Quantification of Visual Fixation in Multiple Sclerosis

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PURPOSE. Eye movement abnormalities are common in multiple sclerosis (MS), and infrared oculography is a noninvasive method for quantification. This study aims to describe and classify abnormalities of visual fixation and their clinical relevance in MS.

METHODS. A validated standardized infrared oculography protocol, Demonstrate Eye Movement Networks with Saccades, was used for quantifying gaze stability during a fixation task in MS patients and healthy controls. Saccadic intrusions, gaze drift, and stability of fixation around the drift line were used to subclassify MS patients by performing receiver operating characteristic analyses of different parameters. The relationship between the presence of abnormalities of fixation and visual functioning was analyzed using logistic regression models, which was adjusted for possible confounders.

RESULTS. This cross-sectional study included 213 subjects with MS and 57 healthy controls. Square wave jerk abnormalities were present in 24% of MS patients. The prevalence was higher in more disabled subjects. The presence of larger square wave jerks (with a higher amplitude) in the MS patients was related to complaints of focusing on stationary objects (odds ratio, 2.2; $P = 0.035$) and a lower vision-related quality of life (odds ratio, 2.56; $P = 0.012$).

CONCLUSIONS. This study provided a comprehensive overview of the characteristics of problems with visual fixation in subjects with MS. The most important and most common finding was the presence of larger square wave jerks during fixation, which was related to visual functioning in daily life.

Keywords: eye movements, ocular fixation, saccadic eye movements, multiple sclerosis, demyelination

Visual fixation is an important part of normal movement control of the eyes. During visual fixation, the central fovea maintains focus on a visual target so that the visual system can process detailed information about what is being looked at. All the while, the eyes are in constant motion because small fixational eye movements (including microsaccades, small ocular drift, and ocular tremor) continually and slightly change the focus on the retina.[1–3] In contrast, saccades are the fast eye movements that are used to move the fovea rapidly from one point of interest to another. Our perception is guided by alternating these sequences of fixations and saccades.[3] The ability to hold a steady gaze depends first of all on an intact retina and optic nerve. Furthermore, a distributed network of neurons in cortical visual centers, the brainstem, and cerebellum is involved in visual fixation. Fixation abnormalities are well-recognized in neurologic disorders as Parkinsonian conditions, Alzheimer's disease, and posterior cortical atrophy.[3–5]

Eye movement abnormalities are various and common in multiple sclerosis (MS). Based on clinical examination, the prevalence is estimated at 36% to 84%.[6–8] Eye movement disorders can result in symptoms such as diplopia, oscillopsia,

difficulties with focusing, or blurred vision. Well-known causes are pendular nystagmus and internuclear ophthalmoplegia.[3,9–11] Furthermore, abnormalities of eye movements are associated with greater general disability in MS.[12,13] Hitherto, studies describing the extensive range of abnormalities were essentially based on clinical examination.[6,14–17] It stands to reason that the clinical diagnosis of many eye movement disorders is difficult and can be challenging. Mild impairments of eye movements can easily be missed in a nonspecialized setting. This has comprehensively been shown for the internuclear ophthalmoplegia.[18] In MS, fixation, abnormalities are not well described. Examples are saccadic intrusions during fixation and nystagmus.[6,14–17] Recently, a first study has quantified fixation abnormalities in MS. In this study of 16 MS patients, an increased fixation instability compared to healthy controls was measured with scanning laser ophthalmoscopy-based eye tracking during optical coherence tomography scanning.[19]

This lends support to further quantify and classify fixation abnormalities and investigate prevalence and clinical correlates in a larger cohort. For visualization and quantification of eye

movements, a noninvasive and accurate eye tracking method is available, namely, infrared oculography.

We developed a standardized protocol for infrared oculography, Demonstrate Eye Movement Networks with Saccades (DEMoNS), by which gaze stability during fixation can be quantified in a reproducible manner.[20] The aim of the present study is to investigate the prevalence and relevance of fixation abnormalities in subjects with MS.

METHODS

Study Design and Subject Population

This study was approved by the Medical Ethical Committee on Human Research of the Amsterdam University Medical Center (location VUmc) and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants before study inclusion.

For this observational cross-sectional study, MS patients and healthy controls were included from the Amsterdam MS cohort, an ongoing observational cohort of the Amsterdam University Medical Center. Participants were at least 18 years of age. All MS patients had to fulfill clinical and radiologic criteria for a diagnosis of clinically definite MS.[21] The disease course was described as relapsing-remitting, secondary progressive, or primary progressive.[22] Exclusion criteria were immunodeficiency syndrome, relapse or course of steroids within 6 weeks to inclusion, pregnancy, or history of drug or alcohol abuse.

Clinical and Ophthalmologic Assessment

All assessments (clinical, infrared oculography, and questionnaires) were performed on the same day and in the same order of sequence.

The disease duration was calculated in years from the first MS symptom. The Expanded Disability Status Scale score[23] was determined by a certified examiner to assess the level of disability. A history of symptomatic MS-associated optic neuritis was based on a consensus protocol,[24] including recording of the best corrected high and low contrast visual acuities using Sloan letter charts (100% and 2.5%, respectively).[25] Spectral-domain optical coherence tomography (Spectralis; Heidelberg Engineering, Heidelberg, Germany) was performed in all subjects as described previously, including quality-control criteria.[26,27] Global peripapillary retinal nerve fiber layer thickness and macular ganglion cell and inner plexiform layer thickness of both eyes were obtained. The vision-related quality of life was assessed with the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25).[28,29] In addition, an in-house questionnaire for complaints specific to problems with eye movements was included (see Supplementary Material S1).

Infrared Oculography

Data were measured and analyzed using our standardized protocol suitable for a multicenter setting, the DEMoNS protocol.[20] In brief, eye movements were measured binocularly with the Eyelink 1000 Plus eye tracker at a frequency of 1,000 Hz (spatial resolution, <0.01 degrees root mean square; average accuracy down to 0.15 degrees). Participants were seated in front of a display monitor, and their head was stabilized by means of a chin and a forehead rest. For this study, the fixation task of the DeMoNS protocol was used. In this task, participants had to fixate a target for 8 seconds, at a central and 4 eccentric locations. These eccentric positions were located 15 degrees of visual angle left and right from the center and 10 degrees of visual angle up and down from the center. Every

target position was measured twice. At least 50% of fixation samples needed to pass quality control for a subject to be included. The first second after target appearance was discarded, resulting in a total of 14 seconds of fixation for every gaze direction. In these fixation periods, different parameters were calculated, taking the mean of the left and right eye. The parameters are visualized in Figure 1. The standard deviation of the horizontal and vertical gaze and the bivariate contour ellipse area of the gaze (the area of a bivariate ellipse encompassing 68% of the highest density samples)[30] provided an overall estimate of gaze stability during the fixation periods. Fixation abnormalities were then classified: (1) saccadic intrusions, (2) drift, and (3) stability of fixation around the drift line.

