

Fig. 4 Visual scanning parameters are the following: **a** scanned area, **b** amplitude of saccades, **c** coefficient of variation (CV) of saccade amplitude, **d** number of saccades, **e** duration of fixation, **f** instability ratio of fixation. The bars show the values of mean and standard error. Gray bars are for SCA patients and white bars for normal subjects. The number of saccades and duration of fixation in SCA patients were identical to those

in normal subjects for all images. The scanned area and instability ratio of fixation in SCA patients were statistically larger than those in normal subjects. The amplitude of saccades and its variation in SCA patients were also larger than those in normal subjects, although both parameters were not statistically significant. Asterisk significant difference between SCA patients and normal subjects

$F_1=2.788, p=0.104$; Fig. 4c, test of within-subject effect, image complexity \times subject-group interaction, $F_{2,479}=2.209, p=0.104$, and $\epsilon=0.826$; tests of between-subject effects, $F_1=1.385, p=0.247$).

subjects (Fig. 4d; test of within-subject effect, image complexity \times subject-group interaction, $F_{2,252}=1.235, p=0.301$, and $\epsilon=0.751$; tests of between-subject effects, $F_1=0.339, p=0.564$; Fig. 4e, test of within-subject effect, image complexity \times subject-group interaction, $F_{2,033}=0.479, p=0.624$, and $\epsilon=0.678$; tests of between-subject effects, $F_1=0.066, p=0.799$).

The number of saccades and duration of fixation in SCA patients were not significantly different from those in normal

Table 2 Visual scanning parameters in SCA patients and normal subjects

| | Image 1 SCA | Normal subjects | Image 2 SCA | Normal subjects | Image 3 SCA | Normal subjects | Image 4 SCA | Normal subjects |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Scanned area (%) | 14.7 \pm 8.1 6.2–39.5 | 9.0 \pm 5.6 3.0–22.1 | 19.6 \pm 9.8 5.9–35.5 | 13.6 \pm 5.5 4.2–23.9 | 21.4 \pm 6.2 12.3–32.7 | 19.5 \pm 4.8 12.6–34.0 | 26.4 \pm 9.8 9.6–47.0 | 24.3 \pm 7.5 12.0–34.7 |
| Amplitude of saccades (degrees) | 4.8 \pm 1.0 3.7–7.0 | 4.3 \pm 1.3 2.5–7.2 | 5.0 \pm 1.3 3.0–7.1 | 4.5 \pm 0.9 3.0–7.1 | 5.1 \pm 1.2 3.3–7.6 | 4.8 \pm 0.8 3.5–6.1 | 5.8 \pm 1.6 3.4–8.9 | 5.1 \pm 1.0 3.3–7.4 |
| CV of saccade amplitude | 0.61 \pm 0.18 0.46–1.19 | 0.55 \pm 0.18 0.38–0.80 | 0.66 \pm 0.13 0.41–0.84 | 0.60 \pm 0.11 0.36–0.77 | 0.67 \pm 0.12 0.51–0.97 | 0.73 \pm 0.14 0.48–1.04 | 0.82 \pm 0.21 0.54–1.41 | 0.74 \pm 0.11 0.59–1.06 |
| Number of saccades (n) | 28.9 \pm 7.7 15–42 | 28.2 \pm 6.1 19–37 | 31.1 \pm 7.5 18–45 | 31.8 \pm 6.2 20–40 | 33.6 \pm 5.5 22–43 | 34.3 \pm 5.3 27–47 | 31.6 \pm 6.3 21–43 | 34.7 \pm 3.7 29–44 |
| Duration of fixation (ms) | 292.9 \pm 92.3 179.8–478.3 | 307.4 \pm 76.4 199.7–468.6 | 261.3 \pm 77.9 174.3–459.5 | 272.2 \pm 69.8 199.2–421.0 | 238.6 \pm 47.7 185.3–386.9 | 237.1 \pm 34.9 160.1–298.5 | 240.2 \pm 53.8 137.6–366.3 | 233.4 \pm 24.4 183.7–275.0 |
| Instability ratio of fixation | 0.19 \pm 0.15 0.05–0.62 | 0.08 \pm 0.06 0.03–0.19 | 0.21 \pm 0.14 0.05–0.57 | 0.08 \pm 0.05 0.03–0.19 | 0.21 \pm 0.12 0.07–0.53 | 0.10 \pm 0.05 0.03–0.22 | 0.22 \pm 0.12 0.08–0.56 | 0.12 \pm 0.06 0.04–0.23 |

Mean \pm standard deviation and range are shown
CV coefficient of variation

The instability ratio of fixation was significantly larger in SCA patients than that in normal subjects, implying unstable ocular fixation in SCA patients (Fig. 4f; tests of within-subject effects, image complexity \times subject-group interaction, $F_{2,279}=0.880$, $p=0.431$, and $\epsilon=0.760$; tests of between-subject effects, $F_1=11.741$, $p=0.002$).

Influence of Visual Scanning Parameters on Scanned Area

As shown in Table 3, in SCA patients, saccade amplitude correlated significantly with the scanned area in most images (images 2–4). In normal subjects, saccade amplitude correlated significantly with the scanned area in only image 2 but not in images 1, 3, and 4.

ROI Analysis of Conspicuous Areas

As shown in Fig. 3, both SCA patients and normal subjects dwelled on certain conspicuous areas of the images (red areas). These were the following: image 1—the intersection on the foreground side of the cube; image 2—the overlapping area of the two pentagons; image 3—the chimney of the house; and image 4—the circle in the Rey-Osterrieth complex figure. These areas were selected as ROIs. In image 1, a circular area (0.85 cm in radius; visual angle 1° in radius) centering on the intersection was selected as the ROI. For all images, the dwell time in each ROI did not differ between SCA patients and normal subjects (image 1 SCA 1.8 ± 1.1 ms, normal subjects 2.3 ± 1.5 ms, $p=0.276$; image 2 SCA 2.3 ± 1.2 ms, normal subjects 2.5 ± 1.3 ms, $p=0.639$; image 3 SCA 0.7 ± 0.4 ms, normal subjects 0.9 ± 0.8 ms, $p=0.430$; image 4 SCA 1.1 ± 0.9 ms, normal subjects 1.3 ± 0.5 ms, $p=0.452$).

Discussion

Scanned Area Is Abnormally Larger in SCA

Using the eye-tracking method, we observed several novel features of the visual scanning of SCA patients. For example, when viewing images with various levels of visual complexity, SCA patients consistently scanned a larger area than normal subjects. However, the number of saccades and duration of fixation in SCA patients were almost identical to those in normal patients. In addition, the amplitude of saccades and the variation of saccade amplitude did not statistically differ between the two groups, although those in SCA patients were slightly larger than those in normal subjects for almost all images.

Since saccade amplitude was significantly correlated with the scanned area in most images, the enlarged scanned area in SCA patients is thought to result mainly from the slightly larger saccade amplitude. One plausible explanation for the larger saccade in SCA patients may be saccadic dysmetria as reported in a number of previous papers [27–32]. In addition, the instability ratio of fixation was considerably higher in SCA patients than that in normal subjects; more than half of the SCA patients were complicated by fixation disturbances such as gaze-evoked nystagmus and downbeat nystagmus, with many gaze drifts occurring during putative ocular fixation.

