Measurement and Analysis of Eye Movements Performance to Predict Healthy Brain Aging

CECILIA E. GARCíA CENA [ID] [1], DAVID GÓMEZ ANDRÉS[2], AND IRENE PULIDO VALDEOLIVAS[3]

[1]Centre for Automation and Robotics, Universidad Politécnica de Madrid, 28012 Madrid, Spain
[2]Paediatric Neurology Unit in Hospital Universitari Vall d'Hebron, 08035 Barcelona, Spain
[3]Center of Neuroimmunology, Department of Neurology, Hospital Clinic of Barcelona, Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS),
University of Barcelona, 08036 Barcelona, Spain

Corresponding author: Cecilia E. García Cena (cecilia.garcia@upm.es)

ABSTRACT Objective: This article presents the healthy pattern of eye movements (EM) in 145 healthy volunteers from 20 to 86 years old. Volunteers were classified into four groups according to their age. A saccadic paradigm, in horizontal and vertical axes, was performed. We described a pattern behavior in healthy volunteers to demonstrate that it can be used to measure the aging and functionality of the brain. Methods: A gaze-tracker based in video-oculography technology was used. Before EM tests, clinical data were collected, participants performed a cognitive test to discard subtle abnormalities and signed an informed consent form. To demonstrate the relationship between EM and brain aging, a linear or quadratic model was computed and statistical analysis among groups was presented. Conclusion: EM variables could be considered as biomarkers to measure the aging effect and functionality of the brain. Video-oculography is a suitable technique for measuring EM in clinical practice. Significance: The ocular healthy pattern as well as the methodology followed in this clinical study, is the base for ongoing studies aiming to incorporate EM analysis at routine practice as markers in early diagnosis for patients with neurodegenerative diseases like Alzheimer's dementia or Parkinson's disease.

INDEX TERMS Aging, biomarker, measurement techniques, statistical analysis, healthy pattern.

I. INTRODUCTION

The ocular movements study is a rich source of information about brain functionality and useful from the clinical and scientific points of view.

The complex and elaborated mechanism that generates the eye movements (EM) involves different regions of the human brain: Dorsolateral Prefrontal Cortex (DLPFC); Frontal Eye Field (FEF); Parietal Eye Field (PEF); Visual Cortex (VC); Superior Colliculus (SC); Brainstem saccade generators; Basal Ganglia (BG); Cerebellum and Thalamus.

Nowadays, in clinical practice, the EMs are mostly evaluated qualitatively and subjectively and thus only some abnormalities in EM can be observed but not quantified or measured. Sometimes, clinicians use their finger, pencil or a lighter to generate a visual target to see or follow. Smooth pursuit, optokinetic reflex, saccadic movement, and vergence are frequently evaluated in this way.

Saccade paradigm offers the best ratio between useful information and a time-consuming test. Saccades are defined

The associate editor coordinating the review of this manuscript and approving it for publication was Nikhil Padhi [ID].

as fast conjugate eye movements that shift the eyes from one target to another, focusing the object of interest into the fovea. The fovea is the central area of the retina that enables the best visual acuity, it has around 2 mm of diameter, causing saccades be accurate. Saccades can be voluntary or involuntary movements with around 500 °/sec and have a duration of 100 ms [1].

To evaluate EM accuracy, it is necessary the use of specific technology and procedure. In 1963, David Robinson [2] published a method for measuring eye movement using a scleral search coil in a magnetic field. Through two magnetic fields in quadrature phase and two coils on the lens, horizontal, vertical, and torsional eye movements were measured simultaneously. The scleral search coil is considered the gold standard in eye movement measurement. However, since it is an invasive method, its use is far from being extended to clinical practice. Furthermore, the test must be performed and interpreted by qualified personnel, which is also a barrier towards its generalized implementation.

During the last four decades non-invasive systems were developed for measuring eye movements. These systems can be classified into two categories from a technological point

of view: electro-oculography (EOG) or video-oculography (VOG). The EOG system measures the electrical signal generated when the eyes move. Here, some electrodes must be placed around the eyes in contact with the skin [2]–[6]. The VOG systems consist of, at least, one camera that records the eye/s movement. Some authors suggest that the VOG system is replacing EOG because of its accuracy and simplicity [7]–[9]. Therefore, thanks to technological improvements, the EM is started to be measured quantitatively in an increasing number of medical centers.

Measurement and characterization of EM may provide important information in several neurological disorders [10]–[13]. Many research studies about EM have been reported in prevalent neurodegenerative diseases such as Alzheimer's dementia, Parkinson's disease, frontotemporal dementia, supranuclear progressive palsy, mind cognitive impairment, and others [14]–[19]. Besides, the alteration of EM could even become early markers for the diagnosis of specific neurological disorders. However, these studies use different technologies and follow different protocols and procedures, therefore it is difficult to obtain conclusions of their measurements.

The first step to EMs being considered in clinical practice is to develop a standard procedure in order to guarantee the reproducibility of the measure. Then, using this standard, clinical trials must be performed to get normal and abnormal values of the movement in healthy and pathological conditions.

This article aims towards establishing the first systematic, standard for measuring the EM using a VOG technique. Normal values of saccadic paradigms (visually-guided saccades, memory-guided saccades, and antisaccades) in 145 healthy volunteers (between 18 years old and 86 years old) are presented.

