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Strong age but weak sex effects in eye movement performance in the general adult population: Evidence from the Rhineland Study

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ABSTRACT

Assessing physiological changes that occur with healthy ageing is prerequisite for understanding pathophysiological age-related changes. Eye movements are studied as biomarkers for pathological changes because they are altered in patients with neurodegenerative disorders. However, there is a lack of data from large samples assessing age-related physiological changes and sex differences in oculomotor performance. Thus, we assessed and quantified cross-sectional relations of age and sex with oculomotor performance in the general population. We report results from the first 4,000 participants (aged 30–95 years) of the Rhineland Study, a community-based prospective cohort study in Bonn, Germany. Participants completed fixation, smooth pursuit, prosaccade and antisaccade tasks. We quantified associations of age and sex with oculomotor outcomes using multivariable linear regression models. Performance in 12 out of 18 oculomotor measures declined with increasing age. No differences between age groups were observed in five antisaccade outcomes (amplitude-adjusted and unadjusted peak velocity, amplitude gain, spatial error and percentage of corrected errors) and for blink rate during fixation. Small sex differences occurred in smooth pursuit velocity gain (men have higher gain) and blink rate during fixation (men blink less). We conclude that performance declines with age in two thirds of oculomotor outcomes but that there was no evidence of sex differences in eye movement performance except for two outcomes. Since the percentage of corrected antisaccade errors was not associated with age but is known to be affected by pathological cognitive decline, it represents a promising candidate preclinical biomarker of neurodegeneration.

1. Introduction

As life expectancies increase, the prevalence of age-related neurological disorders rises (Jaul & Barron, 2017). A thorough understanding of brain changes in healthy aging is a prerequisite to understanding pathophysiological changes underlying neurodegenerative disorders. One functional domain that is impaired in many neurodegenerative disorders is the control of eye movements (EMs) (Anderson & MacAskill, 2013). EMs are controlled by distributed brain system at the interface of perception, cognition and motor control. The neuroanatomy of EMs is well understood (Luna et al., 2008) and examinations are brief and well-tolerated by people of all ages (Noiret et al., 2017). Multiple cognitive processes are involved in EMs, including attention, working memory and learning (Hutton, 2008). Consequently, EMs provide a suitable model for investigating both pathological and normal cognitive changes that occur with age.

The most commonly used oculomotor tasks are the fixation, smooth pursuit eye movement (SPEM), prosaccade and antisaccade tasks. Fixations serve to maintain the alignment of a stationary target with the fovea (Lencer & Trillenberg, 2008). SPEMs are elicited in an attempt to keep the retinal image of a moving target on the fovea (Lencer & Trillenberg, 2008). A saccade is a rapid EM executed to bring an object of interest onto the fovea (Hallett, 1978); prosaccades are saccades towards a sudden-onset peripheral target, whereas antisaccades are

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saccades in the opposite direction (Hallett, 1978).

Good fixation performance reflects high spatial accuracy and low saccade frequency. In SPEM, closely pursuing the target means that eye and target velocity correspond (indicated by the velocity gain) and that saccade frequency is low. For prosaccades and antisaccades, fast saccade initiation (low latency), high peak velocities and high spatial accuracy are indicators of optimal performance. Spatial accuracy of saccades can be indicated by different measures, including amplitude gain and spatial error. Amplitude gain reflects the average landing position relative to the target with values below 100% indicating that the saccade amplitude was too low (saccade undershot the target) and values above 100% indicating that the saccade amplitude was too high (saccade overshot the target). A value of 100% indicates that the saccade perfectly landed on the target. Spatial error reflects the mean deviation from the target position. In the antisaccade task, the antisaccade error rate (percentage of trials where the first saccade is erroneously made towards the target) and the percentage of corrected antisaccade errors are additionally measured, with lower error rates and higher correction rates indicating better performance.

Neurodegenerative conditions are characterised by selective oculomotor deficits (Anderson & MacAskill, 2013). For example, individuals with Alzheimer's disease (Crawford et al., 2013; Garbutt et al., 2008), Parkinson's disease (Antoniades et al., 2015), Huntington's disease (Blekher et al., 2006) and mild cognitive impairment (Levy, Lavidor, & Vakil, 2018) make more antisaccade errors than age-matched controls. Moreover, individuals with Alzheimer's disease correct a substantially lower proportion of antisaccade errors compared to controls (Crawford et al., 2013; Garbutt et al., 2008; Noiret et al., 2018). Further, SPEMs have lower velocity gain in Alzheimer's disease (Garbutt et al., 2008) and Parkinson's disease (Pinkhardt et al., 2012).

Aging in the absence of neurodegenerative disease is also associated with changes in EM performance. Increased prosaccade and antisaccade latency with advancing age (e.g. Munoz et al., 1998; Noiret et al., 2017; Peltsch et al., 2011; Shafiq-Antonacci et al., 1999; Sweeney et al., 2001) and stable antisaccade peak velocity (e.g. Shafiq-Antonacci et al., 1999; Sweeney et al., 2001) are relatively consistent findings. However, as studies on aging effects have mostly used small sample sizes, have included participants of limited age range and have explored only a few EM parameters, aging effects on other EM outcomes are less clear. For example, antisaccade error rate was found to increase with age in most (e.g. Fernandez-Ruiz et al., 2018; Klein et al., 2000; Shafiq-Antonacci et al., 1999; Sweeney et al., 2001) but not all studies (e.g. Noiret et al., 2017) and peak prosaccade velocity was found to either decline with age (e.g. Sweeney et al., 2001) or to remain stable (e.g. Shafiq-Antonacci et al., 1999).

Biological sex is a key cause of variation between humans (Brooks & Clayton, 2017) and a candidate to affect EMs because sex differences are known to exist in brain metabolism in bilateral visual cortex and cerebellum (Gur et al., 1995; Hu et al., 2013), two regions critically involved in EM control. Sex differences in EMs are, however, almost entirely unexplored. One recent study of 1,058 participants reported sex differences in half of the assessed EM outcomes, with men outperforming women in most of them (Bargary et al., 2017). However, that sample was young (mean age = 22 years, range = 16–40 years) and consisted mostly of university students, limiting the capacity for wide-ranging conclusions about sex differences in the general population and across the adult lifespan. This is critical, given evidence of interactions between age and sex in brain metabolism (Kakimoto et al., 2016).