The slightly larger saccade resulting from saccadic dysmetria may prevent SCA patients from recognizing visual objects efficiently, because the ocular fixation position fails to accurately acquire the intended visual target but lands on some other spatially distant object. In addition, fixation disturbances also may disrupt accurate gaze fixation and further impair

Table 3 Results of multiple linear regression analyses for scanned area

| SCA patients | Image 1 ($R^2=0.642$) | | Image 2 ($R^2=0.772$) | | Image 3 ($R^2=0.753$) | | Image 4 ($R^2=0.451$) | |
|-------------------------------|-------------------------|---------|-------------------------|---------|-------------------------|---------|-------------------------|---------|
| | p | β | p | β | p | β | p | β |
| Amplitude of saccades | 0.137 | 0.294 | 0.001* | 0.624 | <0.001* | 0.894 | 0.012* | 0.651 |
| CV of saccade amplitude | 0.035* | 0.462 | 0.653 | -0.073 | 0.878 | -0.027 | 0.674 | 0.097 |
| Number of saccades | 0.142 | 0.722 | 0.017* | 0.574 | 0.361 | 0.262 | 0.891 | -0.034 |
| Duration of fixation | 0.600 | 0.252 | 0.524 | -0.125 | 0.589 | -0.151 | 0.263 | -0.286 |
| Instability ratio of fixation | 0.106 | 0.352 | 0.587 | -0.092 | 0.274 | 0.181 | 0.618 | 0.114 |
| Normal subjects | Image 1 ($R^2=0.646$) | | Image 2 ($R^2=0.649$) | | Image 3 ($R^2=0.377$) | | Image 4 ($R^2=0.309$) | |
| | p | β | p | β | p | β | p | β |
| Amplitude of saccades | 0.095 | 0.333 | 0.013* | 0.593 | 0.817 | 0.086 | 0.616 | 0.158 |
| CV of saccade amplitude | 0.595 | 0.092 | 0.419 | -0.178 | 0.936 | 0.032 | 0.542 | -0.180 |
| Number of saccades | 0.824 | -0.120 | 0.494 | 0.500 | 0.488 | 0.483 | 0.281 | -0.895 |
| Duration of fixation | 0.256 | -0.626 | 0.875 | 0.119 | 0.927 | -0.070 | 0.170 | -1.049 |
| Instability ratio of fixation | 0.216 | 0.231 | 0.229 | 0.237 | 0.200 | 0.488 | 0.941 | -0.022 |

*Significant correlation

accurate perception of visual objects. Therefore, both larger saccade and unstable fixation may prevent SCA patients from recognizing various objects. Consequently, the area scanned by SCA patients was “abnormally” enlarged, which may be a manifestation of “blurred focus” of visual fixation, leading to visual cognitive impairment.

Of course, in practice, shifts in gaze are not determined solely by eye movements; head movements also play a role. Since the head was restrained to allow accurate measurement of eye movements in this study, the larger area scanned by saccades alone cannot be directly equated with larger gaze shifts. However, it has been reported that when SCA patients attempt to make gaze movements with the head unrestrained, their gaze is dysmetric, often hypermetric, as are head movements [33]. Thus, arguably, we may assume that the area scanned by SCA patients is larger than that in normal subjects even in activities of daily living where the head is freely moving. This implies that some part of the visual cognitive impairment in SCA patients could be accounted for by dysmetria in oculomotor control rather than dysmetria of cognition.

Characteristics of Visual Scanning Strategy in SCA

The figures used in this study are just the same as those used in our previous study in PD [19]. Interestingly, the visual scanning area in PD patients was narrowed due to small saccades [19, 34–39], which contrasts with that in SCA patients. Additionally, the visual scanning features of PD patients were different between simple and complex figures; while scanning images of varying complexity, PD patients made fewer saccades with longer fixation compared with normal subjects. As image complexity increased, the saccade number and fixation duration gradually approached those of normal subjects. We interpreted these findings as due to the ocular paradoxical movement (*kinésie paradoxale*) in PD [19, 34, 35, 37, 39]. In contrast, the visual scanning in SCA patients did not change drastically as the complexity of images varied. In other words, SCA patients did not show an obvious ocular paradoxical movement as in PD, which could be considered a characteristic of SCA.

SCA patients gazed at the same conspicuous regions of the images as long as the normal subjects did. This implies that, although the ocular fixation is more widely distributed in SCA patients, the focus of ocular fixation is almost identical to that of normal subjects. These results are similar to those in PD patients: The focus of ocular fixation is almost identical to that of normal subjects. On the other hand, the results of SCA patients stand in sharp contrast to those in patients with Alzheimer’s disease (AD). AD patients show a disorganized pattern of visual exploration due to the impaired spatial perception during clock reading: The focus of ocular fixation in AD patients was located at the less informative part irrelevant

to the task requirement, i.e., the center of clock, which considerably differed from that in normal subjects, i.e., the hands of clock [40]. This suggests that the visual scanning strategy in SCA was almost identical to that in normal subjects and PD, but different from that in AD.

Can Visual Memory Impairment in SCA be Explained by Oculomotor Control?

The question here is whether the oculomotor control in SCA patients can explain the impairment of visual memory and, if so, to what extent. In fact, we demonstrated that the larger saccade and fixation disturbance may be two of the important factors leading to disturbances of visual memory in SCA patients. In particular, the more complex figures contained many features that required the subjects to memorize them with extensive scanning, i.e., with ocular fixation over each of the components in the figures, while they were too complex to be verbally or visually memorized within 10 s (images 3 and 4) using “iconic” memory. To remember objects which the subjects looked at, a certain length of time is required. SCA patients would have been unable to gaze at the components in the images with precision over a certain length of period, which could have led to the lower scores on the visual memory task.

On the other hand, we suppose that there are also other factors that cannot be explained only by oculomotor control, one of which is visual cognitive dysfunction. The reason for this is that the images reproduced by the patients contained transposed elements and reproduced components in the wrong direction or wrong three-dimensional configuration (Fig. 2), which could not be accounted for solely in terms of oculomotor control. In particular, the reproduction inaccuracies were prominent in simple figures (images 1 and 2). Since less complex figures could be verbally memorized as “a cube” or “two overlapping pentagons,” the subjects did not really need to scan the figures to memorize them visually; the subjects could memorize the figures verbally using visual cognitive function rather than visual scanning. Therefore, regardless of the presence of oculomotor abnormalities, they should have been able to memorize the simple figures by converting the visual information into verbal information. Thus, the poor reproduction of simple figures indicates that SCA patients have some visual cognitive dysfunction which cannot be explained by only the oculomotor control.

Conclusion

SCA patients with fixation disturbances visually scan a larger area than normal subjects when viewing images with various

levels of visual complexity. The “abnormally” enlarged area that SCA patients scan is probably caused by the larger and dysmetric saccades. The wide distribution of fixation locations as well as impaired fixation may prevent SCA patients from visually recognizing various objects present in their daily life. This implies that some part of the visual cognitive impairment in SCA patients could be accounted for by dysmetria in oculomotor control rather than dysmetria of cognition.

Conflicts of Interest The authors declare that there are no potential conflicts.

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RESEARCH ARTICLE

Top-Down but Not Bottom-Up Visual Scanning is Affected in Hereditary Pure Cerebellar Ataxia

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Abstract

The aim of this study was to clarify the nature of visual processing deficits caused by cerebellar disorders. We studied the performance of two types of visual search (top-down visual scanning and bottom-up visual scanning) in 18 patients with pure cerebellar types of spinocerebellar degeneration (SCA6: 11; SCA31: 7). The gaze fixation position was recorded with an eye-tracking device while the subjects performed two visual search tasks in which they looked for a target Landolt figure among distractors. In the serial search task, the target was similar to the distractors and the subject had to search for the target by processing each item with top-down visual scanning. In the pop-out search task, the target and distractor were clearly discernible and the visual saliency of the target allowed the subjects to detect it by bottom-up visual scanning. The saliency maps clearly showed that the serial search task required top-down visual attention and the pop-out search task required bottom-up visual attention. In the serial search task, the search time to detect the target was significantly longer in SCA patients than in normal subjects, whereas the search time in the pop-out search task was comparable between the two groups. These findings suggested that SCA patients cannot efficiently scan a target using a top-down attentional process, whereas scanning with a bottom-up attentional process is not affected. In the serial search task, the amplitude of saccades was significantly smaller in SCA patients than in normal subjects. The variability of saccade amplitude (saccadic dysmetria), number of re-fixations, and unstable fixation (nystagmus) were larger in SCA patients than in normal subjects, accounting for a substantial proportion of scattered fixations around the items. Saccadic dysmetria, re-fixation, and nystagmus may play important roles in the

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impaired top-down visual scanning in SCA, hampering precise visual processing of individual items.