1. Square wave jerks were defined as saccades followed between 50 ms and 400 ms by another saccade with an amplitude comparable to the first saccade (<0.75 degree difference) and in the opposite direction (movement direction in the frontal plane of the second saccade between 90 and 270 degrees from the direction of the first saccade).[3] All saccades during fixation that were not part of a square wave jerk were defined as other saccadic intrusions. Both frequency (mean number per second) and amplitude of square wave jerks and other saccadic intrusions were calculated. Subsequently, saccades were removed from the tracing for analysis of gaze drift (2) and stability of fixation (3).

2. Gaze drift was determined for horizontal and vertical gaze separately. The drift was calculated by a linear fit (regression line) through all the consecutive gaze samples of the 14 seconds of the fixation period. The regression coefficient (expressed in degrees per second) of this line was considered as the mean drift during this fixation period.

3. Similar to gaze drift, the stability of fixation around the drift line was determined for horizontal and vertical gaze separately. The standard error of the estimate, reflecting the mean deviation of the gaze from the regression line calculated in (2), defined the fixation stability around the drift line. The rationale behind this parameter was that it reflects any fixation instability that is not caused by either saccadic intrusions or drift.

Statistical Analyses

Data were analyzed visually and statistically for normality. Independent *t*-tests (Gaussian data) and nonparametric tests (non-Gaussian data) were used for the comparison of parameters between MS patients and healthy controls. The chi square test was used for categoric data.

Receiver operator characteristic analyses of the central fixation period were performed to divide the MS group into different subgroups with and without fixation abnormalities. For these analyses, the distribution of the different classification parameters of the healthy control and MS group were used. A threshold with the highest accuracy (combination of sensitivity and specificity) was determined in the specificity range above 95%. All MS patients that exceeded the threshold were classified as having abnormalities in this subgroup. Subjects that showed either more frequent or larger (higher amplitude) square wave jerks were classified as having square wave jerk abnormalities. Likewise, both frequency and amplitude were taken into account for classification of other saccadic intrusion abnormalities. For classification of drift abnormalities, the absolute value of both horizontal and vertical gaze drift was used in the receiver operator characteristic analysis. This resulted in one threshold for horizontal
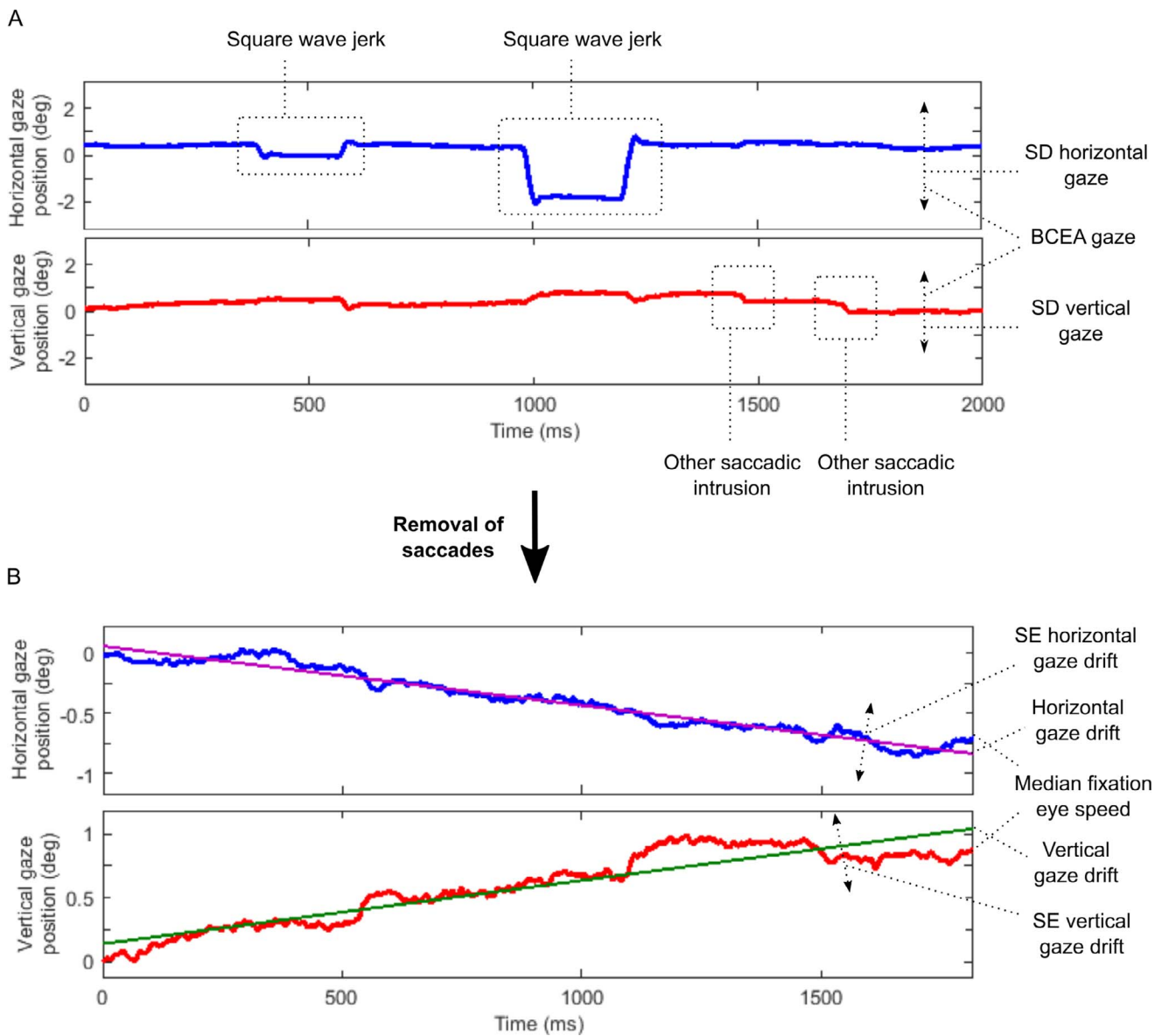
FIGURE 1. The fixation parameters used in this study. Recordings with infrared oculography of the horizontal (*blue*) and vertical (*red*) gaze position of the right eye during 2 seconds of central fixation of a MS patients. A positive value on the *y*-axis represents gaze rightward or downward of the center, and a negative value represents gaze leftward or upward of the center. (**A**) Standard deviation (SD) of horizontal and vertical gaze and bivariate contour ellipse area (BCEA) were calculated. Furthermore, square wave jerks and other saccadic intrusions were detected. (**B**) After removal of saccades from the tracings, the regression line of the horizontal gaze (*purple line*) and vertical gaze (*green line*) were determined. The slope of this line was considered as the mean drift. Consequently, the standard error of the estimate (SE) from the regression line defined the fixation stability around the drift line. Furthermore, median fixation eye speed (combined absolute horizontal and vertical velocity) was calculated. Deg, degrees of visual angle; ms, milliseconds.