Data presented in this article are considered as "healthy pattern" for clinical use in order to compare with pathological conditions and to develop further studies in neurodegenerative disorders.

All volunteers were informed about the main objective of the research and signed informed consent. Previous to EM measure, each subject was interrogated about pathologies and neurological symptoms, and at least a MoCA, Mini-Mental, Stroop, or Viena test were performed to exclude some potential cognitive abnormalities in these subjects. Taking into consideration the age, volunteers were divided into four groups. Group A between 18 and 40 years old (nGA = 33), Group B between 41 and 50 years old (nGB = 14), Group C between 51 and 60 years old (nGC = 29) and Group D more than 61 years old (nGA = 69).

This article is organized as follows: Section II describes the brief background about the relationship between EM and brain functionality. Section III presents the technology used for the measurement. Section IV describes the paradigm used in the clinical trial. Section V describes the results, while the discussion is made in Section VI. Finally, the main conclusions of this research and the futures step are presented.

This research is authorized by the National Spanish Agency for Drugs and Medical Devices (AEMPS) and follows the European protection data law.

II. BACKGROUND ON EYE MOVEMENT AND NEURAL CONNECTIONS

The generation of an eye movement toward a new stimulus in the visual field involves two problems: to control the direction and to control the amplitude of the movement in order to locate the stimulus on the fovea. A *saccade* can be defined as a fast (between 400°/sec and 800°/sec) volunteer or reflex eye movement between two fixed points [20].

The amplitude is controlled by the duration of neuronal activity in the lower motor neurons of the oculomotor nuclei and is correlated with the duration of the burst of action potentials in the abducens neurons [21].

The direction of eye movement is controlled by the local circuit neurons in two gaze centers in the reticular formation, each of them is responsible for generating movements along a particular axis: horizontal and vertical. The horizontal gaze center is a collection of local circuit neurons near the midline in the pons responsible for generating horizontal eye movements. The vertical gaze center is located in the rostral part of the midbrain reticular formation and is responsible for vertical movements. Activation of each gaze center separately results in movements of the eyes along a single axis, either horizontal or vertical [11].

Besides, two structures that project to the gaze centers are demonstrably important for the initiation and accurate targeting of saccadic eye movements: the superior colliculus of the midbrain, and a region of the frontal lobe that lies just rostral to the premotor cortex, known as the frontal eye field (located at Brodmann's area 8) [11], [22].

Commonly, saccadic movements are directed towards a stimulus. Besides, there are two variants of this visually-guided saccades (or prosaccades): memory saccades (in which the target is the position of a previously shown stimulus) and antisaccades (in which an intentional movement must be made towards the opposite direction to a suddenly appearing peripheral visual target) [23].

Some studies in human and nonhuman primates demonstrated that the dorsolateral prefrontal cortex and particularly, area 46 of Brodmann and the adjacent Brodmann area 9, both located in the middle frontal gyrus, are involved in the control of memory-guided saccades [24]–[27].

In the antisaccade paradigm, an intentional saccade must be made in the opposite direction to the target, located at one side of the gaze center (right/left or up/down). To generate these movements at least two mechanisms are believed to be required: the inhibition of the unwanted reflexive saccade toward the stimulus (apparently controlled by intrinsic control of the frontal eye field and the superior colliculus and externally by the dorsolateral prefrontal cortex and the substantia nigra pars reticulata); and then the generation of a volunteer prosaccade in the opposite direction to the target (in

FIGURE 1. Device for measuring Eye movements.

Quantity	Value SI
Measure Limits	Horizontal:40°, Vertical: 24°
Time resolution	10 ms
Precision	Horizontal: 0.03° Vertical: 0.03°
Accuracy	Horizontal: 0.4° Vertical: 0.4°
Resolution	0.0033° (RMS 0.0604°)

TABLE 2. Legal aspects certified in OSCANN desk100.

Normative	Classification
EN 55022:2010 + AC 2011	B Class
EN 60601-1:2006 + AC:2010 + A1:2013	Class II
EN 62471:2008	Equipment free of photobiologica risk
Norm 93/42/CEE	Medical Device Class II-A
Norm 2011/65/EU	RoHS

which lateral intraparietal area and the frontal eye field seems to be involved).

III. DESCRIPTION OF VIDEO-OCULOGRAPHY SYSTEM

A. HARDWARE DESCRIPTION

OSCANN desk100 is a novel gaze-tracker [13], [28], [29] designed for clinical practice use. It is based on VOG technology and the IR-camera captures images at 100 FPS with a resolution of 1 ms. The measurement is made over the dominant eye. Before the eye movement test, the operator must check the dominance of the eyes and move the camera accordingly.

In order to minimize the head movement, the camera and infrared light system were settled on a mechanism attached to a chinrest. This mechanism was designed with 3 degrees of freedom and allows manual adaptation of the system to the subject's anatomy.

In Fig. 1, a photograph of the real system is shown. Two conventional screens with 22" and 120 Hz refreshing rate complete the system. The volunteer is settled in front of the screen at a distance of 60 cm and the view field is free due to a hot mirror located in front of his/her eyes that filter the IR light. The size and the color of the stimulus as well as the background color of the screen were fixed according to the medical protocol (Section IV).

The technical characterization of the measurement [20] is presented in Table 1. The reader should note these values considered the human factor in the measurement and the characterization including people of different ages, nationalities or visual acuity. Moreover, subjects with contact or intraocular lenses were included. The values of precision, resolution, and accuracy make OSCANN desk100 a suitable system for medical application.