Introduction

The cerebellum is intimately involved in coordinating skilled motor behavior, whereas impairment of the cerebellum is associated with cerebellar motor symptoms such as cerebellar ataxic movements, e.g. dysmetria. However, only recently has cognitive dysfunction come to be associated with cerebellar disorders. For example, disturbances of attention, executive functioning, and frontal lobe-like behavioral and affective alterations have been observed after focal primary cerebellar damage, resulting in a fairly common picture of cognitive and affective disturbances [1]. These cognitive impairments are generally thought to be caused by the cerebellar connections with the cerebral cortex [2–5]. The term ‘dysmetria of cognition’ has been proposed to refer to cognitive dysfunctions related to underlying cerebellar conditions [6–8].

However, it is uncertain whether dysmetria of cognition represents a condition caused by a similar mechanism to that of motor dysmetria or a distinct condition more related to cognitive processing and relatively independent of the condition of motor dysmetria. The simplest explanation would be that the cerebellum is involved not only in somatomotor function but also in oculomotor control. Cerebellar patients often present with a variety of oculomotor disorders including saccadic dysmetria [9–15], gaze-evoked nystagmus [9, 16], downbeat nystagmus [9, 17], and square-wave jerks [9, 18], which together can impair ocular fixation and compromise visual processing. Since most of the cognitive processing in daily life involves visual processing, the present study addressed how visual processing is impaired in cerebellar disorders.

Using an eye-tracking device, we recently showed that at least some part of the visual processing impairment in patients with spinocerebellar ataxia (SCA) may be accounted for by ‘dysmetria in oculomotor control,’ such as saccadic dysmetria and nystagmus, rather than dysmetria of cognition [19]. Our previous study, however, did not clarify the contribution of the two types of visual attentional mechanisms, ‘top-down instruction’ and ‘bottom-up salience,’ to deficits in visual cognition, [20–27]. People use these two types of attention when they search for the target among distractors in a search task [20, 28]. In the pop-out search task, where the target and distractors are clearly discernible, attention is captured by a visually conspicuous object (bottom-up salience) and subjects do not need to move their attention (or gaze) from one position to another. Consequently, the search time for detecting the target is independent of the number of items (the target and distractors) included in the display [21, 22]. On the other hand, in the serial search task, where the target has features very similar to the distractors, focused attention (or gaze) has to be allocated to each item serially from one to

another (top-down instruction). As a result, search time increases with increasing number of distractors. Contrasting these two types of search in cerebellar patients should provide insights about impairments in these two types of visual attentional mechanisms, i.e. top-down instruction and bottom-up salience.

Saliency mapping is useful to study the relationship between search tasks and visual attentional mechanisms [27]. It is a conceptually simple computational model of focal visual attention that simulates bottom-up, image-based attentional deployment, accurately identifying the objectively outstanding areas in an image (bottom-up salience) [29, 30]. Analysis using saliency maps has so far been limited to studies of normal subjects [27, 29, 31–33] and has not previously been applied to patients with neurological disorders.

Previous studies of humans and animals with cerebellar damage have found impairment in visual search and suggested that the top-down attentional processes may be disturbed while bottom-up attentional processes are not [34–36]. However, these studies are controversial regarding the involvement of oculomotor movement [36, 37]. Moreover, these previous eye-tracking studies did not formally differentiate between serial and pop-out tasks. Thus, detailed analyses for inefficient top-down visual scanning are required to clarify the involvement of oculomotor control in the impairment of visual search.

In this study, we used two types of search tasks: serial search and pop-out search. To determine the visual attentional mechanisms in the two tasks, we employed a saliency map. Here, we hypothesized that cerebellar patients would need a longer time to search for a target than normal subjects, especially in the serial search task, which requires top-down visual processing. To evaluate the contribution of eye movements to the impairment of top-down visual processing, we also recorded eye movements during search tasks with an eye-tracking device, and compared the results with those of healthy subjects. To elucidate the causes of prolonged search time, we compared the parameters of visual scanning between SCA patients and normal subjects in the tasks that are disturbed in SCA patients: number of saccades, duration of fixation, amplitude of saccades, coefficient of variation (CV) of saccade amplitude, number of repeated fixations, and instability ratio of fixation.

Materials and Methods

Subjects

Eighteen non-demented spinocerebellar degeneration (SCD) outpatients who presented with pure cerebellar ataxia and 18 age-matched healthy volunteers (hereafter, normal subjects) participated in this study. Eleven SCD patients were genetically confirmed as spinocerebellar ataxia type 6 (SCA6) and 7 as spinocerebellar ataxia type 31 (SCA31) [38–41]. The Mini-Mental Status Examination (MMSE) [42] was used to exclude SCA patients with dementia from this study. The characteristics of the SCA patients and normal subjects are shown in [Table 1](#). The mean \pm SD age of the SCA patients was 64.1 ± 12.0 years (range:

Table 1. Characteristics of SCA patients and normal subjects.

| | SCA patients | Normal subjects | <i>p</i> |
|-----------------------------|--------------|-----------------|----------|
| N | 18 | 18 | |
| Male:Female | 8:10 | 11:7 | n.s. |
| Age (years) | | | |
| Mean (SD) | 64.1 (12.0) | 64.6 (11.1) | n.s. |
| MMSE | | | |
| Median (range) | 29 (25–30) | 29 (26–30) | n.s. |
| Duration of illness (years) | | | |
| Median (range) | 9.5 (3–28) | | |
| ICARS | | | |
| Median (range) | 58.5 (5–73) | | |
| Fixation nystagmus (N) | 15 | | |
| Down-beat nystagmus (N) | 11 | | |

MMSE: Mini-Mental Status Examination.
 ICARS: International Cooperative Ataxia Rating Scale.
 n.s.: not significant.

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43–84 years) and that of the normal subjects was 64.6 ± 11.1 years (range: 43–80 years), with no statistically significant difference between the two groups (unpaired *t*-test, $p=0.912$). The median MMSE score of the SCA patients was 29 (range: 25–30) and that of the normal subjects was 29 (range: 26–30), again with no difference between the groups (Mann-Whitney U test, $p=0.845$). The median duration of illness in the SCA patients was 9.5 years (range: 3–28 years). The median value of the International Cooperative Ataxia Rating Scale (ICARS) [43] was 58.5 (range: 5–73). Fifteen SCA patients showed gaze-evoked nystagmus and 11 showed downbeat nystagmus. None of them showed square-wave jerks.

Written informed consent to participate in this study was obtained from all subjects. The procedure was approved by the Ethics Committee of The University of Tokyo and the study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Eye-tracking analysis

The experimental setting was similar to that of our previous studies [19, 27, 44]. Subjects were seated with steady head position maintained by chin and forehead rests. The EyeLink 1000 system (SR Research, Mississauga, Ontario, Canada) was used to acquire ocular fixation position data at a sampling rate of 1000 Hz. This eye-tracking device can compensate for ocular fixation position shifts caused by head movements. Gaze data were acquired from the left eye. Tasks were created using SR Research Experiment Builder version 1.5.58 and images were presented on a Dell E173FPb monitor at 60 Hz. The distance between the screen and the subject was kept at 50cm, so that each image subtended a total visual angle of $38^\circ \times 30^\circ$, with 0.85 cm on the screen corresponding to approximately 1° of visual

angle. Prior to the experiments, the subjects performed a nine-point calibration procedure to map the ocular fixation position onto screen coordinates. The calibration was considered to be valid if the maximum spatial error was less than 1° and the average error was less than 0.5° .