There is thus a strong need to thoroughly characterise the effects of age, sex and their possible interactions on EMs. In this study, we report a comprehensive assessment of age and sex effects on EM performance across the adult life span using data from fixation, SPEM, prosaccade and antisaccade tasks in the Rhineland Study. This study provides the largest and most representative sample for the investigation of the associations of age and sex with EM performance to date.

2. Materials and methods

2.1. Participants

Data analysis is based on the first 4,000 participants of the Rhineland Study (age range = 30–95 years), who underwent baseline assessments between March 2016 and July 2019. The study sample comprised all participants with data in at least one of the four tasks (N = 3,682). The Rhineland Study is an on-going community-based cohort study in Bonn, Germany. Study inclusion criteria are living in one of the two geographically defined areas in Bonn, being 30 years or older and having sufficient command of the German language to provide written informed consent. The study procedures were approved by the ethics committee of the Medical Faculty of the University of Bonn and carried out in accordance with the recommendations of the International Council for Harmonisation Good Clinical Practice standards (ICH-GCP).

2.2. Eye movement recording

Testing took place in a quiet, darkened room in one of two identical recruitment centres. Participants sat in a height-adjustable chair in front of a 22-inch monitor (1680x1050 pixels) whilst resting their chin on a chinrest and their arms on the desk in front of them. Viewing distance between eyes and monitor was 70 cm. EMs were recorded using video-based infrared oculography (EyeLink 1000 and EyeLink 1000 Plus; SR Research Ltd.) at 1,000 Hz.

2.3. Procedure and oculomotor tasks

EM tasks were programmed using ExperimentBuilder (SR Research Ltd.). The target was a white (RGB 255,255,255) circle 0.35° in diameter presented on black (0,0,0) background. After a horizontal-vertical five-point calibration, participants performed fixation, SPEM, prosaccade and antisaccade tasks in fixed order. There was no break between the fixation, SPEM and prosaccade tasks, and participants were instructed to follow the target with their eyes as closely as possible whilst keeping their head still. The antisaccade task was first explained and then practiced with six trials.

In the fixation task, participants had to fixate the target at the centre ($x = 0°$, $y = 0°$), the left ($x = –9.63°$, $y = 0°$), the right ($x = 9.63°$, $y = 0°$), the top ($x = 0°$, $y = 9.63°$) and the bottom ($x = 0°$, $y = –9.63°$). The order within which the target was presented in these positions was randomised across participants but eccentric locations were always followed by the central location. The central position thus had to be fixated four times in total. The target appeared at each eccentric location for 10 s and at the central location for 5 s each time.

In the smooth pursuit task, the target moved between ±9.63° in a sinusoidal waveform in the horizontal plane ($y = 0°$) at a frequency of 0.5 Hz. The target began in the centre, moved left and then completed ten full cycles with a total duration of 21 s.

The prosaccade task was a horizontal 'step' task, comprising 30 trials. In each trial the target appeared first in the centre ($x = 0°$, $y = 0°$) for a random duration of 1–2 s (average 1.5 s). Then it stepped to a peripheral position ($x=±9.63°$, $y = 0°$), where it remained for 1 s before returning to the centre for the next trial. An equal number of steps to the left and right were presented in a random order for each participant.

The antisaccade task began with six practice trials followed by 30 trials. The trial procedure was the same as in the prosaccade task. The only difference was the instruction, as participants were instructed to look at the target whilst in the centre but to immediately look to the mirror image position of the target when it stepped to the periphery.

2.4. Outcome variables

Fixations were defined as periods of at least 100 ms duration without blinks or saccades. We calculated the spatial error of gaze position

during fixation (root mean square error, RMSE, in degree of visual angle), as well as saccade frequency (saccades/second) and blink rate (blinks/second).

All eye movements with velocity $< 30°/s$ and duration ≥ 50 ms were classified as SPEM. SPEM outcomes were mean velocity gain and saccade frequency (saccades/second). SPEM velocity gain was calculated by dividing eye velocity by target velocity and multiplying by 100. A value of 100 indicates perfect eye-target velocity match, whilst values below or above 100 indicate that eye movements are slower or faster than the target, respectively.

In the saccade tasks, saccades were automatically detected on the basis of a minimum velocity criterion (velocity $\geq 60°/s$) or on the basis of minimum velocity and minimum acceleration criteria (velocity $\geq 22°/s$ and acceleration $\geq 3800°/s^2$). Trials were considered valid when there was a fixation on the central fixation point that started at least 100 ms before peripheral target onset and that was no more than 3° off the central fixation point. No saccade or blink was allowed to occur during this interval. Additionally, saccades had to end before the peripheral target timed out for a trial to be considered valid. Saccades with amplitude $< 1°$ or latency < 80 ms were excluded.

For both saccade tasks, we calculated mean latencies, mean peak saccadic velocities, mean amplitude gain and mean spatial error for directionally correct saccades on valid trials. A directionally correct prosaccade was counted when the initial saccade was in the direction of the peripheral target. A correct antisaccade was counted when the initial saccade was performed in the opposite direction of the peripheral target. The saccade latency was defined as the time (in ms) from target appearance to saccade initiation. For the calculation of the mean peak saccadic velocities, the average of the peak saccade velocities from all trials was calculated. The mean amplitude gain was calculated by dividing eye position by target position and multiplying this value by 100. A value of 100 indicates a saccade with perfect spatial accuracy, whilst values below or above 100 indicate that saccades undershot or overshot the target position, respectively. To calculate mean spatial error, target step amplitude was first subtracted from the saccade amplitude of the initial saccade, with the difference then divided by the target step amplitude. Following this, the value was multiplied by 100 and the absolute value was taken. This measure indicates the deviation of landing position from (mirrored) target position. The units are percentages to indicate relative deviation from the target step amplitude.