(both leftwards and rightwards) drift and one threshold for vertical (both upwards and downwards) drift. For comparison of clinical and optical coherence tomography characteristics of subgroups of MS patients, the Holm-Bonferroni method was used as a correction for multiple comparisons.[31]

Linear and logistic regression analyses were used to analyze the relationship between the presence of fixation abnormalities and visual acuity, eye movement complaints, and vision-related quality of life (lowest versus highest two tertiles). These analyses were adjusted for the possible confounders sex, disease duration, Expanded Disability Status Scale score and visual acuity.

Statistical analyses were performed using SPSS (released 2013, IBM SPSS Statistics for Windows, version 22.0; IBM Corp., Armonk, NY, USA).

RESULTS

In total, 226 MS patients and 61 healthy controls were recruited to this study. Of these we had to exclude 13 MS patients and 4 healthy controls. The reasons for exclusion were corrupted data files ($N = 6$), insufficient quality of the data ($N = 3$), very low vision in one eye resulting in absent stereopsis ($N = 7$), and one monoocular measurement.

TABLE 1. Demographic and Clinical Characteristics of the Healthy Controls and MS Patients

Characteristics	MS Patients ($N = 213$)	Healthy Controls ($N = 57$)
Female sex, N (%)	144 (68)	29 (51)
Age, y	54.8 ($\pm$10.7)	52.2 ($\pm$9.3)
Disease duration, y	21.2 ($\pm$8.5)	N/A
Median EDSS score (IQR, total range)	4.0 (3.5, 0.0-8.5)	N/A
Disease course		
Relapsing remitting, N (%)	128 (60)	N/A
Secundary progressive, N (%)	56 (26)	N/A
Primary progressive, N (%)	21 (10)	N/A
Unclassifiable, N (%)	8 (4)	N/A
Internuclear ophthalmoplegia, N (%)	71 (33)	N/A
High-contrast visual acuity (best eye)*	56.2 ($\pm$7.2)	N/A
Low-contrast visual acuity (best eye)†	30.8 ($\pm$12.0)	N/A
Optic neuritis history, N (%)‡	97 (49)	N/A
Disease-modifying treatments, N	IFN, 44; FTY, 2; AZT, 1; MTX, 2; NTZ, 6; GA, 12; Ter, 1	N/A

IFN, interferon beta 1a and 1b; FTY, fingolimod; AZT, azathioprine; MTX, methoxanthrone; NTZ, nataluzimab; Ter, teriflunomide; N, number; EDSS, Expanded Disability Status Scale; IQR, interquartile range; $\pm$, standard deviation; N/A, not applicable.

* High-contrast visual acuity data missing from 18 subjects.

† Low-contrast visual acuity data missing from 59 subjects.

‡ Optic neuritis information missing from 16 subjects.

The demographic and clinical characteristics of the included participants are summarized in Table 1. The percentage of females in the MS group was significantly higher than in the healthy control group (68% vs. 51% respectively, $P = 0.010$). MS patients had a mean disease duration of 21.2 ($\pm$8.5) years and the majority (60%) had a relapsing-remitting disease course.

Fixation in Primary Position

In Figure 2, recordings of the horizontal gaze show a few examples of fixation abnormalities of MS patients. The fixation parameters of the MS and healthy control subjects of the central fixation period are summarized in Table 2. Fixation in primary position was more stable in healthy controls compared to subjects with MS according to a number of variables. Both the standard deviation of the horizontal gaze and the bivariate contour ellipse area of the gaze were significantly different between MS patients and healthy controls (difference in median 0.04 [$P < 0.001$] and 0.11 [$P = 0.011$], respectively). Of the different classification parameters, the amplitude of square wave jerks and other saccadic intrusions were significantly different between MS patients and healthy controls (difference in median 0.13 [$P < 0.001$] and 0.13 [$P = 0.021$], respectively).

One MS patient showed a pendular nystagmus, and this subject was excluded for subclassification. The different thresholds used to classify MS patient and the corresponding specificity are listed in Table 3. Based on these thresholds, the MS patients were classified in different subgroups, as shown in Figure 3. It demonstrates that 90 subjects had fixation abnormalities: 68 (32% of the MS group) showed abnormal saccadic intrusions, 29 (14%) showed abnormal drifts, and 29 (14%) showed abnormal fixation instability around the drift line. In Figure 3, the overlap between the 3 groups is visualized. Of the group with abnormal saccadic intrusions, the majority of subjects showed abnormalities of square wave jerks (75% of the group). In Figure 4, the distribution of the frequency and amplitude of square wave jerks is shown for the healthy control and MS group. The main cause for square wave jerk abnormalities was a larger amplitude of square wave jerks (94% of the group).

Relation With Disease Characteristics

The mean disease duration for MS patients with fixation abnormalities in primary position was 22.2 ($\pm$9.1) years, compared to 20.6 ($\pm$8.1) years in the group without fixation abnormalities ($P = 0.168$). In Table 4, clinical and optical coherence tomography characteristics are compared between

TABLE 2. Fixation Parameters in MS Patients and Healthy Controls

Parameter	MS Patients ($N = 213$) Median (range)	Healthy Controls ($N = 57$) Median (range)	Difference P Value
Standard deviation horizontal gaze, deg	0.20 (0.08 to 3.23)	0.16 (0.08 to 1.12)	**0.001**
Standard deviation vertical gaze, deg	0.17 (0.06 to 1.36)	0.16 (0.08 to 0.92)	0.216
Bivariate controur ellipse area, deg^2	0.26 (0.04 to 8.76)	0.15 (0.05 to 3.25)	**0.011**
Frequency square wave jerks, N/s	0.38 (0.00 to 2.22)	0.37 (0.00 to 1.29)	0.888
Mean amplitude square wave jerks, deg	0.62 (0.17 to 4.04)	0.49 (0.24 to 2.22)	**<0.001**
Frequency other saccadic intrusions, N/s	0.74 (0.07 to 4.40)	0.65 (0.00 to 1.81)	0.517
Mean amplitude other saccadic intrusions, deg	0.49 (0.13 to 6.00)	0.36 (0.13 to 3.97)	**0.023**
Median fixation eye speed, deg/s	3.13 (1.97–16.8)	3.11 (2.23 to 7.74)	0.538
Horizontal gaze drift, deg/s	−0.01 (−0.44 to 0.32)	0.02 (−0.24 to 0.28)	0.079
Vertical gaze drift, deg/s	0.02 (−1.13 to 0.84)	0.05 (−0.25 to 0.61)	0.238
Standard error horizontal gaze drift, deg	0.16 (0.07 to 1.49)	0.15 (0.08 to 0.42)	0.178
Standard error vertical gaze drift, deg	0.16 (0.08 to 0.86)	0.15 (0.07 to 0.62)	0.322