Behavioral paradigm: visual tasks

The following five different tasks were conducted: a simple reaction task, discrimination tasks (direction and color), and visual search tasks (serial and pop-out).

1. Simple reaction task: somatomotor task

The subjects were instructed to press the button connected to the eye-tracking device as soon as a Landolt figure appeared at the center of the monitor. They were presented with a total of 10 images. The reaction time to press the button in this task was termed the simple reaction time, which was considered to reflect the speed of their somatomotor response.

2. Discrimination tasks: cognitive tasks

In the discrimination tasks, every time the experimenter pressed the button, a Landolt figure appeared the center of the monitor.

2-1. Direction discrimination task: The subjects were instructed to judge whether the Landolt figure was oriented upward (gap at the top) or downward (gap at the bottom; [Fig. 1A](#)). If the Landolt figure was oriented upward (target), the subjects were instructed to press the button as soon as possible, upon which the figure was extinguished. Ten figures in total were presented (5 upward and 5 downward). The direction discrimination time was calculated by the following formula: $\text{direction discrimination time} = \text{total time in this task} - \text{simple reaction time}$. The time to judge the direction of the Landolt figure in this task was considered to reflect the subject's cognitive speed of discriminating orientation.

2-2. Color discrimination task: In this task, the subjects were instructed to judge whether a Landolt figure appearing at the center of monitor was red or black ([Fig. 1B](#)). If the color of the Landolt figure was red (target), the subjects were instructed to press the button as soon as possible, at which point the image was extinguished. A session consisted of 10 image presentations (5 red and 5 black figures). Color discrimination time was calculated by the following formula: $\text{color discrimination time} = \text{total time in this task} - \text{simple reaction time}$. The time to judge the color of the Landolt figure was considered to reflect the subject's cognitive speed of discriminating color.

3. Search tasks: cognitive and oculomotor tasks

In the visual search tasks, a display of a Landolt figures appeared when the subject pressed the button.

3-1. Serial search task: The subjects were instructed to visually search for a single target Landolt figure out of distractor Landolt figures ([Fig. 2A](#)). The direction of the target Landolt figure was oriented upward whereas the other non-target

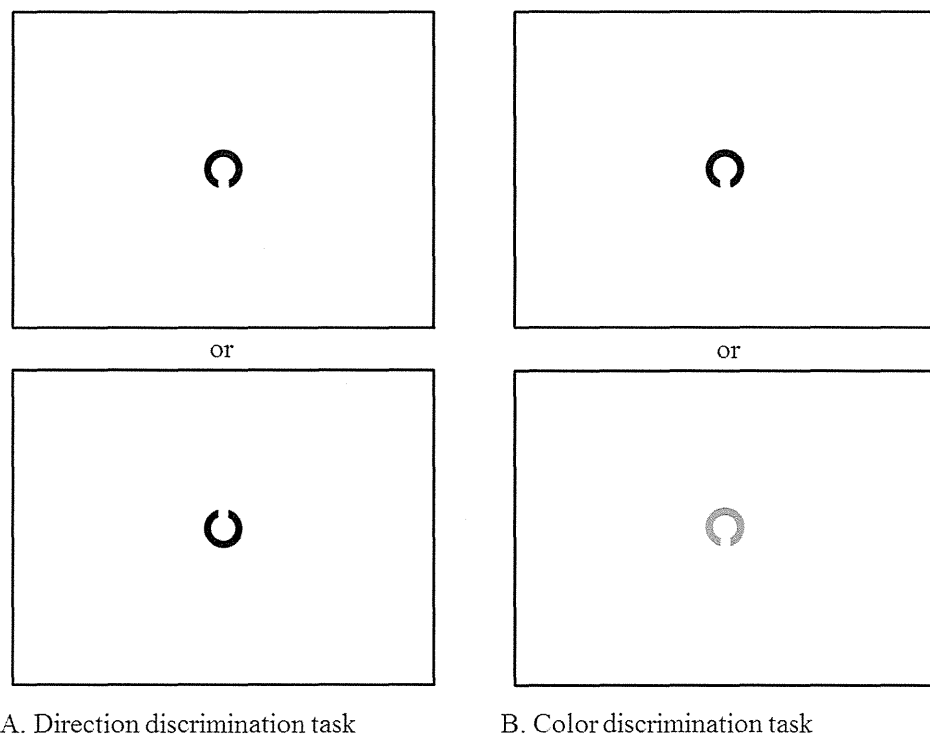


Fig. 1. Discrimination tasks. A: direction discrimination task, B: color discrimination task. In the direction discrimination task, the subject was instructed to push the button connected to the eye-tracking device as quickly as possible only when an upward-facing Landolt figure appeared at the center of monitor. In the color discrimination task, the subject was instructed to push the button only when a red Landolt figure appeared. The direction and color discrimination times were measured by the following formula: discrimination time = total time – simple reaction time.

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Landolt figures were oriented downward. Each display contained a single target Landolt figure among multiple distracting Landolt figures. After the detection of the target Landolt figure, the subjects were instructed to gaze at it and to press the button, at which point the image was extinguished. They scanned a total of 10 similar images each for the 4- and 48-item tasks. Serial search time was calculated by the following formula: serial search time = total time in this task – simple reaction time.

3-2. Pop-out search task: The subjects were instructed to visually search for a single target Landolt figure out of distractor Landolt figures (Fig. 2B). The target Landolt figure was red while the non-target Landolt figures were black. After detecting the target Landolt figure, the subjects were instructed to gaze at it and to press the button, at which point the image was extinguished. As in the serial search task, the display contained either 4 or 48 items including the target (Fig. 2B). Subjects scanned a total of 10 similar images for each display size. Pop-out search time was calculated as follows: pop-out search time = total time in this task – simple reaction time. The search time to reach the target was considered to reflect the subject's oculomotor and cognitive function.

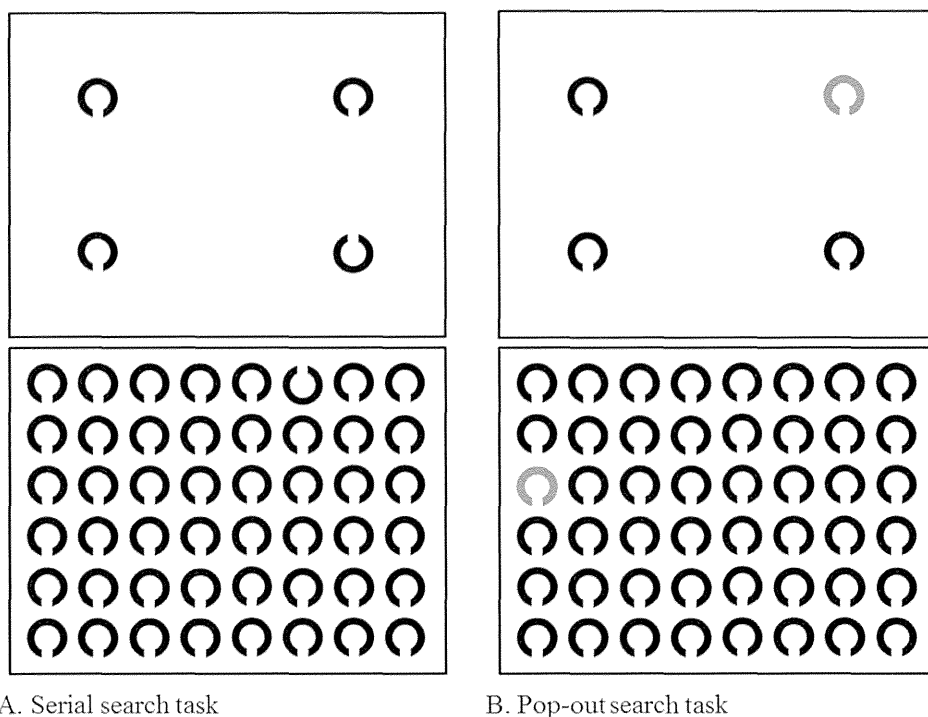


Fig. 2. Search tasks. A: serial search task, B: pop-out search task. Upper panels show 4-item tasks and lower panels show 48-item tasks. In the serial search task, the subject was instructed to push the button connected to the eye-tracking device when he/she found an upward-facing Landolt figure. In the pop-out search task, the subject was instructed to push the button when he/she found a red Landolt figure. The serial and pop-out search times were measured by the following formula: search time = total time – simple reaction time.