Due to the main sequence relationship of saccades (i.e. the strong correlation between saccade amplitude and peak velocity) (Bahill et al., 1975; Dodge & Cline, 1901), we also calculated amplitude-adjusted peak velocities, dividing peak velocity by amplitude gain. For the antisaccade task, we additionally calculated the antisaccade error rate, antisaccade costs (antisaccade latency minus prosaccade latency) and the percentage of corrected antisaccade errors.

2.5. Missing and invalid data

Across tasks, 318 out of 4,000 participants had no EM data. Missing data were primarily due to technical issues during data acquisition or post-processing of the data (75.4%), with a lesser number of missing cases due to contraindications (8.5%), exclusion after visual inspection of data (8.2%), non-compliance (5.7%), or refusal (0.6%). A few cases (1.3%) had no data due to at least two of the aforementioned reasons, which results from independent evaluations of data quality for the different EM tasks.

At task level, we excluded participants from the entire prosaccade or antisaccade task if they had < 7 valid trials in the task (number of participants excluded from the antisaccade task: 91; prosaccade task: 18). Participants with > 4 antisaccade errors were required to have performed at least one corrective saccade to ensure that participants understood the task instructions (number of participants excluded: 1).

All saccade outcomes except antisaccade error rate and percentage of corrected antisaccade errors were calculated only if a participant had ≥ 7 trials that were correct and therefore could be included in the calculation. For the percentage of corrected antisaccade errors the criterion was set to ≥ 5 direction errors.

For blink rate during fixation we excluded participants who had a value that was more than three times the interquartile range above the third quartile of their age group (30–39, 40–49, 50–59, 60–69, 70–79, 80+) because such values could reflect signal loss that was falsely classified as blink.

2.6. Statistical analysis

Skewed EM outcomes (prosaccade and antisaccade latency and spatial error, as well as mean spatial error, saccade frequency and blink rate during fixation) were log transformed.

We generated one scatterplot for each EM outcome for a first visual inspection of the association of age with EM performance and possible interaction effects between age and sex (Supplement A).

We quantified change in EM performance per one-year increase in age and differences in EM performance between men and women by using a separate multivariable regression model for each EM outcome (except for the EM outcome correction rate of antisaccade errors, see explanation below). All initial models included age and sex as independent variables with further adjustment for best-corrected visual acuity and educational level. Next, we included an additional term of age^2 in each model to evaluate potential nonlinear relationships between age and EM performance. Age and age^2 were mean-centred to prevent collinearity (Iacobucci et al., 2016). Missing covariate data were imputed using predictive mean matching (Hmisc package, 10 bootstrap replicates). For a detailed description of the model assumptions of the multivariable regression models see Supplement B.

To compare the strength of age and sex effects on EM outcomes, we calculated Cohen's f^2, which measures the proportion of variance in the outcome that is uniquely accounted for by either age or sex (Cohen, 1988). We presented the effect sizes visually in a forest plot. As a rule of thumb, $f^2 = 0.02$ indicates a small effect, $f^2 = 0.15$ indicates a medium effect and $f^2 = 0.35$ indicates a strong effect (Cohen, 1988, pp. 410–414). Further information on the calculation of f^2 is in Supplement B. The effect sizes did not only allow us to make a ranking of the strength of association but also allowed us to evaluate whether those aging effects that were significant in the regression model were of relevant effect size. We wanted to rule out the possibility that associations just became significant due to high statistical power resulting from our large sample size. Thus, we considered the results of the regression models and the effect sizes together in the interpretation of the results.

To evaluate whether relations between age and EMs differed between men and women, we constructed an additional model for each outcome, which included age*sex and age^2*sex terms in addition to age, age^2, sex, best-corrected visual acuity and education. For each EM outcome we carried out a likelihood-ratio test that compared the interaction model to the model without interaction terms.

Since the percentage of corrected antisaccade errors was severely skewed (most participants corrected 100% of their errors), we fitted a one-inflated beta regression model instead of a multivariable linear regression model (gamlss package). The one-inflated beta regression model is a mixture model consisting of two parts. The first part models whether or not somebody corrected all direction errors by using a logistic regression model and the second part is a beta regression model that models the data of those participants who did not correct all direction errors. Since this model requires that all values range from 0 to 1, we first transformed the variable by dividing it by 100.

Additionally, we calculated for each age group the standard deviation as a measure of interindividual variability in performance and inspected whether the variability within each group increased from the youngest to the oldest age groups.

We further examined whether the stability of performance during a test differed across age. We assessed this intraindividual variability in

performance by calculating for each participant for latency, amplitude gain, spatial error and peak velocity in both saccade tasks as well as for SPEM velocity gain the standard deviation in performance across all valid trials (saccade tasks) or segments of pursuit (SPEM). We calculated for each outcome a multivariable regression model that included age and sex as predictors and best-corrected visual acuity and education as potential confounders. All outcomes except for intraindividual variability in smooth pursuit velocity gain were log-transformed due to a high skewness of the regression residuals. In a second step we added age^2 to the model to evaluate nonlinear associations.

Statistical analyses were carried out in R using an alpha level of 0.05. Point estimates of association are presented with 95% confidence intervals.

3. Results

3.1. Study sample

Table 1 gives descriptive characteristics of the study sample. The sample had a high level of education and high best-corrected visual acuity.