Bold P values represent significant differences. N, number; deg, degrees of visual angle; s, seconds.
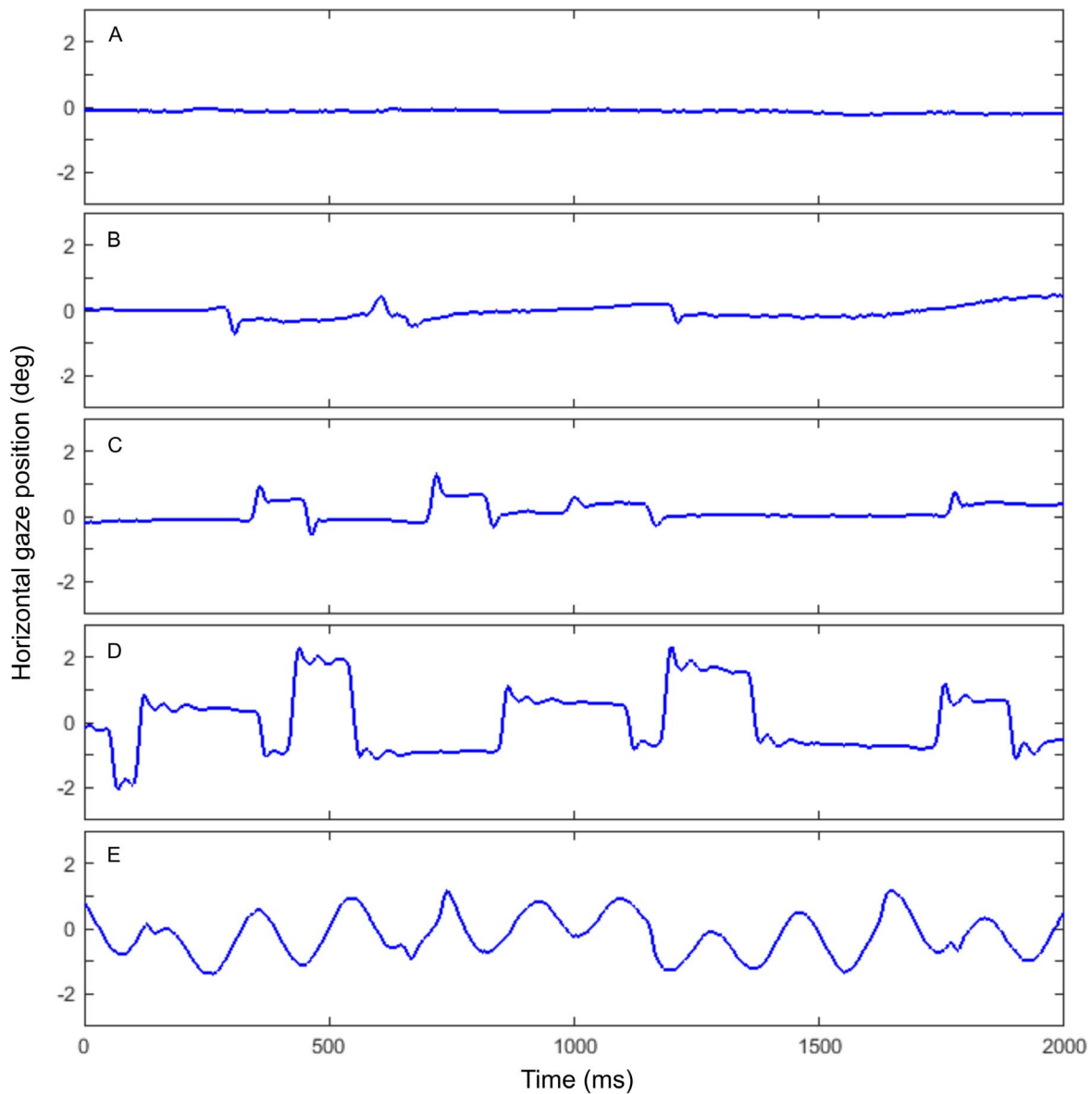
FIGURE 2. Examples of fixation abnormalities in patients with MS. Recordings with infrared oculography of the horizontal gaze position of the right eye during a fixation task in primary position. A positive value on the *y*-axis represents gaze rightward of the center, and a negative value represents gaze leftward of the center. (**A**) Stable fixation of a healthy control. (**B**) MS patient with a small rightward drift. (**C**) MS patient with small square wave jerks. (**D**) MS patient with larger square wave jerks. (**E**) MS patient with pendular nystagmus.

TABLE 3. Thresholds for Classification of Fixation Abnormalities in MS

Parameter	Threshold	MS+, %	Specificity, %
Frequency square wave jerks, *N*/s	1.29	2.4	100.0
Amplitude square wave jerks, deg	1.10	24.5	96.0
Frequency other saccadic intrusions, *N*/s	1.54	6.1	96.5
Amplitude other saccadic intrusions, *N*/s	2.00	8.9	98.2
Horizontal gaze drift, deg/s	0.28	5.2	98.2
Vertical gaze drift, deg/s	0.27	8.5	96.5
Standard error horizontal gaze drift, deg	0.30	2.8	96.5
Standard error vertical gaze drift, deg	0.34	8.5	96.5