Considering the medical regulatory issues, OSCANN desk100 is a certified medical device under international regulation and can be considered as a "safe device for clinical practice". Table 2 shows the legal requirements follow by the device.

B. SOFTWARE DESCRIPTION

We developed two software systems that run independently: OSCANN Capture® and OSCANN Analyzer®.

Fig. 2 shows the concepts of software development. The eye movement is captured through the device (.cls file format file) and analyzed automatically returning a report (.pdf file format) to the specialist. The round-trip time is between 3 and 5 minutes and depends on the number of visual tests performed.

OSCANN Capture software application allows the configuration of the test session, records the video from the IR camera, and processes it to get gaze localization (positive, velocity and acceleration) in a file.cls file format. It has two human-machine interfaces which are described below: Patient-Machine Interface and Staff-Machine Interface.

The Staff-Machine Interface has many options. A list of tests can be selected and configured; three different types of calibration modes are available. Moreover, it is possible to visualize the graphical results of a test and compared it with the video recording. This is very useful to evaluate some unusual eye movements such as nystagmus.

Through Patient-Machine Interface, the stimulus is showed to the patient. A dot is used as a visual target and its color changes, from red to green, when the eye movement is recorded.

A "demo" version is available to assist technicians in this stage and it is especially useful with patients in cognitive impairment.

IV. BRIEF DESCRIPTION ON MEDICAL PROTOCOL

One hundred and forty-five healthy volunteers were recruited according to the following inclusion criteria:

- Age between 18-86 years old. Table 3 summarizes the main data of each group. The choice of these groups is not arbitrary and was done in response to the needs of the ongoing clinical trials (carried out in diseases with
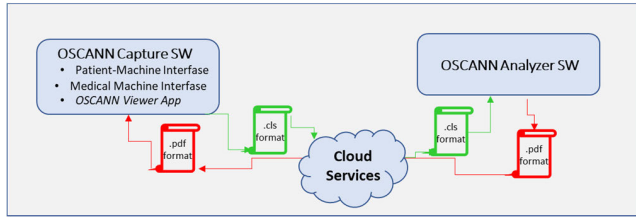
FIGURE 2. Concept of communication and cloud service.

TABLE 3. Volunteers group classification.

GROUP	AGE	Size (n)	Gender	MoCA
Group A	28.7±6.5	33	20 (M), 13 (F)	28.1±1.5
Group B	44.5±2.9	14	9 (M), 5(F)	27.3±2.2
Group C	57 ±2.9	29	13 (M), 16(F)	26.8 ±2.4
Group D	69.2 ±5.6	69	38 (M), 31 (F)	26.2±2.1

TABLE 4. Default parameters for visual guide saccades test.

MODE	VISUAL FIELD [°]	Duration [sec]	Repetitions
Horizontal	5, 10, 20	36	22
Vertical	5, 12	24	12

Instruction to the volunteer: "Look to the green dot"

FIGURE 3. Visually guided saccade test.

FIGURE 4. Main variables computed for visual guided saccade test.

different age onset) and the previous literature. We split the study sample into 4 age groups.

- No personal history of neurological diseases (such as epilepsy, multiple sclerosis, other neuroimmunological pathology, neurodegenerative disease, or neurodevelopmental disorders) that may alter the EM.
- MoCA (Montreal Cognitive Assessment test) score higher than 24.
- No personal history of ophthalmological diseases (such as retinopathy, optic nerve disorders, or others) that affect visual acuity despite the use of lens correction.
- Visual acuity higher than 0.5 and the absence of uncorrected refractive errors.
- Signed informed consent agreement.

A. BATTERY DESCRIPTION

Healthy volunteers carried out the visually-guided saccades test, memory-guided saccades test, and antisaccades test in horizontal and vertical axes. The stimulus was a green dot with a 2 cm diameter and the background color is black.

Fig. 3 describes the horizontal *visually guided saccade test*. The stimulus appears in the center of the screen during 1500 ms and the jumps to the right and left (horizontal test) or up and down (vertical test) randomly. Table 4 presents the test parameters.

In *visually guided saccade test,* variables like latency toward the stimulus, latency back to the center of the screen, gain (ratio between stimulus and gaze amplitude), accuracy (hypermetric or hypometria dysmetria), number of blinks, velocity and anticipated saccades (those performed before 80 ms after the appearance of the stimulus) are measured. Fig. 4 presents the main variables measured in this visual test.
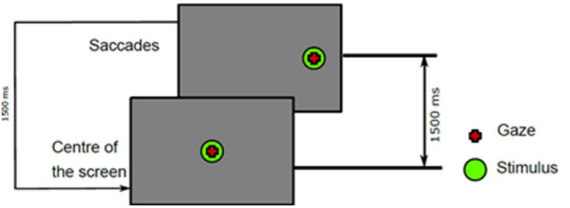
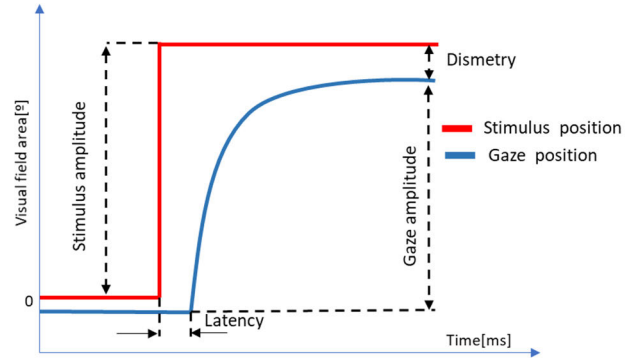*Definition*: The *Latency* is the time (Δt) elapsed between the change of the stimulus ($t_{stimulus}$) and the first eye movement performed by the volunteer in response to the stimulus change $\left(t_{gaze}\right)$. We compute it by (1). In the measure of latency variable [ms], the anticipated saccades were discarded.

