4.24 × 10<sup>−14</sup></u></b>
	Picture arrangement	8	4	11	3	−0.90	7	<b><u>1.49 × 10<sup>−10</sup></u></b>
	PSI	82	17	111	13	−2.05	17	<b><u>7.56 × 10<sup>−35</sup></u></b>
	Digit symbol coding	7	3	12	3	−1.85	17	<b><u>3.00 × 10<sup>−52</sup></u></b>
Symbol search	7	3	12	3	−1.78	15	<b><u>1.47 × 10<sup>−30</sup></u></b>	

Group differences in eye movement measures and WAIS-III scores are presented. For the values of the eye movement score, horizontal position gain, and duration of fixations, residual values from multiple regression analysis were used; consequently, the mean in healthy subjects equaled zero. Bonferroni-corrected *p* values are given (raw *p* values times four for eye movement measures, raw *p* values times eighteen for WAIS-III scores). The bold and underlined *p* values represent *p* < 0.05.

Abbreviations HS: healthy subjects; SZ: patients with schizophrenia; SD: standard deviation. FIQ: full-scale IQ; VCI: verbal comprehension index; WMI: working memory index; POI: perceptual organization index; PSI: processing speed index.

scanpath length and vocabulary score ( $R = 0.18, p = 2.75 \times 10^{-2}$ ), between scanpath length and performance speed index score ( $R = 0.20, p = 8.90 \times 10^{-3}$ ), and between scanpath length and symbol search score ( $R = 0.19, p = 1.96 \times 10^{-2}$ ) were significant (Table 4). After correction for multiple testing, there were no significant correlations between eye movement measures of horizontal position gain and WAIS scores or between duration of fixations and WAIS scores (Tables S1 and S2). The correlations seen in eye movement score were similar to those seen in scanpath length (Table S3). We performed an additional analysis using a subgroup of 113 healthy subjects matched in age (Table S4). Performance of both eye movement and cognitive measures differed from patient groups in a similar way (Table S5). However, no significant correlations were found after correcting for multiple comparison in this healthy subject group (Table S6).

### 3.4. Interaction effects of diagnosis

We focused on the correlations that were significant within either subject group and tested for associations characteristic of subjects with schizophrenia. There were no cognitive measures with significant correlations in both subject groups, but four measures had significant correlations with scanpath length in either subject group. The correlation between scanpath length and these four measures; matrix

reasoning scores ( $R = 0.31, p = 3.92 \times 10^{-12}$ ), digit symbol coding scores ( $R = 0.44, p = 4.11 \times 10^{-25}$ ), vocabulary scores ( $R = 0.40, p = 5.75 \times 10^{-21}$ ), and symbol search scores ( $R = 0.44, p = 2.45 \times 10^{-25}$ ) were significant in the total subject sample. Interaction effects between diagnosis and scanpath length on subtest scores were tested using hierarchical multiple linear regression analysis. Subtest scores were the dependent variables; scanpath length and diagnosis were added as independent variables in step one, followed by the interaction variable of scanpath length  $\times$  diagnosis in step two. A significant interaction effect was seen only for the matrix reasoning score, with a stronger relationship in subjects with schizophrenia than in healthy subjects (coefficient, 0.05; 95% confidence interval, 0.03 to 0.07;  $p = 1.72 \times 10^{-5}$ ; Fig. 1).

### 3.5. Effect of demographic confounders on the association between scanpath length and matrix reasoning scores in subjects with schizophrenia

To consider which factors may confound our result of correlation between scanpath length and matrix reasoning scores in subjects with schizophrenia, we first conducted bivariate correlation analysis between these two measures and demographic factors. Scanpath length was significantly correlated with estimated cognitive decline, PANSS negative symptom score, and medication. Matrix reasoning scores