MS+, percentage of MS patients that exceed the threshold based on the ROC analysis. *N*, number; deg, degrees of visual angle; s, seconds.
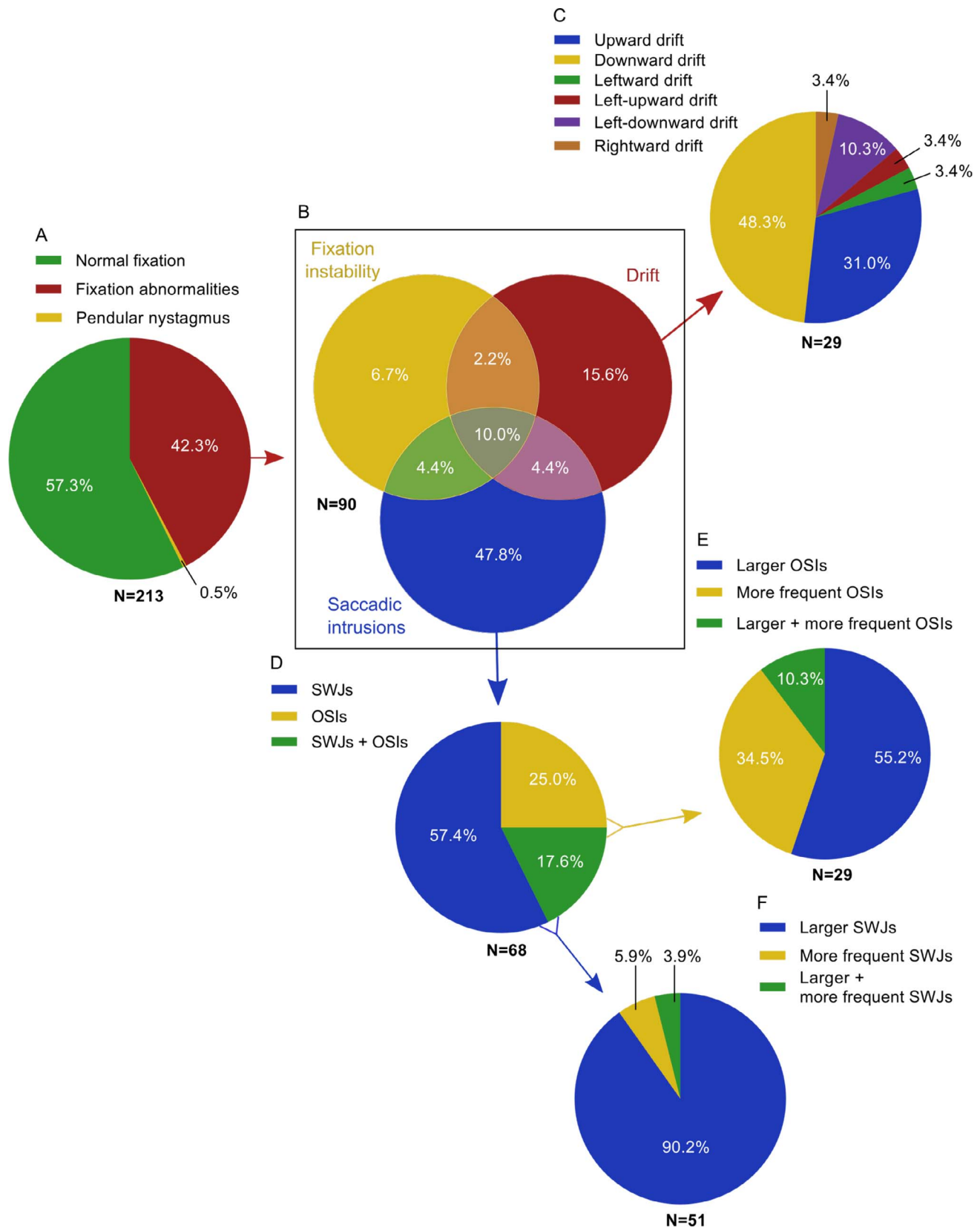
FIGURE 3. Prevalence of fixation abnormalities in the MS group. Fixation abnormalities were found in 90 (42.3%) of the MS patients (pie chart, **A**). Of these subjects, the central Venn diagram (**B**) is showing (overlap between) the main categories of fixation abnormalities. These mains categories were further classified in pie charts in (**C–F**). These show the prevalence of different subcategories of fixation abnormalities in the MS groups, determined with threshold based on the receiver operating characteristic (ROC) analysis. SWJs, square wave jerks; OSIs, other saccadic intrusions.
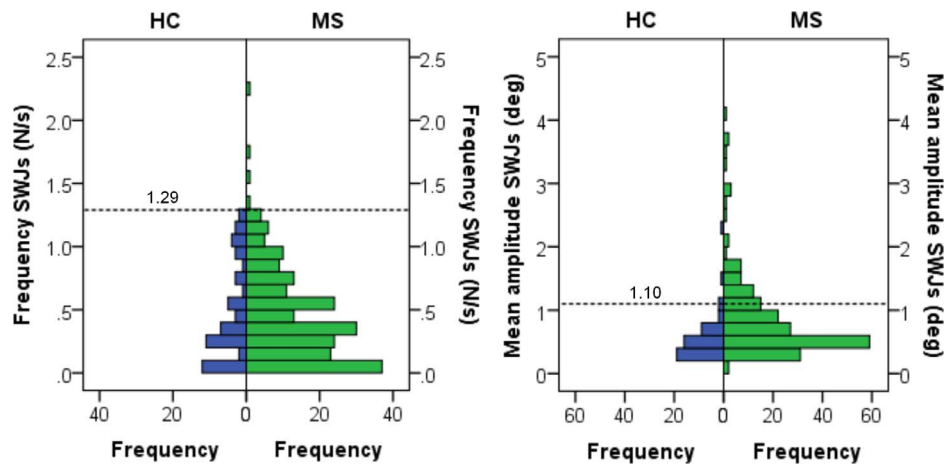
FIGURE 4. Square wave jerks (SWJs) distributions. Distribution of SWJs in the healthy control group (HC) and MS group (MS). The *dashed line* indicates the threshold based on the ROC analysis. (*Left*) Frequency of SWJs, expressed as number of SWJs per second. (*Right*) Mean amplitude of SWJs in degrees of visual angle. N, number.

the subgroups of MS patients with and without square wave jerk abnormalities, corrected for multiple comparisons. The disease duration was significantly longer in the subgroup with square wave jerk abnormalities (mean difference, 4.3 ±1.3 years; $P = 0.014$) Furthermore, the Expanded Disability Status Scale score was significantly higher in this group. There was a similar prevalence of optic neuritis history in both groups and a tendency toward lower retinal layer thicknesses in the subgroup with square wave jerk abnormalities (without

reaching statistical significance after adjustment for multiple comparisons). The median amplitude of square wave jerks in the group with a history of optic neuritis was 0.62 (interquartile range [IQR], 0.54) degrees of visual angle, which was not significantly different from the group without a history of optic neuritis (0.69 [IQR, 0.72] degrees of visual angle; $P = 0.450$).

In Figure 5, the prevalence of fixation abnormalities is shown for different groups of MS patients, divided by

TABLE 4. Disease and Optical Coherence Tomography Characteristics of Patients With MS in Relation to the Presence (SWJ+) or Absence (SWJ−) of Abnormal Square Wave Jerks