$$\Delta t\,(t) = t_{gaze} - t_{stimulus} \tag{1}$$

Definition: The *Gain* (2) of the saccade is computed by the ratio between stimulus amplitude ($Amp_{stimulus}$) and gaze amplitude (Amp_{gaze}).

$$Gain = \frac{Amp_{gaze}}{Amp_{stimulus}} \tag{2}$$

Definition: Peak of Velocity [°/ms] is computed by the maximum absolute value of the velocity in the saccade movement (3). Here, t_{ini} is the time at the first saccadic movement while t_{end} is the time of the last saccadic movement in the test.

$$V_p(t) = \max\left(abs\left(V_t\right)\right) \quad t \in [t_{ini}t_{end}] \tag{3}$$

The accuracy of the saccadic movement is an important value to evaluate brain ageing. The precision of the saccadic movement must be measured and computed as an error. In general, this error is called *dysmetria* and is computed by (4), where $P_{i_{stm}}$, $P_{e_{stm}}$, $P_{i_{gz}}$ and $P_{e_{gz}}$ represent the initial and final position of the stimulus and the gaze, respectively:

$$e(t) = sign(P_{i_{gz}} - P_{e_{stm}}) * (P_{i_{gz}} - P_{e_{gz}}) \tag{4}$$

If $e(t) > 0$ the saccade is hypermetria and if $e(t) < 0$ it is hypometria.

In the *memory-guided saccade test*, volunteers are inquired to remember the position of the stimulus after it disappears.
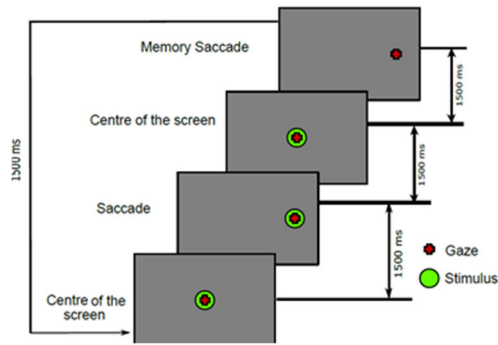
FIGURE 5. Memory guided saccade test.

TABLE 5. Default parameters for memory guide saccades test.

MODE	VISUAL FIELD [°]	Duration [sec]	Repetitions
Horizontal	5, 10, 20	72	22
Vertical	5, 12	48	12

Instruction to the volunteer: "Remember the position of the last stimulus and moves yours eyes toward it."
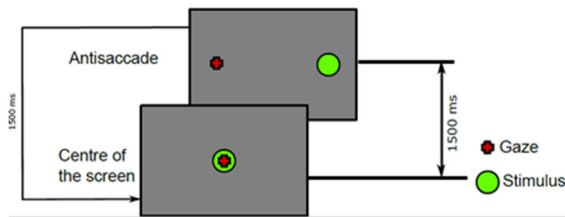

FIGURE 6. Antisaccade test.

Then, he/she must perform a saccadic movement toward the last position the stimulus appeared. Fig. 5 sketches the test. The stimulus appears in the center of the screen after 1500 ms a visually guided saccade is done, then the stimulus comes back to the center and the volunteer must perform "memory" saccade, that means he/she must move his/her eyes to the last position of the stimulus. Table 5 presents the main parameters of the test. In the memory-guided saccade test, the same variables of the visually guided saccade test are computed. Additionally, the number of correct memory saccades are measured. The accuracy parameter was measured in the memory saccade.

Fig. 6 describes the *antisaccade test* paradigm. The volunteer must perform a movement in the opposite direction of the stimulus. Table 6 summarizes the main parameters of the test.

An antisaccade is correct if the volunteer performs a saccade movement in the opposite direction to the stimulus. When the volunteer performs a movement in the direction to the stimulus and then corrects the gaze to the opposite side, this saccade is called "reflexive". In order to measure the latency of the antisaccade we used (1) and, with (4) antisaccade dysmetria was computed.

Other variables such as latency, velocity, and duration of reflexive saccades, antisaccade latency, and its velocity,

TABLE 6. Default parameters for antisaccade test.

MODE	VISUAL FIELD [°]	Duration [sec]	Repetitions
Horizontal	5, 10, 20	36	22
Vertical	5, 12	24	12

Instruction to the volunteer: "Look to the opposite site to the green dot"
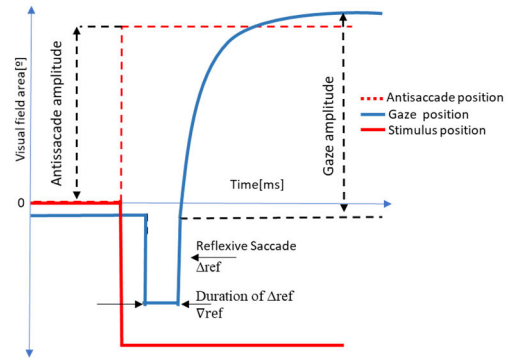

FIGURE 7. Main variables computed for Antisaccede Test.

accuracy, and ratio of anticipated, corrected, and successful antisaccades are measured. The main variables are represented in Fig. 7.