3.2. Age effects

The associations between age and EM performance are displayed in Table 2. The strength of association of each EM outcome with age is presented visually in Fig. 1 (forest plot). Taking the results of the regression models and the effect sizes together, we concluded that there were age-related performance declines in log of spatial error (RMSE) ($f^2 = 0.05$) and log of saccade frequency ($f^2 = 0.07$) during fixation, SPEM velocity gain ($f^2 = 0.21$), saccade frequency during SPEM ($f^2 = 0.04$), log of prosaccade ($f^2 = 0.28$) and antisaccade latency ($f^2 = 0.21$), prosaccade amplitude gain ($f^2 = 0.04$), log of prosaccade spatial error ($f^2 = 0.06$), amplitude-adjusted and unadjusted peak prosaccade velocity (both $f^2 = 0.02$), antisaccade error rate ($f^2 = 0.09$) and antisaccade costs ($f^2 = 0.04$). Nonlinear effects of age, indicating more rapid performance decline with advancing age, were statistically significant in all of these outcomes. Since f^2 represents the combined effect size of both linear and nonlinear associations of age with EM performance, aging effects were numerically strongest in saccade latencies and SPEM velocity gain. In contrast, amplitude-adjusted peak antisaccade velocity did not show any significant decline with advancing age ($p = 0.859$). In addition, antisaccade peak velocity, antisaccade amplitude gain, antisaccade spatial error and log of blink rate during fixations all had very low linear and nonlinear associations with age ($f^2 \leq 0.01$) and are, therefore, also considered to be relatively stable across age. Associations between best-corrected visual acuity and EM outcomes were – if present – of negligible size ($f^2 \leq 0.004$) and did therefore not account for differences in EM performance.

Table 1
Descriptive Characteristics of the Total Sample and Stratified by Sex.

	Total sample	Women	Men
Number of participants, N (%)	3682 (100)	2107 (57.2)	1575 (42.8)
30–39 years	647 (17.6)	345 (16.4)	302 (19.2)
40–49 years	721 (19.6)	433 (20.6)	288 (18.3)
50–59 years	976 (26.5)	580 (27.5)	396 (25.1)
60–69 years	712 (19.3)	415 (19.7)	297 (18.9)
70–79 years	481 (13.1)	259 (12.3)	222 (14.1)
80+ years	145 (3.9)	75 (3.5)	70 (4.4)
Age, M (SD) in years	54.7 (14.1)	54.6 (13.7)	54.8 (14.5)
Education level, N (%)	3646 (99.0)	2083 (98.9)	1563 (99.2)
High	1915 (52.5)	988 (47.4)	927 (59.3)
Middle	1659 (45.5)	1040 (49.9)	619 (39.6)
Low	72 (2.0)	55 (2.6)	17 (1.1)
Best-corrected visual acuity, N (%)	3661 (99.4)	2099 (99.6)	1562 (99.2)
High (≥0.8)	3168 (86.5)	1801 (85.8)	1367 (87.5)
Middle (0.32–0.63)	465 (12.7)	284 (13.5)	181 (11.6)
Low (<0.32)	28 (0.8)	14 (0.7)	14 (0.9)

Note. N = number of participants, M = mean, SD = standard deviation. Education level was determined using the International Standard Classification of Education 2011 (ISCED) and was coded as low (lower secondary education or below), middle (upper secondary education to undergraduate university level) and high (postgraduate university study). Assessment of best-corrected visual acuity was based on visual scores from the right eye and was measured using an automated refractometer (Ark-1 s, NIDEK CO., Tokyo, Japan). Categorization of the visual acuity values was based on the guidelines of the International Council of Ophthalmology.

Table 3 depicts the results for the association between age, sex and percentage of corrected antisaccade errors. Age influenced whether or not all antisaccade errors were corrected but had no influence on the percentage of corrected antisaccade errors in those participants who corrected less than 100% of their errors. When age^2 was added to the model, it showed the same pattern of results as the linear age term.

The descriptive results of EM performance for each age group showed that interindividual differences in performance within each age band increased with age, particularly in saccade frequency during fixation, SPEM velocity gain, saccade latencies, antisaccade error rate and costs, but remained rather stable in all other outcomes (Supplement C).

Intraindividual variability in EM performance increased with age in all modelled outcomes except prosaccade and antisaccade peak velocity (Supplement D). The age effect was statistically significant for prosaccade peak velocity but Cohen's f^2 indicates that the effect is negligible ($f^2 < 0.01$). Age-related changes were strongest for prosaccade and antisaccade latency (prosaccades: $f^2 = 0.14$, antisaccades: $f^2 = 0.10$) and small for all other modelled outcomes ($0.01 \leq f^2 \leq 0.04$).

3.3. Sex differences

Sex was significantly associated with eight EM outcomes (Table 2). However, Cohen's f^2 indicated that these sex differences were small in SPEM velocity gain (higher gain in men) and blink rate during fixation (fewer blinks in men) (both $f^2 = 0.03$), with all other sex differences being negligible in size ($f^2 \leq 0.01$) (Fig. 2).

3.4. Interaction effects between age and sex

Testing for interactions between age and sex and between age^2 and sex yielded interactions for SPEM velocity gain, log of prosaccade latency, peak prosaccade velocity, amplitude-adjusted peak velocity in both saccade tasks, and antisaccade error rate (Supplement E). Inspection of the scatterplots (Supplement A) revealed that women had higher peak prosaccade velocity, amplitude-adjusted peak prosaccade and antisaccade velocity than men until approximately the age of 65 years, after which the direction of the effect reversed. Sex differences in log of prosaccade latency, antisaccade error rate and SPEM velocity gain increased across the measured age range (Supplement A).

4. Discussion

With nearly 4,000 participants and men and women almost equally represented from age group 30 to age group 80+, this is the largest and most representative study of associations of age and sex with EM performance to date. Our findings clarify the heterogeneous results from previous studies with smaller sample sizes, enable a ranking of age effects on EM performance and thereby contribute to a better understanding of EM changes that occur with age and in neurodegenerative disorders.

4.1. Age effects

We observed age-related decline in EM performance in 12 of 18 outcomes, with the largest declines in saccade latencies and SPEM velocity gain. However, EM performance was relatively stable across age

Table 2
Associations between Age, Sex and Eye Movement Outcomes.