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Data analysis and statistical assessment

Saliency mapping

Using the method detailed in a previous report [27], we created saliency maps from the search tasks using MATLAB 2009a and custom software implemented in MATLAB [45, 46]. This software was designed on the basis of a bottom-up visual saliency model: the saliency mapping technique can predict human eye-fixation patterns successfully using the algorithms of Itti et al. [47]. The accuracy of saliency mapping predictions has been confirmed through comparison with data on human eye-fixation patterns while viewing the same scene [29]. For creating a saliency map, the visual input image is first decomposed into a set of topographic feature maps through several pre-attentive feature detection mechanisms (colors, orientations, contrast, and intensity). Different spatial locations then compete for saliency within each map, such that only locations which locally stand out from their surround can persist. All feature maps feed, in a purely bottom-up manner, into a master saliency map, which topographically codes for local conspicuity over the entire visual image [47].

Heat mapping

Heat maps, or graphical color-coded maps showing the distribution of ocular fixation positions, were created for each image using SR Research Data Viewer ver. 1.3.137. One heat map per image was created for each group, yielding a total of eight heat maps. To create a heat map, a two-dimensional Gaussian was applied to each of the fixation points. The Gaussian center was located at the ocular fixation position, while the width of the Gaussian was influenced by an adjustable sigma value (set at 0.8) in degrees of visual angle, and the height of the Gaussian was weighted by the duration of individual fixations. After the above process was applied to all fixation points, these Gaussians were normalized and overlaid in a color-coded fashion onto the original image.

Time in visual tasks and visual scanning parameters

The visual search times were measured in the serial and pop-out search tasks and were compared between SCA patients and normal subjects. The following data analyses were performed with programs in the SR Research Data Viewer ver. 1.3.137. To identify the causes of delay in search time in the visual search tasks (serial or pop-out search task), the number of saccades per second (n/sec), mean duration of fixation (ms), mean amplitude of saccades (degrees), CV of saccade amplitude, number of repeated fixations, and instability ratio of fixation were also measured as visual scanning parameters. The number of saccades per second was calculated as total number of saccades divided by search time. The duration of fixation indicates the mean duration of individual ocular fixations measured from the end of one saccade to the beginning of the next saccade. To count the number of repeated fixations, we selected the outline of the target Landolt figure (the circle surrounding the target Landolt figure) as the region of interest. Repeated fixations were defined as fixations which exited and re-entered this region. Based on the inspection of the eye movement records, the slow phase of nystagmus accounted for almost all of the instability of gaze due to impaired ocular fixation, and the ratio of gaze instability corresponds to the total time occupied by the slow phase of nystagmus within the total duration of the record. The instability ratio of fixation was therefore defined as the ratio of the duration of the slow phase in nystagmus to the total duration of the eye movement record. We followed the definition of the slow phase of nystagmus employed by previous studies, namely, slow oculomotor movements ranging from 5 to 10 degrees per second in an eye movement record [48, 49].

We performed the following statistical analyses: To compare the response times in the simple reaction and discrimination tasks (simple reaction time, direction discrimination time, and color discrimination time) between SCA patients and normal subjects, we used the unpaired *t*-test. Search times in the serial and pop-out search tasks were analyzed using the two-way repeated measures analysis of variance (ANOVA) with a within-subject factor: numbers of items (2 levels, 4 and 48 items); and a between-subject factor: subject group (2 levels, SCA patients-normal subjects). Post-hoc analyses were also conducted, if necessary, using the Bonferroni's method.

To investigate the difference in visual scanning parameters (number of saccades, duration of fixation, amplitude of saccade, CV of saccade amplitude, number of repeated fixations, and instability ratio of fixation) between SCA patients and normal subjects, we used a two-way repeated measures ANOVA with a within-subject factor: numbers of items (2 levels, 4 and 48 items); and a between-subject factor: subject group (2 levels, SCA patients-normal subjects). Post-hoc analyses were also conducted, if necessary, using the Bonferroni's method.

P values of less than 0.05 were considered significant (correction for multiple comparisons by Bonferroni's method: $p < 0.025$). Statistical analysis was performed using the SPSS software package (ver. 16.0; SPSS Inc., Chicago, Illinois, USA).

Results

Saliency maps and heat maps

[Fig. 3](#) shows the saliency maps in the search tasks. A saliency map color-coded according to the strength of salience was overlaid onto each image. Higher salience areas are depicted in red, intermediate areas in yellow, and lower areas in blue. Meanwhile, [Figs. 4](#) and [5](#), respectively, show the heat maps color-coded overlaid onto each image according to the duration of gaze fixations in the serial search and the pop-out search tasks in 18 SCA patients and 18 normal subjects. Here, areas attracting longer fixations are shown in red, those attracting intermediate length fixations in yellow, and those attracting shorter eye fixations in green. The shortest durations (i.e., the lowest 5 percentile) were eliminated automatically as a default setting. Since the eye-fixation position was located at the center of the image at the start of each task, the center was colored despite the absence of items at this location. In all visual tasks, gaze fixations were distributed over a larger area in SCA patients than in normal subjects. In other words, the areas scanned by SCA patients tended to be enlarged relative to those by normal patients. Note that the gaze distribution almost coincided with the most salient regions of the image in the color discrimination tasks, meaning that the pop-out task actually drew attention (and gaze) to the most salient positions of the image, i.e. target positions (bottom-up visual scanning). In contrast, salient regions were more widely distributed throughout the images in the serial tasks, as were the positions of gaze fixation over the image. This reflects the fact that these images indeed require processing of items serially with gaze movements (top-down visual scanning).

Impaired visual scanning in SCA: oculomotor trajectory

We observed at least two abnormal eye movement patterns during the visual search tasks in SCA patients. One was saccadic dysmetria and the other was slow phase of nystagmus. Actually, the ocular fixation positions frequently did not

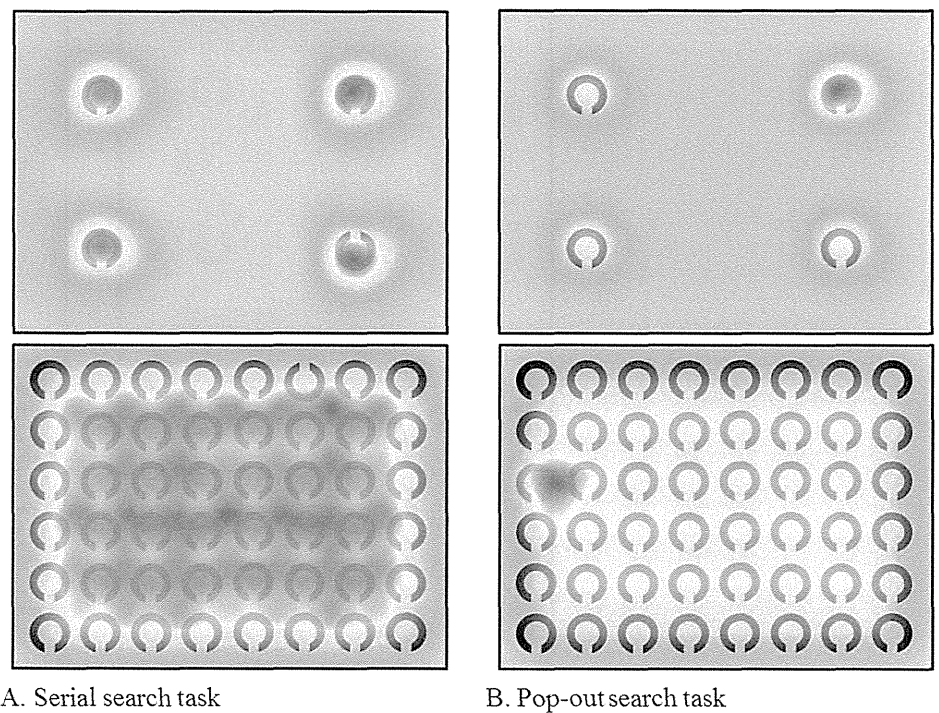


Fig. 3. Saliency maps in search tasks. A: serial search task, B: pop-out search task. In the pop-out search task, the target red Landolt figure is clearly colored in red, suggesting that the subjects performed bottom-up visual scanning due to the high saliency of the target. In the serial search task, high saliency areas are uniformly distributed over the images and the target upward Landolt figure is completely masked, suggesting that the subjects performed top-down visual scanning due to the low saliency of the target.