Definition: The *Latency of Reflexive Saccade* [ms] (Δt_{ref}) is the time elapsed from the time of first gaze's fixation (t_{gazeA}) toward the stimulus and the time of the stimulus change ($t_{stimulus}$). It is computed by (5).

$$\Delta t_{ref}(t) = t_{gazeA} - t_{stimulus} \tag{5}$$

Definition: The *Duration of reflexive saccades*, ∇t_{ref}, [ms], is computed by (6) and it is the difference between the time at which volunteer fixes the gaze on the stimulus (t_{iniFIX}) and the time in which the gaze starts the movement to the opposite direction (t_{endFIX}):

$$\nabla t_{ref}(t) = t_{endFIX} - t_{iniFIX} \tag{6}$$

V. RESULTS OF CLINICAL STUDY
In this section, the most relevant results are described. Data are presented together with the linear or quadratic estimation that best fit to real data. It is made to verify the data tendency to know when healthy brain ageing is starting. In the following figures and equations, the abscissa axis (**y**) represents the studied variable while the ordinate axis (**x**) represents the age of volunteers.

A. VISUALLY GUIDED SACADDE TEST
Volunteers performed the visually guided saccades in horizontal and vertical with parameters presented in Table 4. The latency toward the stimulus and the latency coming back to the center of the screen are computed independently. Fig. 8 presents the mean values of the horizontal latency during the test (go to the stimulus and back to the center).
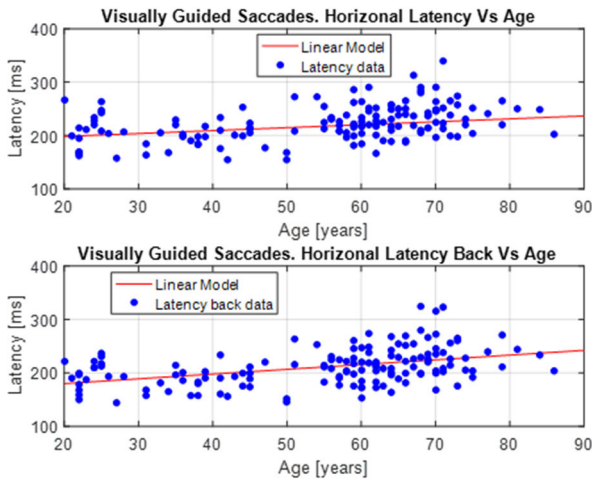
FIGURE 8. Visually Guided Saccade Test. Horizontal Latency. a) Go to stimulus, b) Back from stimulus.
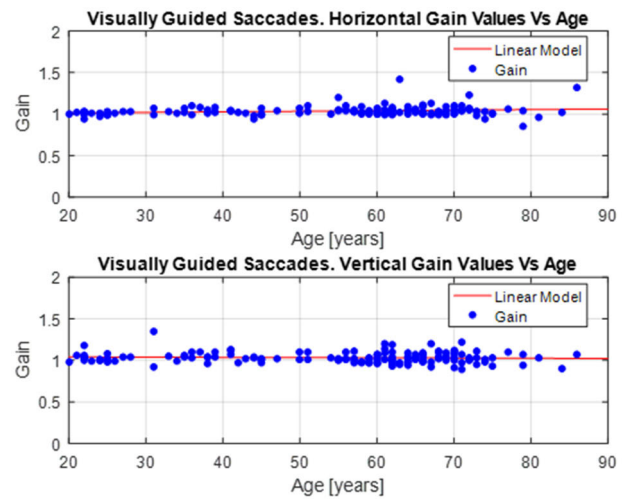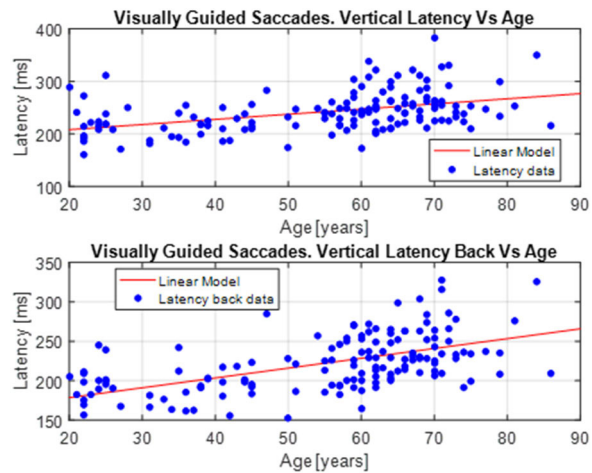

FIGURE 9. Visually Guided Saccade Test. Vertical. Latency. (a) Go to stimulus, (b) Back from the stimulus.