Characteristics	SWJ+, N = 51	SWJ−, N = 161	Raw *P* Value	Adjusted *P* Value
	MS Patients			
Disease duration, y	24.5 (±9.4)	20.2 (8.0)	**0.001**	**0.014**
EDSS score, median (IQR, total range)	4.5 (2.5, 1.0–8.0)	3.5 (2.0, 0.0–8.5)	**<0.001**	**0.001**
Disease course				
Relapsing-remitting, *N* (%)	22 (43)	106 (66)	**0.013**	0.091
Secundary progressive, *N* (%)	22 (43)	33 (21)		
Primary progressive, *N* (%)	5 (10)	16 (10)		
Unclassifiable, *N* (%)	2 (4)	6 (4)		
Internuclear ophthalmoplegia				
Unilateral to the right, *N* (%)	6 (12)	17 (11)		0.999
Unilateral to the left, *N* (%)	7 (14)	13 (8)	0.681	
Bilateral, *N* (%)	6 (12)	21 (13)		
High-contrast visual acuity (best eye)*	53.7 (±8.1)	57.0 (±6.6)	**0.005**	0.059
Low-contrast visual acuity (best eye)†	26.8 (±11.3)	32.3 (±11.6)	**0.012**	0.120
Optic neuritis history‡				
Unilateral right, *N* (%)	5 (10)	23 (16)		0.999
Unilateral left, *N* (%)	8 (16)	25 (17)	0.841	
Bilateral, *N* (%)	9 (18)	26 (18)		
pRNFL thickness MSNON eyes, μm§	86.5 (±11.3)	89.9 (±11.9)	0.220	0.880
pRNFL thickness MSON eyes, μm§	70.1 (±12.4)	76.7 (±15.7)	0.074	0.369
mGCIPL thickness MSNON eyes, μm§	81.3 (±12.1)	81.9 (±12.2)	0.741	0.999
mGCIPL thickness MSON eyes, μm§	60.8 (±13.1)	69.1 (±14.2)	**0.014**	0.084

SWJ+, MS patients with abnormal square wave jerks; SWJ−, MS patients without abnormal square wave jerks; MSNON, no MS-associated optic neuritis; MSON, MS-associated optic neuritis; pRNFL, peripapillary retinal nerve fibre layer; mGCIPL, macular ganglion cell and inner plexiform layer; ±, standard deviation. Adjusted *P* values were the result of the Holm-bonferroni method for multiple comparisons. Bold *P* values represent significant differences.
  * High-contrast visual acuity data missing from 18 subjects.
  † Low-contrast visual acuity data missing from 59 subjects.
  ‡ Optic neuritis information missing from 16 subjects.
  § Optical coherence tomography data missing from 133 eyes.
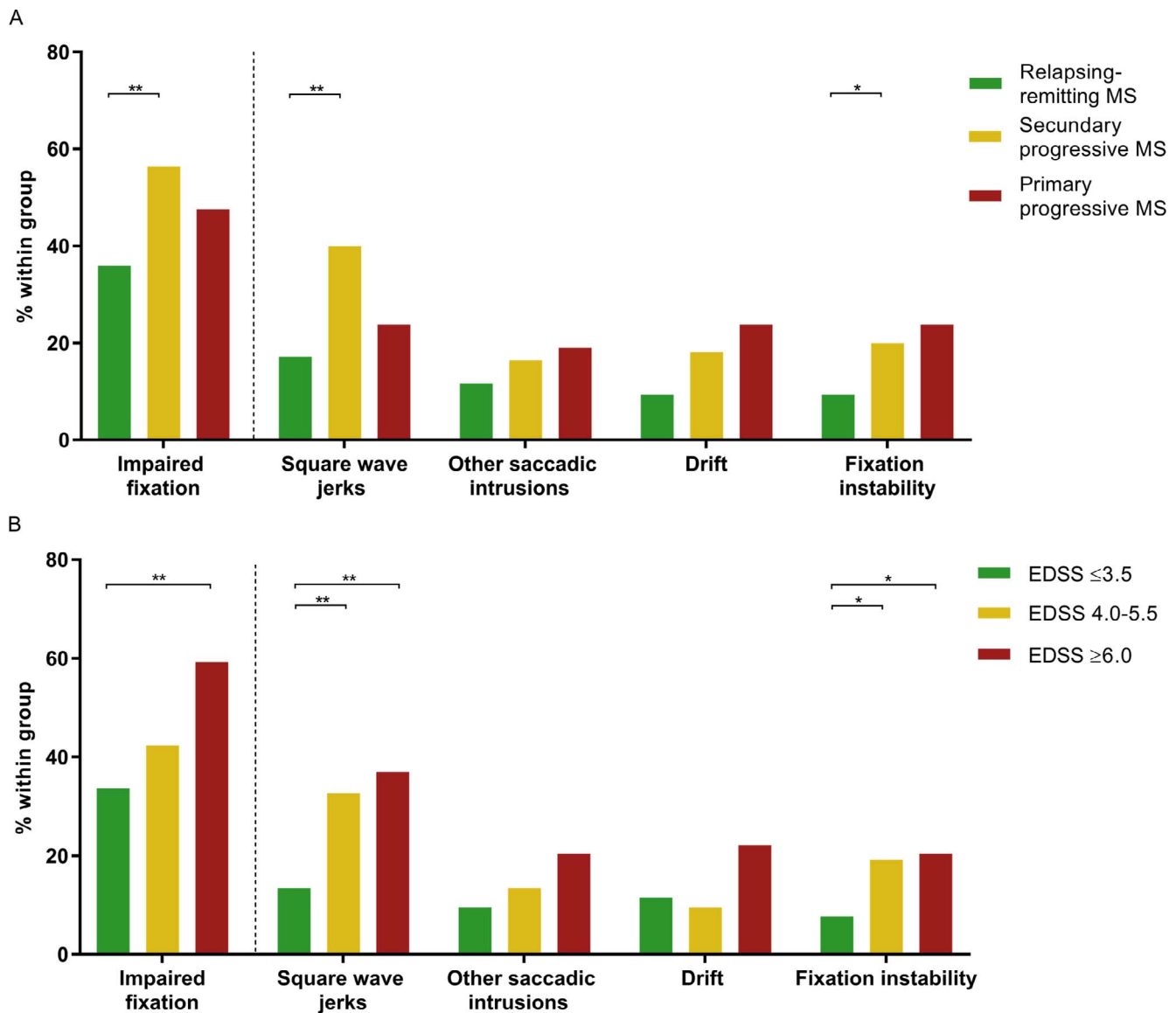
A

B

FIGURE 5.   Prevalence of fixation abnormalities in MS subgroups. Prevalence of fixation abnormalities and subgroups of fixation abnormalities in different groups of MS patients. **$P < 0.01$, *$P < 0.05$. (A) MS group divided by disease course, relapsing remitting MS ($n = 128$), secondary progressive MS ($n = 55$), and primary progressive MS ($n = 21$). (B) MS group divided by Expanded Disability Status Scale score, up to 3.5 ($n = 104$), from 4.0 to 5.5 ($n = 52$) and at least 6.0 ($n = 54$). EDSS, Expanded Disability Status Scale.

Expanded Disability Status Scale score and disease course. In general, the prevalence of fixation abnormalities, especially square wave jerk abnormalities, was significantly higher in subjects with a higher Expanded Disability Status Scale score and a progressive disease course. The frequency of square wave jerk abnormalities was 40% in the secondary progressive MS group and 37% in the group with an Expanded Disability Status Scale score of 6.0 and higher.