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exactly fall on the visual target, but landed at a point somewhat removed from the target, suggesting saccadic dysmetria (Fig. 6). A slow eye movement following a saccade was often encountered throughout the visual tasks, suggesting the slow phase of nystagmus. Careful visual inspection suggested that the enlarged scanned areas can be explained by oculomotor dysfunction such as saccadic dysmetria and gaze drift due to the slow phase of nystagmus. This suggests an impairment of visual scanning in SCA patients.

Analysis of gaze movements during the search task revealed that these abnormal gaze movements in SCA patients actually hampered visual processing of items. They frequently looked directly (within central vision) or relatively close to the items (target or distractors), but the distance of their gaze from the items again increased, with the gaze finally returning close to the target (Fig. 7A). In many instances, gaze fixation around the target was accompanied by slow drifting of gaze position, representing the slow phase of nystagmus. The same phenomenon occurred only rarely in normal subjects (Fig. 7B). As a result, SCA patients made significantly more saccades than normal subjects.

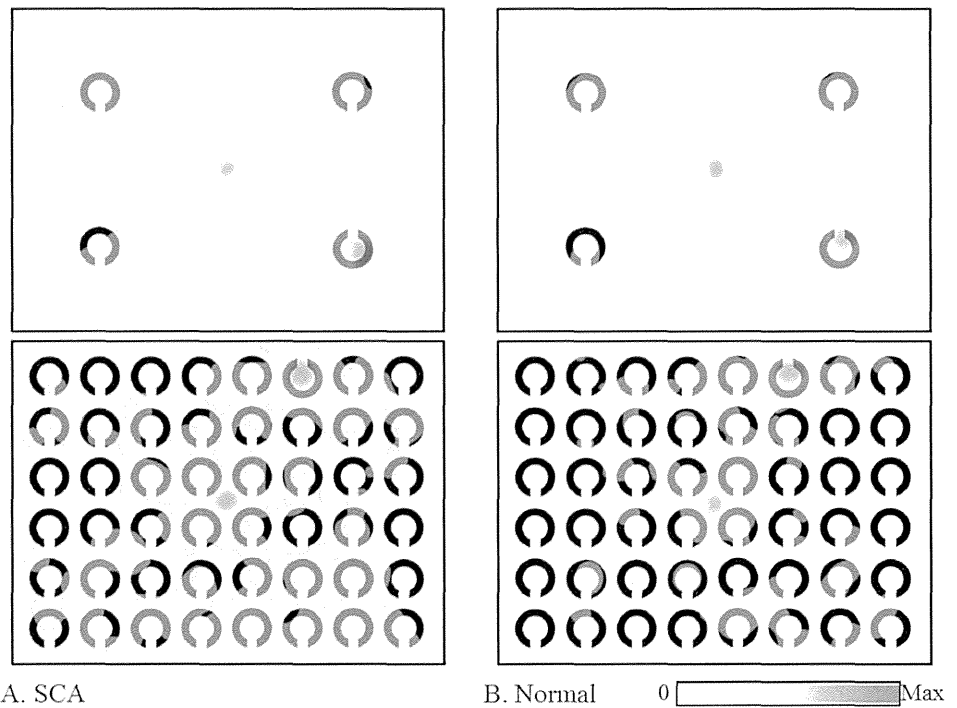


Fig. 4. Heat maps in serial search tasks. A: SCA patients, B: normal subjects. In both 4- and 48-item tasks, the areas (colored areas) scanned by SCA patients were distributed more widely than those of normal subjects. The center was also colored because the starting eye-fixation position was located at the center of image.

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Search time in visual tasks

Table 2 and Fig. 8 show the performance in all five visual tasks. Simple reaction time was longer in SCA patients than in normal subjects ($p=0.004$, Fig. 8A). The direction and color discrimination times were not different between SCA patients and normal subjects (Fig. 8B; direction: $p=0.411$, color: $p=0.692$). ANOVA and post-hoc analyses revealed that the serial search time in SCA patients was significantly longer than that in normal subjects in both 4-item and 48-item serial search tasks (Fig. 8C; test of within-subject effect: number of items \times subject-group interaction, $F_1=5.293$, $p=0.028$; post hoc analyses: 4 items $p=0.007$, 48 items $p=0.009$). Serial search time increased with the number of items for SCA patients and normal subjects (test of within-subject effect: number of items, $F_1=44.000$, $p<0.001$). On the other hand, the pop-out search time in both the 4-item and 48-item tasks was not different between SCA patients and normal subjects (test of within-subject effect: number of items \times subject-group interaction, $F_1=3.256$, $p=0.080$; tests of between-subjects effects: $F_1=0.051$, $p=0.822$). Pop-out search time also increased with the number of items for both groups, but with a much smaller increase than with the serial search task (test of within-subject effect: number of items, $F_1=28.370$, $p<0.001$).

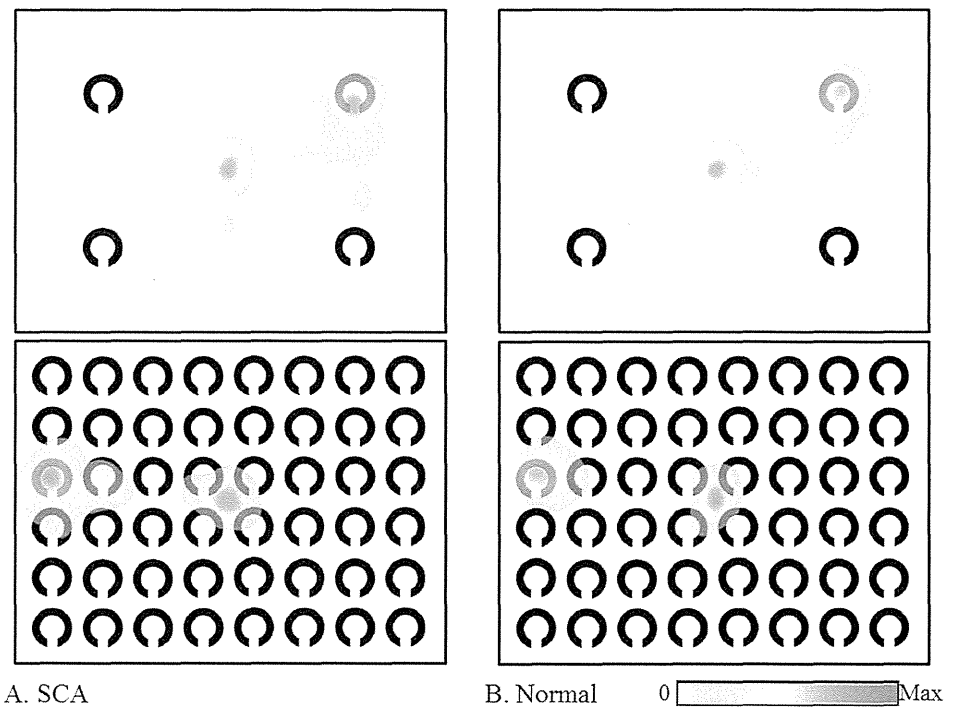


Fig. 5. Heat maps in pop-out search tasks. A: SCA patients, B: normal subjects. In both 4- and 48-item pop-out search tasks, the areas (colored areas) scanned by both SCA patients and normal subjects were more localized than those in serial search tasks.