Fixation Task			
Outcome	**Predictor**	**b (95%-CI)**	**p-value**
Log of spatial error (RMSE) [log °]; N = 3662	Age	0.02 (0.02, 0.02)	**< 0.001**
	Sex	0.00 (−0.01, 0.01)	0.518
Log of saccade frequency [log(N/s)]; N = 3662	Age	0.04 (0.04, 0.04)	**< 0.001**
	Sex	0.02 (0.01, 0.03)	**0.002**
Log of blink rate [log(N/s)]; N = 3613	Age	0.00 (0.00, 0.00)	**< 0.001**
	Sex	−0.02 (−0.02, −0.02)	**< 0.001**
Prosaccade Task (N = 3651)			
Outcome	**Predictor**	**b (95%−CI)**	**p-value**
Log of latency [log ms]	Age	0.02 (0.02, 0.02)	**< 0.001**
	Sex	0.01 (0.00, 0.01)	**0.001**
Amplitude gain [%]	Age	−1.00 (−1.10, −0.80)	**< 0.001**
	Sex	−0.44 (−0.89, 0.02)	0.057
Log of spatial error (RMSE) [log %]	Age	0.04 (0.03, 0.04)	**< 0.001**
	Sex	0.03 (0.02, 0.04)	**< 0.001**
Peak Velocity [°/s]	Age	−5.00 (−6.44, −3.56)	**< 0.001**
	Sex	−3.08 (−6.93, 0.77)	0.117
Amplitude-adjusted peak velocity	Age	−0.01 (−0.03, 0.00)	**0.047**
	Sex	−0.01 (−0.05, 0.03)	0.610

Smooth Pursuit Task (N = 3665)			
Outcome	**Predictor**	**b (95%-CI)**	**p-value**
Velocity gain [%]	Age	−4.90 (−5.20, −4.50)	**< 0.001**
	Sex	4.69 (3.72, 5.67)	**< 0.001**
Saccade frequency [N/s]	Age	0.10 (0.10, 0.10)	**< 0.001**
	Sex	−0.10 (−0.14, −0.07)	**< 0.001**
Antisaccade Task			
Outcome	**Predictor**	**b (95%-CI)**	**p-value**
Log of latency [log ms]; N = 3184	Age	0.02 (0.02, 0.02)	**< 0.001**
	Sex	−0.00 (−0.01, 0.00)	0.126
Amplitude gain [%]; N = 3184	Age	−0.35 (−1.10, 0.41)	0.368
	Sex	−0.88 (−2.84, 1.08)	0.380
Log of spatial error (RMSE) [log %]; N = 3184	Age	0.01 (0.01, 0.02)	**< 0.001**
	Sex	0.01 (0.00, 0.03)	0.116
Peak Velocity [°/s]; N = 3184	Age	−2.06 (−3.90, −0.22)	**0.028**
	Sex	−3.26 (−8.03, 1.51)	0.180
Amplitude-adjusted peak velocity; N = 3184	Age	0.00 (−0.02, 0.02)	0.859
	Sex	−0.01 (−0.06, 0.05)	0.841
Error rate [%]; N = 3555	Age	5.02 (4.45, 5.58)	**< 0.001**
	Sex	−3.85 (−5.38, −2.34)	**< 0.001**
Costs [ms]; N = 3172	Age	5.83 (4.67, 7.00)	**< 0.001**
	Sex	−4.39 (−7.41, −1.37)	**0.004**

Note. The table displays the change per 10-years of age and the mean sex difference in performance for different eye movement outcomes. N = number, b = unstandardized regression coefficient, 95%-CI = 95%-confidence interval. Unstandardized regression coefficients were obtained from the following multivariable linear regression model: EM outcome ~ b_0 + age*b_1 + sex*b_2 + educational level + best-corrected visual acuity + residual error. Unstandardized regression coefficients for age indicate the change in outcome variable per 10-years of age. Each unstandardized regression coefficient for sex expresses the difference in eye movement outcome between men and women with women as reference group.