Relation With Visual Complaints and Functioning

Linear regression analyses showed a significant relationship between the presence of fixation abnormalities in primary position in the MS group and visual acuity (β, −2.8 [95% confidence interval {CI}, −4.8 to −0.7]; $P = 0.008$), indicating that, without adjustment, fixation abnormalities were associated with a lower visual acuity. This effect was considerably lower when adjusted for sex, disease duration, and Expanded

Disability Status Scale score (β, −1.9 [95% CI, −3.9 to −0.0]; $P = 0.045$). Of the different subcategories of fixation abnormalities, the presence of larger square wave jerks had the highest effect on visual acuity (β, −3.4 [95% CI, −5.8 to −1.0]; $P = 0.004$), and this effect was also reduced after adjustment (β, −1.8 [95% CI, −4.1 to 0.4]; $P = 0.109$). Data on visual acuity were missing in 18 subjects.

Likewise, the effect of the presence of (subcategories of) fixation abnormalities in the MS group on the presence of eye movement complaints was investigated with logistic regression analyses. After adjustment for sex, disease duration, Expanded Disability Status Scale score, and visual acuity, the presence of larger square wave jerks had a significant effect on the presence of complaints of focusing on stationary objects (OR, 2.2 [95% CI, 1.1-4.4]; $P = 0.035$). The one subject with pendular nystagmus reported constant complaints of oscillopsia, severe complaints of double vision and blurred vision, and
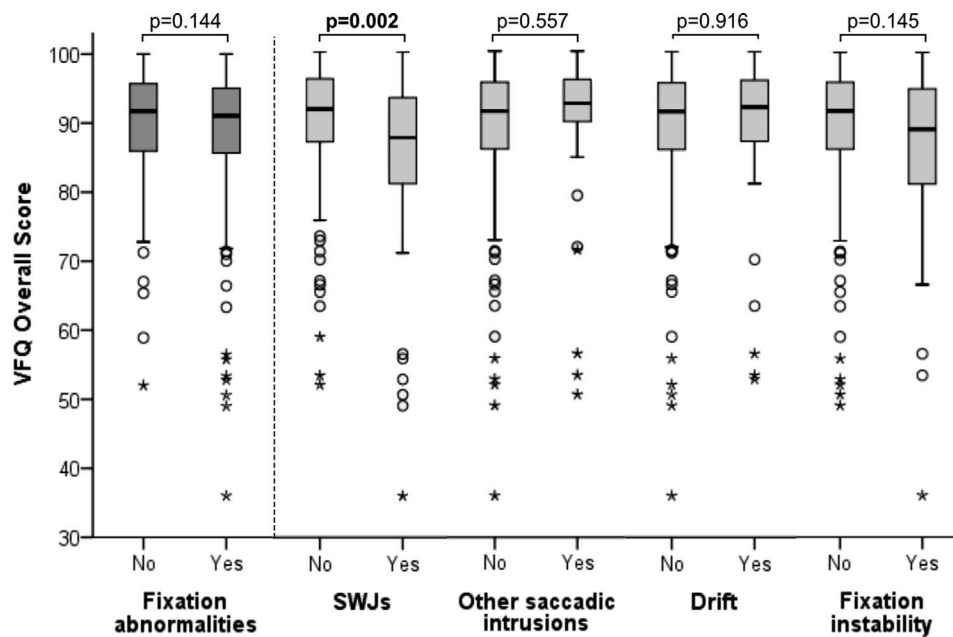
FIGURE 6. Visual Function Questionnaire overall score of MS patients with and without fixation abnormalities. Box-and-whisker plots showing the overall vision-related quality of life scores of MS patients with and without (subgroups of) fixation abnormalities. The boxes extend from the 25th to 75th percentiles, and the horizontal line in the box is plotted at the median.

moderate complaints with focusing and finding new lines while reading.

The overall vision-related quality of life scores of different subgroups of MS patients are shown in Figure 6. Subjects that suffered from fixation abnormalities reported a median overall vision-related quality of life of 91.0 (IQR, 10.4). This was not significantly different from subjects without fixation abnormalities (median, 91.7 [IQR, 10.0]; $P = 0.144$). However, the subgroup of subjects that showed square wave jerk abnormalities reported a significant lower overall vision-related quality of life (median, 87.7 [IQR, 13.4]) than subjects without square wave jerk abnormalities (median, 91.7 [IQR, 9.1]; $P = 0.002$). This difference was significant at different subdomain scores and most prominently in the subdomains near activities (median, 83.3 [IQR, 22.9] and 91.7 [IQR 16.7], respectively; $P = 0.001$) and role difficulties (median of 85.5 [IQR, 37.5] and 100.0 [IQR, 25.0], respectively; $P = 0.001$). The one subject with pendular nystagmus reported an overall vision-related quality of life of 44.1, and the lowest scored subdomains were general vision (20.0) and distance activities (16.7).

Logistic regression analyses revealed a significant effect of the presence of larger square wave jerks on the presence of a low overall vision-related quality of life score, with an OR of 2.89 (95% CI, 1.44–5.81; $P = 0.004$). This effect was maintained after adjustment for sex, disease duration, Expanded Disability Status Scale score, and visual acuity (Table 5). A similar pattern was found for the subdomains near activities and role difficulties (Table 5).

Fixation Eccentric Gaze

The descriptive values of the fixation parameters of the eccentric gaze directions of both the MS and healthy control group were similar to the values of the central fixation. In all eccentric gaze directions, the amplitude of square wave jerks was significantly higher in MS patients than in healthy controls. Upward directed drift was slightly more pronounced in eccentric positions in the MS group. Investigation of the subjects with a substantial drift (>0.75 degrees/s in one or

more directions) revealed a downbeat nystagmus in 4 subjects. This was apparent in the downward gaze position in all 4 subjects, and in 2 subjects the jerk waveform was visible in all gaze positions. Additionally, all 4 subjects showed a clear bilateral internuclear ophthalmoplegia. We did not find clear gaze-evoked nystagmus in any eccentric gaze position.

Comparable to central gaze and using the thresholds listed in Table 3, the presence of larger square wave jerks in eccentric gaze was related to disease duration, disease course, general disability, and vision-related quality of life. In addition to the relation with visual focusing on stationary objects, in subjects with larger square wave jerks in rightward and leftward gaze, more frequent complaints with focusing on moving objects were found, which were most prominent for rightward gaze (OR, 2.67 [95% CI 1.32–5.44]; $P = 0.007$). Additionally, the presence of larger square wave jerks in rightward, leftward, and downward gaze was related to complaints with reading a new line, most clearly in leftward gaze (OR, 2.65 [95% CI, 1.24–5.67]; $P = 0.012$).