Using a linear estimation model to evaluate the progression of the values, it is observed that the latency of saccadic movement is higher with aging in both, horizontal and vertical movements (7).

$$y_{h_{go}} = 187.16 + 0.55x$$
$$y_{h\_back} = 162.22 + 0.89 \quad (7)$$

Fig. 9 shows the latencies measured in the vertical tests while (8) shows the linear estimation of the values (going toward the stimulus and going back to the center of the screen).

$$y_{v\_go} = 188.44 + 0.98x$$
$$y_{v\_back} = 153.59 + 1.25x \quad (8)$$

Fig. 10 shows the linear estimation and measured values of visually guided saccades gain. It could be observed that gain remains constant with aging, then a potential deviation could reveal a possible neurological impairment

FIGURE 10. Visually Guided Saccade Gain vs Age. Horizontal andVertical.

TABLE 7. Hypermetria in visual guide saccades.

	Horizontal		Vertical	
Group	Value	SD	Value	SD
A	0.51	0.32	0.51	0.29
B	0.52	0.34	0.52	0.29
C	0.47	0.37	0.50	0.30
D	0.91	0.63	0.64	0.44

TABLE 8. Hypometria in visual guide saccades.

	Horizontal		Vertical	
GROUP	VALUE	SD	Value	SD
A	-0.47	0.46	-0.25	0.01
B	-0.29	0.20	-0.19	0.11
C	-0.57	0.96	-0.40	0.13
D	-0.92	0.51	-0.29	0.19

Comparing (7) with (8), the behavior of latencies in healthy volunteers seems to be analogous: linear increase and a higher slope with the age in the returning saccades.

The following Tables, 7 and 8, show the accuracy values in the saccadic movement. Both, horizontal and vertical axes, mean accuracy of the age groups is lower in groups with older volunteers but existing a wide dispersion inside age groups.

B. MEMORY-GUIDED SACADDE TEST

The test was performed following the parameters given in Table 5. In this case, the latency is computed only in the memory saccade and the anticipated memory saccades are discarded from the latency value. Table 9 shows these measured values.

Figs. 11 and 12 show the latencies of memory guide saccades in horizontal and vertical axes respectively. According to linear models, (9) and (10), latency increases with the age in both axes and directions.

$$y_{h\_go} = 176.72 + 2.3x$$
$$y_{h\_back} = 193.65 + 2.3x \quad (9)$$

TABLE 9. Correct and anticipated memory saccades ratio.

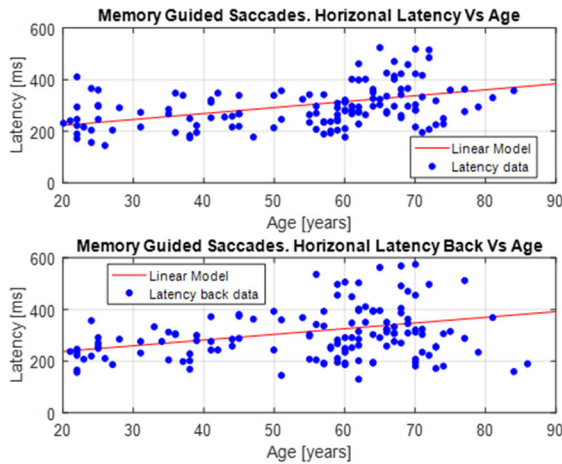|	Correct Memory Saccade		Anticipated Memory Saccade	
Group	Horizontal	Vertical	Horizontal	Vertical
A	96,88	99,98	4.3	3.34
B	95,56	99,02	3.14	3.21
C	94,79	98,44	3.68	2.75
D	87,12	81,25	4.38	3.24

FIGURE 11. Memory-Guided Saccade Test. Horizontal Latency. (up) Go to the stimulus. (down) Back from stimulus.

TABLE 10. Hypermetry in memory-guided saccades.

	Horizontal		Vertical	
Group	Value	SD	Value	SD
A	1.04	0.75	0.70	0.54
B	1.37	1.00	0.99	0.69
C	1.54	1.73	1.29	0.54
D	2.01	1.46	1.21	0.70

$$y_{v\_go} = 183.2 + 2.19x$$
$$y_{v\_back} = 177.02 + 2.19x \tag{10}$$

Gain values are presented in Fig. 13. As can be easily observed, in this test, gain values also remain constant along with the age.

Table 10 and 11 show the accuracy values in memory-guided saccadic movement in the horizontal and vertical tests. In this test, median hypometric and hypermetric errors also increase with age, but again there is a wide dispersion between subjects in the same group making difficult to find significant differences. See sub-section D for further discussion.

C. ANTISACCADE TEST

Figs. 14 to 17 show the latency and reflexive latency values in horizontal and vertical antisaccades tests.