**Table 3**  
Correlations between eye movement measures and demographics.

		Eye movement score		Scanpath length		Horizontal position gain		Duration of fixations	
		SZ	HC	SZ	HC	SZ	HC	SZ	HC
Age	<i>R</i>	−0.14	−0.07	−0.07	0.01	−0.09	−0.06	0.11	−1.20 × 10 <sup>−16</sup>
	<i>p</i> value	1.47 × 10 <sup>−1</sup>	1.65 × 10 <sup>−1</sup>	4.30 × 10 <sup>−1</sup>	9.02 × 10 <sup>−1</sup>	3.27 × 10 <sup>−1</sup>	2.18 × 10 <sup>−1</sup>	2.60 × 10 <sup>−1</sup>	NS
Education years	<i>R</i>	0.03	0.06	0.04	0.05	0.01	−0.003	0.02	0.03
	<i>p</i> value	7.41 × 10 <sup>−1</sup>	2.51 × 10 <sup>−1</sup>	6.60 × 10 <sup>−1</sup>	2.93 × 10 <sup>−1</sup>	9.41 × 10 <sup>−1</sup>	9.58 × 10 <sup>−1</sup>	8.74 × 10 <sup>−1</sup>	5.25 × 10 <sup>−1</sup>
JART-25	<i>R</i>	0.17	0.09	0.14	<b><u>0.12</u></b>	0.16	0.03	−0.002	−0.07
	<i>p</i> value	6.75 × 10 <sup>−2</sup>	6.16 × 10 <sup>−2</sup>	1.49 × 10 <sup>−1</sup>	<b><u>1.55 × 10<sup>−2</sup></u></b>	9.80 × 10 <sup>−2</sup>	5.93 × 10 <sup>−1</sup>	9.87 × 10 <sup>−1</sup>	1.80 × 10 <sup>−1</sup>
Estimated cognitive decline	<i>R</i>	0.16	NA	<b><u>0.25</u></b>	NA	0.04	NA	−0.11	NA
	<i>p</i> value	8.74 × 10 <sup>−2</sup>	NA	<b><u>7.83 × 10<sup>−3</sup></u></b>	NA	6.68 × 10 <sup>−1</sup>	NA	2.36 × 10 <sup>−1</sup>	NA

Pearson's correlation coefficients (*R*) and raw *p* values are presented. Bold and underlined values represent *p* < 0.05. NS: Not significant; NA: Not applicable.

**Table 4**  
Correlations between scanpath length and WAIS scores.

	Subjects with schizophrenia		Healthy subjects	
	R	p value	R	p value
FIQ	0.31	NS	0.18	NS
VCI	0.23	NS	0.20	<b><u><math>1.02 \times 10^{-2}</math></u></b>
Vocabulary	0.27	NS	0.18	<b><u><math>2.75 \times 10^{-2}</math></u></b>
Similarities	0.22	NS	0.18	NS
Information	0.09	NS	0.14	NS
Comprehension	0.23	NS	0.09	NS
WMI	0.17	NS	0.08	NS
Arithmetic	0.10	NS	0.14	NS
Digit span	0.14	NS	0.01	NS
Letter–number sequencing	0.18	NS	0.03	NS
POI	0.31	NS	0.05	NS
Picture completion	0.09	NS	0.12	NS
Block design	0.22	NS	−0.01	NS
Matrix reasoning	0.39	<b><u><math>2.25 \times 10^{-3}</math></u></b>	0.03	NS
Picture arrangement	0.23	NS	0.07	NS
PSI	0.32	NS	0.20	<b><u><math>8.90 \times 10^{-3}</math></u></b>
Digit symbol coding	0.33	<b><u><math>4.72 \times 10^{-2}</math></u></b>	0.16	NS
Symbol search	0.27	NS	0.19	<b><u><math>1.96 \times 10^{-2}</math></u></b>