DISCUSSION

This study provided a comprehensive overview of the characteristics of visual fixation in MS patients and a systematic approach for quantifying and classifying fixation abnormalities with infrared oculography. The most important and most common finding in MS was the presence of larger square wave jerks during fixation compared to healthy controls, which was related to visual functioning in daily life. Square wave jerk abnormalities were more common in more advanced MS, but the relation with vision-related quality of life appeared independent of general disability.

The prevalence of the well-described pendular nystagmus[9,32] was exceedingly rare in our group, namely, at 0.5%. This one subject showed that this type of nystagmus can be a very distressing oculomotor finding in MS, with continuous visual complaints that interfere with daily activities. Both gaze drift and fixation instability around the drift line abnormalities

TABLE 5. Logistic Regression of Large SWJs on Vision-Related Quality of Life

VFQ-25 Component	Logistic Regression	β	OR (95% CI)	P Value
Overall score	Crude	1.06	2.89 (1.44–5.81)	0.003
	Adjusted model 1	1.11	3.04 (1.48–6.27)	0.003
	Adjusted model 2	1.07	2.92 (1.41–6.08)	0.004
	Adjusted model 3	1.07	2.92 (1.40–6.11)	0.004
Near activities score	Crude	1.09	2.98 (1.49–5.99)	0.002
	Adjusted model 1	1.07	2.92 (1.43–5.99)	0.003
	Adjusted model 2	0.99	2.68 (1.29–5.56)	0.008
	Adjusted model 3	0.94	2.56 (1.23–5.32)	0.012
Role difficulties score	Crude	0.88	2.41 (1.19–4.87)	0.014
	Adjusted model 1	0.92	2.50 (1.20–5.21)	0.014
	Adjusted model 2	0.86	2.36 (1.12–4.95)	0.024
	Adjusted model 3	0.88	2.40 (1.14–5.08)	0.022

Crude, unadjusted model; Adjusted model 1, adjustment for sex and disease duration; Adjusted model 2, adjustment for sex, disease duration, and EDSSe score; Adjusted model 3, adjustment for sex, disease duration, EDSS score and visual acuity (best eye); VFQ-25, vision-related quality of life questionnaire; OR, odds ratio (lowest tertile compared to highest two tertiles); CI, confidence interval.

were not prevalent in our group, and the magnitude not significantly different. Furthermore, drift was not related to visual complaints or vision-related quality of life. This suggests that relevant fixation instability in MS patients is mainly caused by saccadic intrusions. However, in a few subjects drift was more pronounced and a small downbeat nystagmus was visible. The finding of bilateral internuclear ophthalmoplegia in all of these subjects suggests damage of neurons of the paramedian tract, which lies close to the medial longitudinal fasciculus. These neurons code vertical eye position signals and project into the cerebellar flocculus. It is hypothesized these neurons play an important role in the connection with the system that maintains gaze holding.[3,33,34]

Different studies have shown increased fixation instability in patients with vision loss, for example, in patients with amblyopia and macular degeneration. However, it is not yet established if instability of fixation could also contribute to vision loss or visual complaints. Furthermore, as MS patients experience both afferent and efferent visual dysfunction, it is not directly clear what mechanism could cause abnormal square wave jerks. The prevalence of optic neuritis in the group with and without square wave jerk abnormalities was similar. Likewise, no significant difference in amplitude of square wave jerks was found between MS patients with and without an optic neuritis history. Therefore, a contribution of efferent dysfunction in the occurrence of larger square wave jerks in MS patients is plausible. The tendency toward thinner retinal layers could indicate that more retrograde degeneration have occurred in the group with square wave jerk abnormalities. This is in line with the longer disease duration and higher Expanded Disability Status Scale score in this group. These findings could also play a role in the relations with visual acuity. The relationship between fixation abnormalities (especially larger square wave jerks) and visual acuity was diminished by adjustment for Expanded Disability Status Scale score. Probably both measures deteriorate with advancing disease and the relation is not (or at least not exclusively) causal. In contrast to this finding, the different relations with visual functioning appeared independent of disease disability and visual acuity. Taken together, we hypothesize that square wave jerk abnormalities in MS patients are at least partly caused by efferent dysfunction and can contribute to visual problems in daily life.

Square wave jerks are a common finding in healthy persons, and the frequency is increased by many factors such as increasing age and smoking.[3] Therefore their pathologic significance is still under debate. In our population, some healthy controls showed square wave jerks in a frequency of more than 1 Hz, which is slightly more frequent than previously reported.[3,35] We did not find a statistically significant difference in frequency of square wave jerks between healthy controls and MS patients. In contrast, the mean amplitude of square wave jerks was significantly larger in MS patients than in healthy controls. A threshold of 1.1 degrees in our study for defining abnormal large square wave jerks resulted in a high specificity combined with relevant clinical correlates in the MS group. Especially, the presence of larger square wave jerks was associated with more complaints with visual focusing and a lower vision-related quality of life. Possibly, small square wave jerks do not cause a (subjective feeling of) loss of fixation in daily activities but larger square wave jerks could.

The pathologic significance of square wave jerks is supported by studies that found more frequent or larger square wave jerks in a few neurologic diseases, such as Friedrich's ataxia and Parkinsonian disorders.[3,4,36–38] A comparison of frequencies and amplitude of square wave jerks with those in our study indicates that the square wave jerk abnormalities are more subtle in MS patients. Furthermore, large macrosaccadic oscillations and intrusions, such as those found in certain cerebellar diseases and Alzheimer's disease,[3,39,40] were not seen in our MS group. However, aggravation of fixation instability in other tasks or daily situations in MS patients cannot be ruled out.[41] A comparison of different types of saccadic intrusions in neurologic diseases and detailed characterization[38] might help to unravel the complex mechanisms that cause them.

Accurate quantification of eye movements, especially for the subtle abnormalities, as found in this study, is essential. It eliminates interobserver differences and can monitor changes over time. Infrared oculography is a noninvasive, precise, and easily incorporated technique for measuring eye movements in clinical practice. An advantage above scanning laser ophthalmoscopy is that various tasks could be measured in one session that gives a broad assessment of oculomotor functioning.[11,20] We believe that detecting (subclinical) fixation and saccadic abnormalities with infrared oculography can aid in differentiating misunderstood visual complaints in MS patients. This is even more important for disabled MS patients who will depend more on their visual abilities as they lose other abilities. This highlights the relevance of the increasing prevalence of square wave jerk abnormalities with increasing Expanded Disability Status Scale score. Finally, we found a clear relationship of square wave jerk abnormalities with problems with near

activities in daily life. This has functional consequences given the fact that nowadays near vision is an essential part of our daily life, with the increasing use of digital devices.

Taken together, the systematic infrared oculography-based approach in this study provided a quantitative definition of different subcategories of fixation abnormalities. Nearly 25% of the MS patients showed square wave jerks that were larger than those in healthy controls, and the presence of these larger square wave jerks was related to visual functioning in daily life.

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