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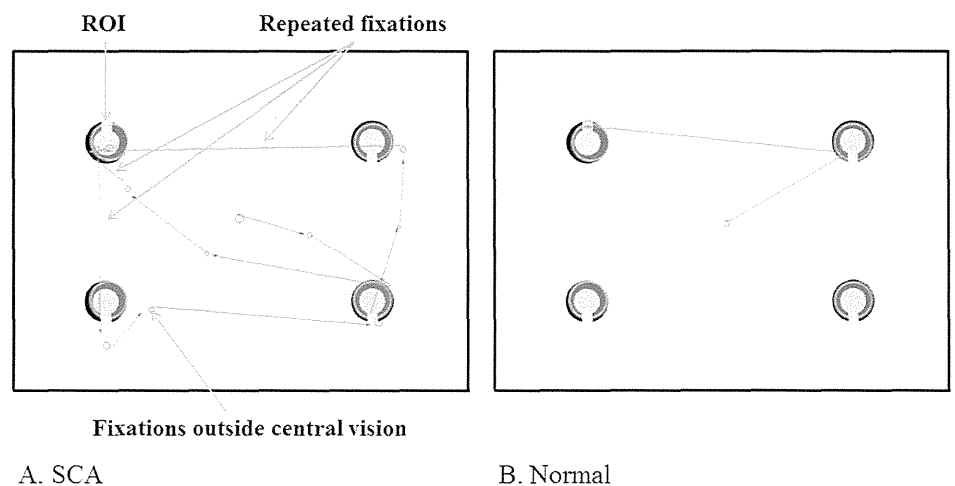


Fig. 6. Representative eye movements. Eye movements in the 4-item serial search task are shown for an SCA patient (A) and a normal subject (B). In the SCA patient, the ocular fixation positions frequently did not fall exactly on the visual target, but landed at points somewhat removed from the target (saccadic dysmetria). In addition, we also observed something we term “repeated fixations (re-fixations)”. Here, the gaze initially captures the target item and then moves away before returning to the target item. To count the number of re-fixations, the target Landolt figure was selected as the region of interest.

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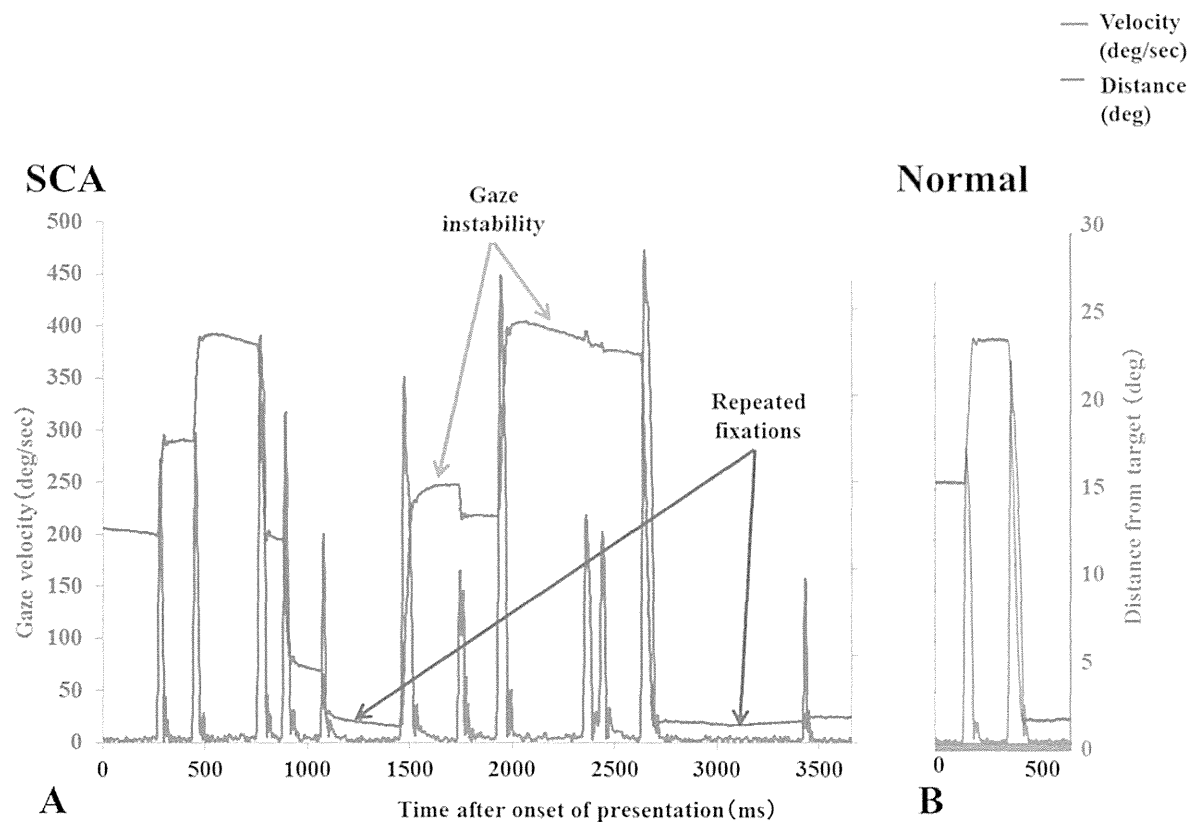


Fig. 7. Oculomotor trajectories. Careful visual observation of oculomotor trajectories provides information on saccadic dysmetria, repeated fixations (re-fixations) and nystagmus. These figures show recordings of the gaze trajectory during visual search (abscissa: time; ordinate: the distance of gaze position from the target (zero deg. in the abscissa corresponds to the target position) [blue curve]; and instantaneous velocity of gaze [red curve]) in an SCA patient (A) and a normal subject (B). Note that with time the gaze eventually approaches the target (distance becomes zero at the right end of each figure) but for an SCA patient it takes more time, with the gaze alternately approaching and leaving the target. After approaching the target, the gaze leaves the target once and eventually comes back to the target later (repeated fixations). In addition, the gaze position shows slow drifts, representing the slow phase of nystagmus, even during presumed fixation, whereas this rarely occurs in normal subjects.

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Table 2. Time in all visual tasks.

| Time (ms) | SCA patients | Normal subjects | p |
|-------------------------------|-----------------|-----------------|--------|
| Simple reaction time | 508.3 ± 125.5 | 401.8 ± 76.8 | 0.004* |
| Direction discrimination time | 353.1 ± 196.3 | 305.8 ± 140.1 | 0.411 |
| Color discrimination time | 212.2 ± 136.9 | 197.7 ± 91.1 | 0.692 |
| Serial search time | | | |
| 4 items | 1270.8 ± 1019.3 | 564.2 ± 180.1 | 0.007* |
| 48 items | 5926.4 ± 4597.4 | 2821.9 ± 1136.1 | 0.009* |
| Pop-out search time | | | |
| 4 items | 145.2 ± 144.4 | 167.6 ± 107.3 | 0.600 |
| 48 items | 273.7 ± 210.6 | 231.1 ± 83.7 | 0.430 |

Data are shown as mean ± standard deviation; *significant difference.