Although the antisaccade latency can be adjusted to a linear model in the horizontal axis (11) and the vertical axis (13), the reflexive latency is better approximated by a quadratic
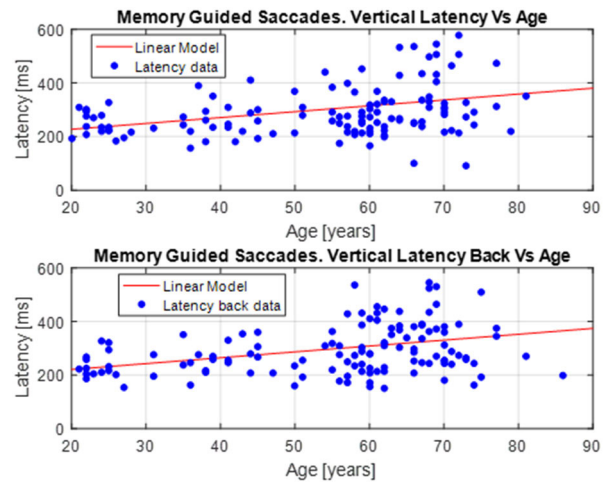
FIGURE 12. Memory Guide Saccade Test. Vertical Latency. (up) Go to the stimulus. (down) Back from the stimulus.
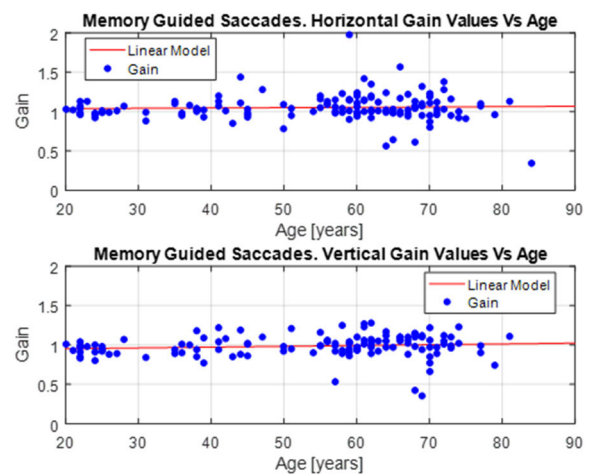
FIGURE 13. Memory-Guided Saccade Gain Vs Age. (up) Horizontal, (down) Vertical.

TABLE 11. Hypometry in memory-guided saccades.

	Horizontal		Vertical	
Group	Value	SD	Value	SD
A	-0.78	0.53	-0.92	0.32
B	-0.90	0.69	-0.90	0.17
C	-1.05	1.12	-1.07	0.59
D	-1.48	1.13	-1.24	0.89

polynomial function in both axes (12) and (14).

$$y_{h\_go} = 201.37 + 3.54x$$
$$y_{h\_back} = 220.01 + 2.08x \tag{11}$$
$$y_{h\_RefSaccade} = 487.63 - 6.43x + 0.12x^2$$
$$y_{h\_\Delta RefSaccade} = 221.96 - 5.65x + 0.08x^2 \tag{12}$$
$$y_{v\_go} = 255.26 + 2.54x$$
$$y_{v\_back} = 241.44 + 1.53x \tag{13}$$
$$y_{v\_RefSaccade} = 661.67 - 13.85x + 0.18x^2$$
$$y_{v\_\Delta RefSaccade} = 374.21 - 13.25x + 0.16x^2 \tag{14}$$
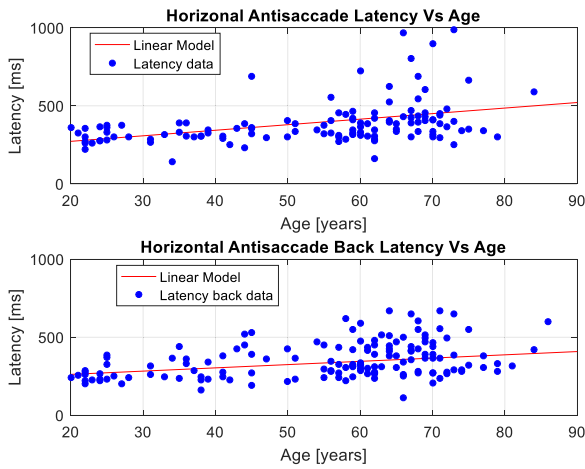
FIGURE 14. Antisaccade latency. horizontal test.

FIGURE 15. Latency and duration of horizontal reflexive saccade.

FIGURE 16. Antisaccade latency. vertical test.
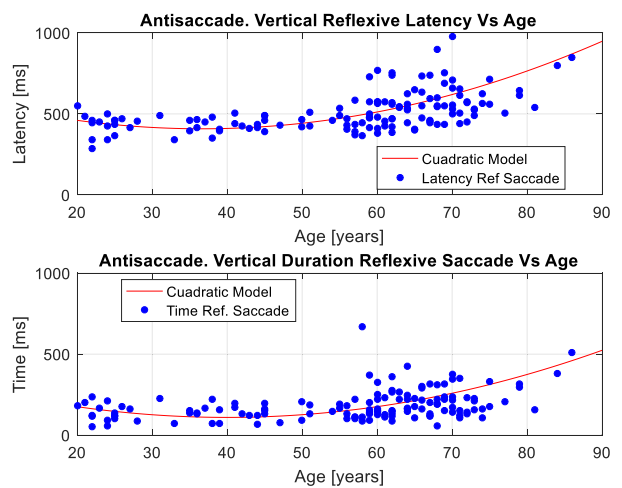
FIGURE 17. Latency and duration of vertical reflexive saccade.