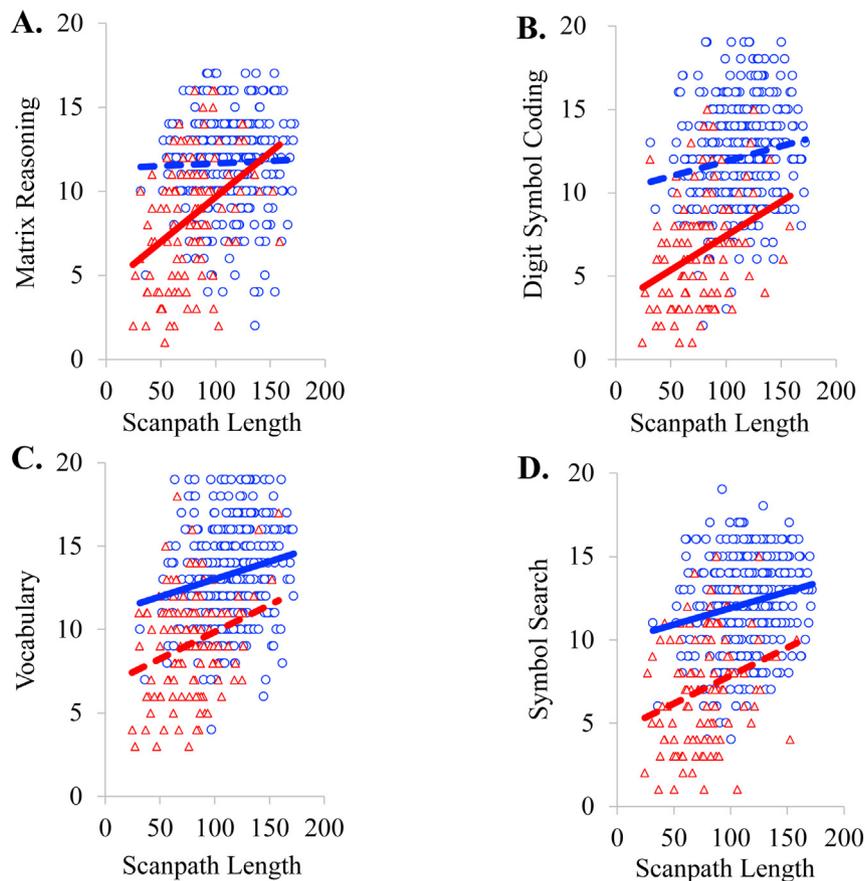
Pearson's correlation coefficients (R) and Bonferroni-corrected p values (raw p values times 144) are presented. Bold and underlined p values represent  $p < 0.05$ . The correlation results of other eye movement measures are presented in Tables S1–S3. Abbreviations HS: healthy subjects; SZ: subjects with schizophrenia; FIQ: full-scale IQ; VCI: verbal comprehension index; WMI: working memory index; POI: perceptual organization index; PSI: processing speed index. NS: not significant.

were significantly correlated with education years, JART-25, estimated cognitive decline, onset age, all three PANSS symptom scores, and PANSS total scores (full results are given in Table S7).

We next included these significant confounders in hierarchical multiple regression models examining the effects of scanpath length on matrix reasoning scores. For PANSS scores, we included only one score to avoid the effect of collinearity of the scores. The PANSS total score was used in one model and the PANSS negative symptoms score in another model because the PANSS negative symptom score was the only PANSS score correlated with both scanpath length and matrix reasoning scores. In step one, we included the matrix reasoning score as the dependent variable and education years, JART-25, estimated cognitive decline, onset age, medication, and either the PANSS total score or the PANSS negative score as the independent variables, followed by scanpath length in step two. The unique contribution of scanpath length to matrix reasoning scores above other confounders was significant in both models: the model using the PANSS total score (coefficient, 0.04; 95% confidence interval, 0.02 to 0.06;  $p = 1.19 \times 10^{-3}$ ) and the one using the PANSS negative symptom score (coefficient, 0.04; 95% confidence interval, 0.01 to 0.06;  $p = 2.15 \times 10^{-3}$ ).

**4. Discussion**

In this study, we investigated the association between eye movement abnormalities and cognitive ability in a large sample of healthy subjects and subjects with schizophrenia. Among the independent



**Fig. 1.** Association between scanpath length and subtest scores. Scatter plots of the correlations between scanpath length and matrix reasoning (A), digit symbol coding (B), vocabulary (C), and symbol search (D) scores are presented. The blue circles represent healthy subjects. The red triangles represent subjects with schizophrenia. Lines represent the regression lines; bold lines represent correlations having within-group significance, and dotted lines represent nonsignificant correlations. Interaction effects of diagnosis and scanpath length on subtest scores were tested using hierarchical multiple linear regression analysis. Statistical values for the hierarchical multiple linear regression analyses, which focused on the interaction effect of diagnosis and scanpath length on WAIS-III subtest scores, were as follows: matrix reasoning score (coefficient, 0.05; 95% CI, 0.03 to 0.07;  $p = 1.72 \times 10^{-5}$ ), digit symbol coding score (coefficient, 0.02; 95% CI, 0.001–0.05;  $p = 5.67 \times 10^{-2}$ ), vocabulary score (coefficient, 0.01; 95% CI, −0.01 to 0.03;  $p = 3.40 \times 10^{-1}$ ), and symbol search score (coefficient, 0.01; 95% CI, −0.01 to 0.04;  $p = 2.24 \times 10^{-1}$ ). Abbreviations 95% CI: 95% confidence interval.