doi:10.1371/journal.pone.0116181.t002

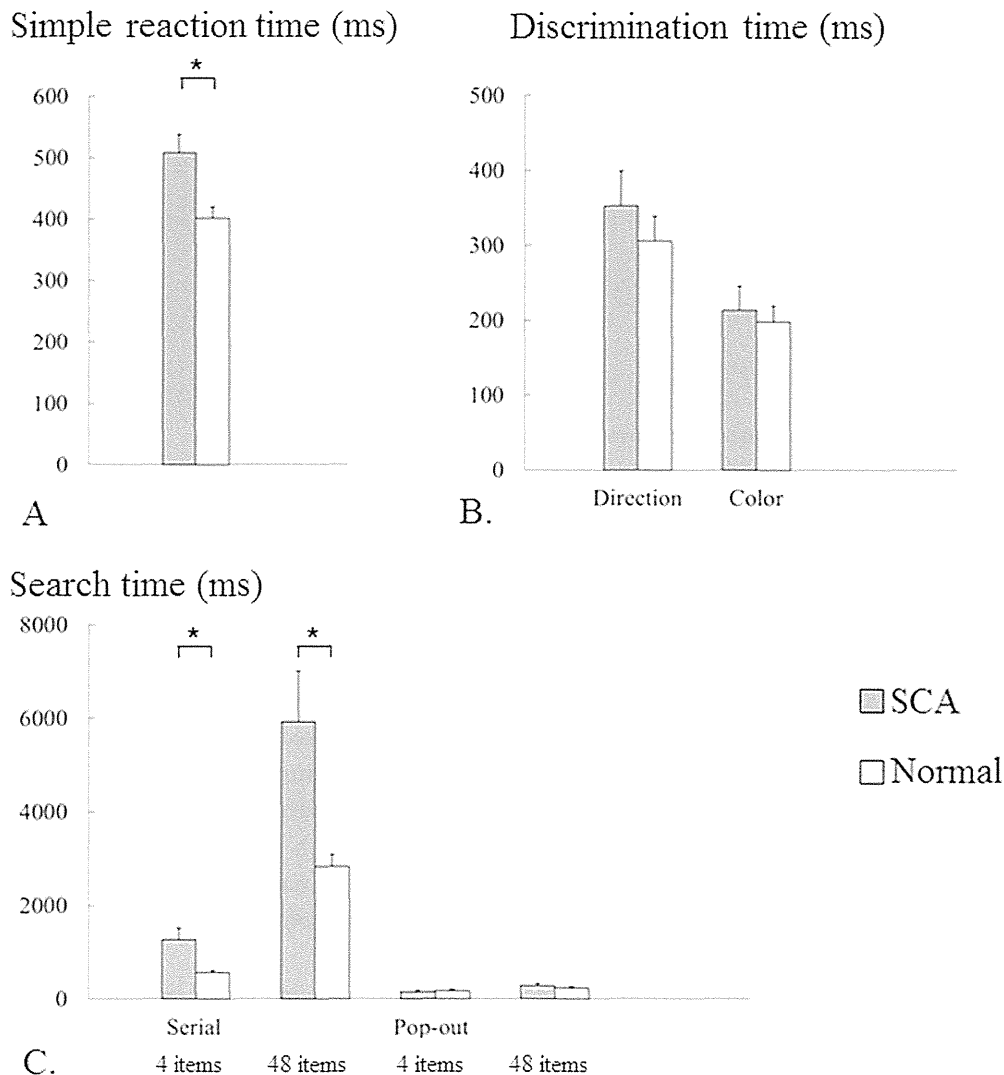


Fig. 8. Search time of visual tasks. A: simple reaction time, B: direction and color discrimination time, C: serial and pop-out search time. The bars show the values of mean and standard error. Grey bars are for SCA patients and white bars for normal subjects. The simple reaction time was longer in SCA patients than in normal subjects. The direction and color discrimination time had no statistical differences. The 4- and 48-item serial search time was longer in SCA patients than in normal subjects, whereas the 4- and 48-item pop-out search time in SCA patients was almost identical to that in normal subjects. The serial search time was markedly longer than the pop-out search time in both SCA patients and normal subjects.

doi:10.1371/journal.pone.0116181.g008

Visual scanning parameters

Saccade parameters during the serial search task were compared between the two subject groups to reveal possible causes for the impaired top-down visual scanning in SCA patients. Table 3 and Fig. 9 show the visual scanning parameters for SCA patients and normal subjects. The number of saccades per second in SCA patients was very similar to that in normal subjects (Fig. 9A; tests of within-subjects effects: number of items \times subject group interaction, $F_1=1.278$, $p=0.311$; tests of between-subjects effects: $F_1=0.109$, $p=0.744$). The number of saccades did not

Table 3. Visual scanning parameters in serial search tasks.

| | 4 items | | | 48 items | | |
|---------------------------------|--------------|-----------------|----------|--------------|-----------------|----------|
| | SCA patients | Normal subjects | <i>p</i> | SCA patients | Normal subjects | <i>p</i> |
| Number of saccades (n/ sec) | 3.6 ± 0.4 | 3.5 ± 0.5 | 0.479 | 3.5 ± 0.5 | 3.5 ± 0.4 | 0.924 |
| Duration of fixation (ms) | 194.4 ± 32.2 | 184.0 ± 24.4 | 0.281 | 231.8 ± 40.8 | 214.1 ± 22.0 | 0.114 |
| Amplitude of saccades (degrees) | 9.5 ± 1.6 | 10.6 ± 1.6 | 0.054 | 5.8 ± 0.6 | 6.4 ± 0.8 | 0.028 |
| CV of saccade amplitude | 0.69 ± 0.12 | 0.49 ± 0.09 | <0.001* | 0.79 ± 0.13 | 0.78 ± 0.16 | 0.873 |
| Number of repeated fixations | 0.17 ± 0.23 | 0.03 ± 0.06 | 0.019* | 0.47 ± 0.44 | 0.14 ± 0.17 | 0.007* |
| Instability ratio of fixation | 0.22 ± 0.10 | 0.12 ± 0.06 | 0.001* | 0.20 ± 0.10 | 0.12 ± 0.02 | 0.004* |

Data are shown as mean ± standard deviation; CV: coefficient of variation; *significant difference in post hoc analyses.

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change with the number of items for both groups (tests of within-subjects effects: number of items, $F_1=0.001$, $p=0.979$).

The duration of fixation in SCA patients was also almost comparable to that in normal subjects (Fig. 9B; tests of within-subjects effects: number of items × subject group interaction, $F_1=0.726$, $p=0.400$; tests of between-subjects effects: $F_1=2.289$, $p=0.139$). The mean duration of fixation increased with the number of items for both groups (tests of within-subjects effects: number of items, $F_1=62.206$, $p<0.001$). However, these did not differ between the two groups as noted above and cannot explain the much longer search time in SCA patients. Thus, we looked for another reason why SCA patients make more saccades while searching for the target during visual search, with consequently longer overall search time.

First, saccadic dysmetria may have resulted from the impaired oculomotor control in SCA patients. The mean amplitude of saccades decreased with the number of items for both groups (test of within-subject effect: number of items, $F_1=200.825$, $p<0.001$). The amplitude of saccades in SCA patients was significantly smaller than that in normal subjects (Fig. 9C; test of within-subject effect: number of items × subject-group interaction, $F_1=0.914$, $p=0.346$; tests of between-subjects effects: $F_1=6.705$, $p=0.014$). The CV of saccade amplitude in SCA patients increased with the number of items in both groups (test of within-subject effect: number of items, $F_1=35.809$, $p<0.001$). It was significantly larger than that in normal subjects only in the 4-item serial search task (Fig. 9D; test of within-subject effect: number of items × subject-group interaction, $F_1=9.413$, $p=0.004$; post hoc analyses: 4items $p<0.001$, 48 items $p=0.875$). These findings indicate that saccadic hypometria predominated in SCA patients, and that the saccade amplitude was more variable in SCA patients.

The number of re-fixations increased with the number of items for both groups (test of within-subject effect: number of items, $F_1=26.669$, $p<0.001$). There were significantly more re-fixations in SCA patients than in normal subjects (Fig. 9E; test of within-subject effect: number of items × subject-group interaction,