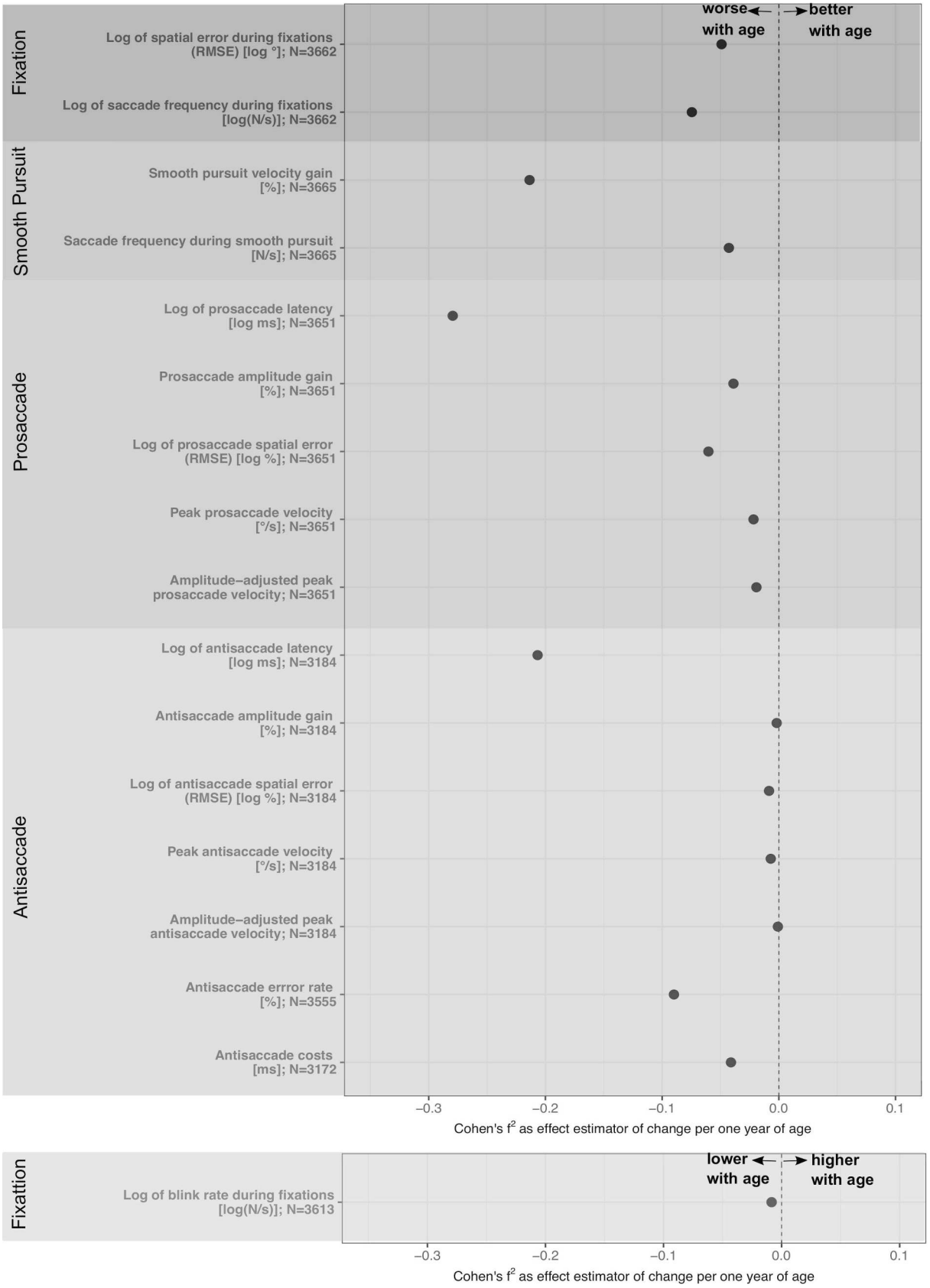

Fig. 1. Effect Sizes (Cohen's f^2) for Change in Eye Movement Performance per Year of Age. Cohen's f^2 indicates the effect size of change per one year of age for different eye movement outcomes (see y-axis). Some outcomes have been reversed so that all outcomes that show a decrease in performance across the lifespan have the effect size depicted on the left side of the vertical line and all outcomes that cross the vertical line indicate lifetime stability. For blink rate during fixation, performance cannot be classified as good or bad and therefore the trend (higher or lower with age) is indicated.

Table 3
Associations between Age, Sex and Percentage of Corrected Antisaccade Errors.

	Coefficient	Beta regression model - Exp. Coef. (95%- CI)	p-value	Logistic regression model - Exp. Coef. (95%-CI)	p-value
Percentage of corrected antisaccade errors; N = 2369	Intercept	3.32 (2.64, 4.18)	**< 0.001**	2.51 (1.76, 3.62)	**< 0.001**
	Age	1.00 (0.99, 1.00)	0.108	0.97 (0.96, 0.97)	**< 0.001**
	Sex	1.02 (0.88, 1.19)	0.768	1.40 (1.13, 1.72)	**0.002**

Note. For the EM outcome "percentage of corrected antisaccade errors" we calculated a one-inflated beta regression model, which is a mixture model consisting of a logistic regression and a beta regression model. The table displays the exponentiated coefficients (Exp. Coef) and their 95%-confidence intervals. The logistic regression part models whether or not somebody corrects all mistakes is associated with age and sex. The beta regression part models the associations between age, sex and the proportion of corrected errors in those participants who did not correct all of their errors. The exponentiated coefficients represent odds ratios.

in blink rate during fixation and in five antisaccade outcomes, namely amplitude-adjusted and unadjusted peak velocity, as well as amplitude gain, spatial error and percentage of corrected antisaccade errors (in those who corrected not all of their errors). In all outcomes that declined with age, we observed an accelerated decline with advancing age as indicated by significant age^2 terms. Generally, interindividual variability in performance increased with age, particularly in saccade frequency during fixation, SPEM velocity gain, saccade latencies, antisaccade error rate and costs across age groups, suggesting that age reinforces existing interindividual differences and that some individuals age more successfully than others. Intraindividual variability in performance also increased with age, except for antisaccade and prosaccade peak velocity, which indicates less stable task performance with increasing age for most EM outcomes.

The age-related increases in RMSE ($f^2 = 0.05$) and saccade frequency ($f^2 = 0.07$) during fixation demonstrated decreased fixational stability with advancing age. Fixations and saccades are interdependent because higher activations in fixation neurons go along with lower activations in saccade neurons. Fixation and saccade neurons are found in the superior colliculus (Munoz & Fecteau, 2002) and frontal eye fields (Hanes et al., 1998). Therefore, these results suggest age-related changes in activity patterns in saccade and fixation neurons.

In the smooth pursuit task, we observed lower velocity gain ($f^2 = 0.21$) and higher saccade frequency ($f^2 = 0.04$) with advancing age. Reduced velocity gain is typically associated with increased saccade frequency, as many saccades are used to compensate for slow SPEMs (Lencer & Trillenberg, 2008). Whilst numerous cortical and subcortical areas are involved in SPEMs (Krauzlis, 2004; Lencer & Trillenberg, 2008), the medial superior temporal area (Krauzlis, 2004) and the frontal pursuit area in the frontal eye fields (Tanaka & Lisberger, 2001) have been associated with on-line gain control in terms of direction and speed of SPEMs. Thus, the moderate decrease in velocity gain with advancing age suggests age-related changes that affect these areas. However, it is also plausible that age has small effects on many involved brain areas, which lead in sum to age-related decreases in SPEM velocity gain.

Aging had the strongest effects on saccade latencies (prosaccades: $f^2 = 0.28$; antisaccades: $f^2 = 0.21$), which supports the findings of previous studies (Munoz et al., 1998; Noiret et al., 2017; Peltsch et al., 2011; Shafiq-Antonacci et al., 1999; Sweeney et al., 2001) and extends this to the general adult population. Saccade latency depends on processes such as attention, target expectation, speed of target detection, response-related decision-making and response execution (Hutton, 2008). Thus, increases in saccade latencies indicate age-related slowing in saccade execution but it remains unclear which of the aforementioned components cause age-related decline.

Antisaccade costs also increased with age ($f^2 = 0.04$), suggesting that antisaccade latencies showed a disproportionally higher increase than prosaccade latencies. The cognitive processes required for saccade execution are more complex for antisaccades than prosaccades (Munoz & Everling, 2004); therefore, age may affect execution speed of complex cognitive processes. According to parallel programming models, a reflex-like prosaccade and a voluntary antisaccade are programmed in parallel; a successful antisaccade is executed if it reaches the activation threshold earlier than the prosaccade (Massen, 2004). Thus, the higher increase in antisaccade latencies corresponds to the finding of higher antisaccade error rate ($f^2 = 0.09$) with age, given that prolonged antisaccade programming is expected to increase the likelihood of antisaccade errors (Massen, 2004).