eye movement measures used in this study, only scanpath length was significantly correlated with any of the cognitive measures. In subjects with schizophrenia, scanpath length was correlated with matrix reasoning score and digit symbol coding score. In healthy subjects, scanpath length was significantly correlated with vocabulary, symbol search, and related WAIS-III index scores. Diagnosis  $\times$  scanpath length interaction effects were observed only for the association between scanpath length and matrix reasoning score, showing a stronger association in subjects with schizophrenia than in healthy subjects. On the other hand, we did not find any significant correlations between horizontal position gain and cognitive measures, and between duration of fixations and cognitive measures. The correlation coefficients were generally small, suggesting that these eye movement measures are independent from cognitive measures.

Three of the four cognitive measures associated with scanpath length – the matrix reasoning score, the digit symbol coding score, and the symbol search score – are measures from subtests requiring subjects to search visually for relevant stimuli to complete the tests. A shorter scanpath length would involve fewer fixations and saccades, resulting in a less extensive search of the visual field; therefore, this association seems reasonable. There have been reports of poor visual search strategies during digit symbol coding tasks in subjects with schizophrenia (Elahipanah et al., 2011), which may be related to our findings. The digit symbol coding score was the cognitive measure with the largest difference between the schizophrenia and healthy subject groups in this study and has been recognized as a hallmark of the cognitive impairments seen in schizophrenia (Dickinson et al., 2007). However, in this study, the association between digit symbol coding scores and scanpath length was not significantly stronger in subjects with schizophrenia than in healthy controls. The same was true for the association between scanpath length and symbol search score. The most prominent and novel result of this study was the association between scanpath length and matrix reasoning scores, which was shown to be significantly stronger in subjects with schizophrenia than in healthy subjects. Stronger correlations between eye movements and cognitive measures imply neither better nor worse performance in scores, but show that performance in one measure is more interconnected to performance in the other.

Matrix reasoning is a subtest of the WAIS-III modeled on Raven's Progressive Matrices, which is a measure of visual information processing and abstract reasoning (Raven et al., 1998). Together with the block design and the picture completion subtests, it is a test of perceptual organization. Perceptual organization is a process in which visual information is classified into coherent patterns. In the current study, we did not find a direct relationship between WAIS-III perceptual organization index scores and scanpath length in subjects with schizophrenia, although there was a relatively strong correlation between the two measures ( $R = 0.31$ ,  $p = 1.46 \times 10^{-1}$ ). Previous studies on subjects with schizophrenia have revealed an association between visual exploration abnormalities in the block design subtest (Kojima et al., 1992) and the picture completion subtest (Kurachi et al., 1994), both of which also contribute to the perceptual organization index score. Together with these studies, our results imply an association between visual exploration and perceptual organization in schizophrenia.

One key factor of perceptual organization tasks, such as matrix reasoning, is their high demand on top-down cognitive processes. Subjects with schizophrenia are known to be impaired in perceptual organization ability (Panton et al., 2016; Silverstein and Keane, 2011; Uhlhaas and Silverstein, 2005), and studies have emphasized the importance of top-down control and feedback in this impairment (Carr et al., 1998; Silverstein and Keane, 2011; Van Assche and Giersch, 2011). The neural mechanisms underlying perceptual organization impairments in schizophrenia have also been shown to be independent from those underlying processing speed, an aspect of cognition measured by symbol search and digit symbol coding tests (Sehatpour et al., 2010). This difference between perceptual organization and other cognitive measures requiring visual search may be related to our findings.