Performance in prosaccade amplitude gain ($f^2 = 0.04$) and spatial error ($f^2 = 0.06$) decreased with age, whereas antisaccade amplitude gain and spatial error remained relatively stable. Spatial accuracy of prosaccades is mainly influenced by cerebellar integrity (Optican, 2005), whereas programming of antisaccade amplitudes relies heavily on non-standard sensorimotor transformations in posterior parietal cortex (Herweg et al., 2014) and frontal eye fields (Moon et al., 2007). Since cerebellar brain volume declines with age but the (inferior) parietal lobe appears to be spared (Raz et al., 2001), prosaccade but not antisaccade spatial accuracy may be expected to decline with age. Additionally, previous research shows that Parkinson's disease patients differ from controls in prosaccade but not antisaccade gain (Mosimann et al., 2005), making hypometric prosaccades (Mosimann et al., 2005). This pattern of EMs supports the need to further investigate cerebellar involvement in Parkinson's disease (Wu & Hallett, 2013) and stresses the importance of understanding age-related brain changes as a prerequisite for understanding pathological brain changes. However, it should be noted that measures of saccade performance are highly sensitive to task design. Specifically, the amplitude of the target step was fixed on either side in the saccade tasks, which might have reduced the difficulty to perform spatially accurate saccades. This issue is particularly pertinent for the antisaccade task, where multiple target eccentricities place greater demands on sensorimotor transformations (Herweg et al., 2014). Therefore, it remains unclear whether the antisaccade task would have been more sensitive in detecting (age-related) differences in spatial accuracy if the target eccentricity had been varied.

Amplitude-adjusted peak velocity was relatively stable across the investigated age range for antisaccades, but showed a small decline for prosaccades ($f^2 = 0.02$), corresponding to previous research (Sweeney et al., 2001). Intraindividual variability in peak velocity was constant across the investigated age range in both tasks. In terms of neurophysiology, peak saccadic velocities are determined by the duration, number of spikes generated and maximal firing rate of saccadic burst cells in the brainstem reticular formation (Sparks, 2002). Since humans perform about 200,000 saccades each day, these cells can be considered to be continuously trained (Pratt et al., 2006). Amplitude-adjusted peak velocity was significantly lower for antisaccades compared to prosaccades. This means that maximal firing rates of burst cells and firing durations are lower for antisaccades than prosaccades and might explain why age-related differences occurred only for prosaccades. Further, this finding indicates that maximal firing rates of burst cells decline at some point despite constant training.

4.2. Sex differences

Sex differences were mostly absent or negligible. We found small sex differences in blink rate during fixation (men blinked less, $f^2 = 0.03$) and SPEM velocity gain (men had higher gain, $f^2 = 0.03$). SPEM velocity gain

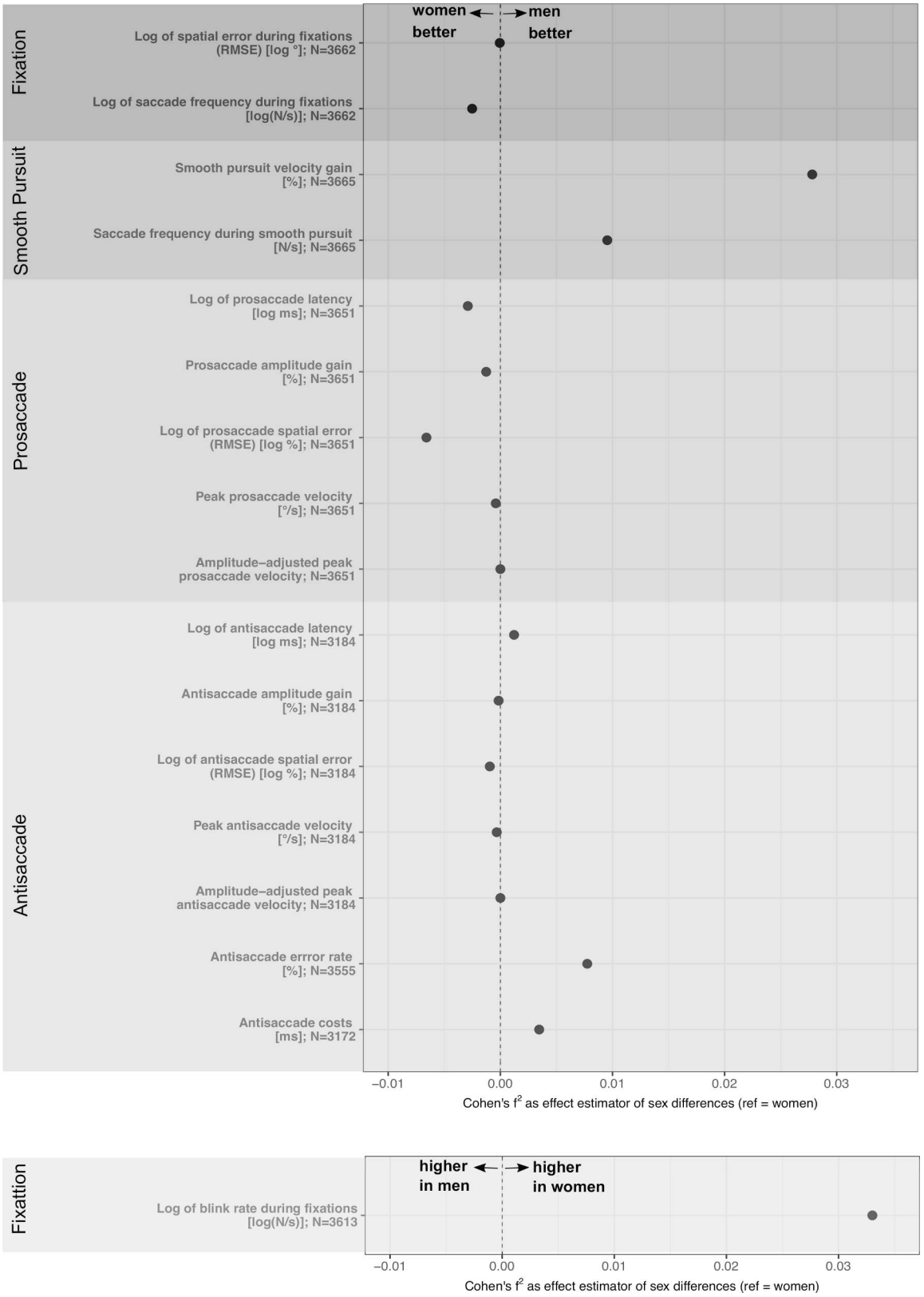

Fig. 2. Effect Sizes (Cohen's f^2) for Sex Differences in Eye Movement Performance. Cohen's f^2 indicates the effect size of change for sex for different eye movement outcomes (see y-axis). Reference group for sex: women. Cohen's f^2 for sex expresses the effect size of the difference in eye movement outcome between men and women. Outcomes in which women performed better where multiplied by −1 so that all points that lie on the left side of the vertical line indicate that women outperformed men in this outcome and vice versa. For blink rate during fixation, performance cannot be classified as good or bad and therefore the trend (higher or lower in men) is indicated.

is associated especially with activity in the medial superior temporal area (Krauzlis, 2004) and the frontal pursuit area in the frontal eye field (Tanaka & Lisberger, 2001). Thus, small sex differences in these areas might account for our finding. The finding of higher SPEM velocity gain in men is also in line with the results reported in Bargary et al. (2017). However, we could not confirm their finding of considerable sex differences in antisaccade error rate even if the trend was the same (higher error rates in women) (Bargary et al., 2017). The spontaneous blink rate is a marker of striatal dopamine (the more dopamine, the higher the blink rate) (Taylor et al., 1999) and is, for example, reduced in Parkinson's disease (Deuschl & Goddemeier, 1998). Our finding of lower blink rate in men is, therefore, compatible with evidence that women have higher striatal dopamine levels (Mozley et al., 2001).

4.3. Interaction effects between age and sex

Aging affected EM performance differently in men and women for six EM outcomes. Inspection of scatterplots revealed that performance declined more strongly in women than men in amplitude-adjusted and unadjusted prosaccade velocity and antisaccade error rate. The reverse pattern was observed for prosaccade latency. Additionally, performance declines earlier in women than men in SPEM velocity gain and amplitude-adjusted antisaccade velocity. These findings correspond to the presence of interactions between age and sex in brain metabolism (Kakimoto et al., 2016) and atrophy (Xu et al., 2000). Further, sex differences in aging are also known to exist in cognition, for example in reaction times (Der & Deary, 2006).

4.4. Potential of EMs as biomarkers of neurodegeneration

The importance of the current findings extends beyond characterising age and sex effects in the general, healthy population. Individuals with early signs of cognitive decline have impaired EM performance (Levy et al., 2018), making EMs a candidate preclinical biomarker of neuropathological changes. Since it is difficult to distinguish between normal age-related and pathological changes, an EM outcome that is unaffected by aging but impaired in neurodegenerative diseases would be an ideal biomarker of pathological cognitive decline.

In the antisaccade task, most participants corrected 100% of their errors, and in those who corrected less than 100% of their errors, age did not predict the amount of corrected errors. Interestingly, the percentage of corrected errors is decreased in Alzheimer's disease (Crawford et al., 2013; Garbutt et al., 2008; Noiret et al., 2018), making a low percentage of corrected antisaccade errors a suitable indicator of pathological brain changes as it cannot solely be explained by aging processes. However, it may be argued that its use as biomarker might be more applicable to those participants with higher visual acuity. Even if best-corrected visual acuity did not impact EM performance, 75% of the missings in our sample occurred due to technical issues during data acquisition or post-processing of the data and technical failures were more likely for participants wearing high dioptric glasses and for participants with artificial lenses or eye diseases. Nevertheless, calibration and validation did also succeed in some participants with low and medium visual acuity.

Correcting antisaccade errors requires error monitoring, which has been associated with activity in anterior cingulate cortex (Botvinick et al., 2004) and supplementary eye fields (Stuphorn et al., 2000). The ability to correct antisaccade errors has also been linked to general cognitive functioning and spatial working memory capacity in Alzheimer's disease patients (Crawford et al., 2013). Slow saccade latencies are unlikely to account for the low percentage of corrected antisaccade errors because healthy participants are able to initiate both an initial as well as a corrective saccade within less than one second (Crawford et al., 2013; Noiret et al., 2017). Individuals with dementia, however, have longer saccade latencies (Crawford et al., 2013) and, therefore, the possibility that participants with cognitive impairment do not correct antisaccade errors due to time constraints cannot be ruled out. A related limitation of the current work is that the measure of corrected errors in this study is based on a lower number of trials, requiring replication with a larger number of trials. Also, further work is needed to compare the sensitivity of EM performance in detecting pathological changes with the sensitivity of traditional cognitive tasks.

5. Conclusions

This study demonstrated that (i) EM performance declines with age in two thirds of outcomes, (ii) small sex differences exist in SPEM velocity gain and blink rate during fixation, and (iii) interindividual differences and intraindividual variability in EM performance increase with age. Although still requiring further validation, the best EM candidate preclinical biomarker of neurodegeneration may be the percentage of corrected antisaccade errors.

CRediT authorship contribution statement

Annabell Coors: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Visualization, Writing - review & editing. **Natascha Merten:** Validation, Investigation, Writing - review & editing. **David D. Ward:** Visualization, Writing - review & editing. **Matthias Schmid:** Formal analysis, Writing - review & editing. **Monique M.B. Breteler:** Conceptualization, Methodology, Validation, Resources, Data curation, Supervision, Project administration, Funding acquisition, Writing - review & editing. **Ulrich Ettinger:** Conceptualization, Methodology, Validation, Investigation, Supervision, Project administration, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.visres.2020.10.004.

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