Top-down processes are also required to carry out effective visual search. During visual search tasks, subjects with schizophrenia have been shown to perform relatively well when required to follow salient bottom-up signals but show impairments when required to use top-down control mechanisms (Gold et al., 2007). This may be related to results from a visual exploration study in which subjects with schizophrenia showed a tendency to implement “ambient” search modes less and rely more on “focal” search modes (Sprenger et al., 2013), which are known to be susceptible to effects of bottom-up stimuli (Follet et al., 2011; Pannasch et al., 2011). Humans are known to implement both “ambient” and “focal” strategies during visual exploration even without being instructed to do so (Follet et al., 2011; Pannasch et al., 2011; Unema et al., 2005), and this effect can even be seen in monkeys, in which there would be no effect related to instructional bias (Ito et al., 2017). The tendency of people with schizophrenia to use “focal” search modes would be a reasonable explanation for the shorter scanpaths seen in this subject group (Sprenger et al., 2013) and, together with our results, implies that patients with longer scanpaths may have alternative strategies for visual exploration that are advantageous in cognitive tasks such as perceptual organization, which impose heavy loads on top-down cognitive processes. This presents the exciting possibility of developing tools to aid learning of such strategies. Scanpaths could be used as an objective index of performance in these tools, and recent advances in computational models of visual exploration (Ito et al., 2017; Le Meur and Liu, 2015) would also make it possible to implement effective, systematic approaches to the strategy learning process.

There was also a significant correlation in healthy subjects between scanpath length and vocabulary score. This subtest contains only verbal questions as stimuli and is difficult to associate with visual exploration. The vocabulary score is known to be highly correlated with other subtests of the WAIS-III (Tulsky et al., 2003), which may have led to a positive correlation with scanpath length.

There are several limitations that need to be taken into account. Results from an additional analysis using a matched healthy subject group revealed no significant correlations between scanpath length and cognitive measures. This may be due to the smaller sample size or differences in age. There is a possibility that other cognitive factors, such as motivation and attention, are confounders as well. There is also a possibility that medication affects eye movements. This has been investigated in previous studies, but the results are still controversial (Beedie et al., 2012; Hori et al., 2002; Obayashi et al., 2001). We have kept this fact in mind and have shown that the effect of scanpath length on matrix reasoning score was not accompanied by any effect of current antipsychotic use. However, the effect of accumulated antipsychotic use is still a possible confounder, and we have not ruled out the possibility of medication confounding our other results. Further research is needed to investigate these possibilities.

This study has examined the association between eye movement abnormalities and cognitive impairments seen in schizophrenia. We report a novel finding of correlation between WAIS-III scores and scanpath length, a measure of visual exploration. In particular, the positive correlation between scanpath length and matrix reasoning, a subtest assessing perceptual organization, was found to be stronger in subjects with schizophrenia than in healthy subjects. This association was also independent of demographical confounders. Our findings strengthen the understanding of two distinct impairments known to exist in schizophrenia, namely, visual exploration abnormalities and perceptual organization impairments, both which have been linked to top-down control mechanisms. The results further suggest that effective visual exploration strategies can benefit people with schizophrenia by offsetting cognitive impairments in tasks that place high demands on top-down cognitive processes such as perceptual organization.

#### Conflict of interests

The authors declare no financial or non-financial competing interests.

## Contributors

Kentaro Morita was critically involved in the analysis of the data and wrote the first draft of the manuscript. Kenichiro Miura was critically involved in the study design and analysis of the data, and contributed to the interpretation of the data and the writing of the manuscript. Michiko Fujimoto, Hidenaga Yamamori, Yuka Yasuda, Noriko Kudo, and Hirotsugu Azechi were involved in the subject recruitment process and the clinical diagnostic assessments and contributed to the data interpretation. Naohiro Okada, Daisuke Koshiyama, Manabu Ikeda, and Kiyoto Kasai contributed to the interpretation of the data and the writing of the manuscript. Ryota Hashimoto supervised the entire project, collected the data and was critically involved in the design, analysis, and interpretation of the data. All authors contributed to and have approved the final manuscript.

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The funders had no role in the study design, data collection and analyses, decision to publish, or preparation of the manuscript.

## Appendix A. Supplementary data

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