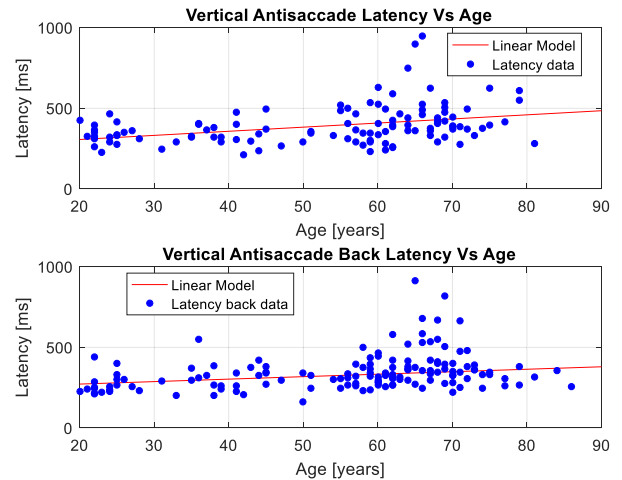In Table 12, the successful antisaccade ratio is presented for each age group. It is demonstrated that the inhibitory control is becoming worse with the age as well as the precision of antisaccade movement (Table 13 and 14). See sub-section D for further discussion.

D. STATISTICAL ANALYSIS BY GROUP

Tables 15, 16, and 17 (at the end of the article) show the values of variables measured in eye movement tests. Values are expressed in terms of mean±SEM (standard error of the mean). Differences between groups were analyzed using one-way ANOVA followed by post-hoc Tukey's multiple comparison test for parametric variables, and the Kruskal-Wallis test followed by Dunn's test for non-parametric variables. In all tables, non-parametric variables are indicated with a letter (a). There are significant differences among groups if the p-value is less than 0.05 and non-significative p-values are indicated as "*ns*".

In the saccadic paradigm presented in this article, there are no significant differences in eye movement in

TABLE 12. Success antisaccade ratio [%].

	Horizontal	Vertical
Group	Value	Value
A	56.38	54.17
B	55.01	52.33
C	35.30	31.17
D	25.31	22.89

TABLE 13. Hypermetry in antisaccades test.

	Horizontal		Vertical	
Group	Value	SD	Value	SD
A	2.38	1.63	1.32	0.99
B	2.67	2.31	1.92	1.41
C	2.67	1.82	1.39	0.97
D	3.40	2.25	1.89	1.17

Groups A and B. It suggests that brain ageing starts at 40-years-old as it was stated in previous studies with MRI (magnetic resonance image) [30], [31].

TABLE 14. Hypometry in antisaccades test.

Group	Horizontal		Vertical	
	Value	SD	Value	SD
A	-2.58	1.78	-2.03	1.18
B	-2.41	1.59	-2.00	1.30
C	-2.87	2.57	-2.38	1.18
D	-4.45	4.06	-4.23	1.89

Groups C and D have significant differences in visually guided saccades test in blinks number, back latency, and latency in vertical. In [32] a study with MRI was performed to 140 healthy adults (50-81 years old), it was demonstrated that change in the volume of the prefrontal cortex is associated with age.

In memory-guided saccade tests, latency and success rate of memory saccades present the most significative difference between groups C and D. In [33] it was demonstrated that memory task and visual perception was altered: older brains tend to show more symmetrical activation between hemispheres (either because the activation increases in the less activated hemisphere or because there is a reduction in the most activated hemisphere with age).

Many studies relate ageing with the success rate in the antisaccade test [34], [35]. In this article, we demonstrate that reflexive saccade latency, as well as its duration, have a nonlinear relation with age and it is a significative variable in group classification.

If A-B and C-D groups are considered together, there are significant differences in a large number of parameters in all eye tests. The latency of saccadic movement is significant.

VI. DISCUSSION

OSCANN desk100 is the first gaze tracker measurement platform designed for use in clinical practice. To compare and analyze the pathological eye alterations, it is necessary to know the normality pattern in the same way as normal values for sugar or cholesterol in the blood. Due to the novelty of the hardware and software, it is not possible to compare it with the existing devices, then clinical trials were necessary.

In order to guarantee the repeatability of the measures they must be done systematically, then in this work, we established a standard protocol for studying the saccade paradigm and we explicitly defined parameters to assess it by OSCANN desk100.

Most of the gaze trackers available are research-oriented, allowing the configuration of the experiment and therefore varying the number of repetitions, the scanned visual field, or the colour of the stimulus, among others. If any external parameter is altered, it is not possible to compare the results since the input or reference signal is not the same, then it cannot be ensured that measured alteration is due to a specific brain condition.

Moreover, measuring pure eye movement to get conclusions about the functionality of the brain, the head must remain fixed, since the subject/patient could perform compensatory cephalic movements and thus alter the measurement.

When measures are made under the same external conditions (patient position, head fixation, form, shape, and colour of both, background and stimulus, order to be done to volunteer/patient, etc.) it is possible to consider it as a standard.

Moreover, we have built a relevant dataset with a relatively large number of healthy subjects from a wide spectrum of age and a systematic evaluation of the different paradigms of saccadic movement.

The main limitation of our study is its transversal design. This limitation is overcome by the relatively large number of subjects that we evaluated and using our study and others [36], [37], we can establish that longitudinal studies should be targeted in the future for older ages in which changes are of higher magnitude.

Eye movements are altered in several neuropsychiatric diseases such as Parkinson's disease or Alzheimer's disease. These movements can be a source of biomarkers that may improve diagnostic and monitoring performance in clinical practice for a large number of disorders [38]. The development of biomarkers requires the construction and interpretation of database from healthy subjects in each acquisition system. First, data from healthy subjects is needed to understand the normal evolution of eye movements during ageing. Apart from the importance of understanding the neurobiology of aging in eye movements, this is also critical in the design of trials for search biomarkers. Second, data from adequate control subjects are important to adequately interpret results from individual patients with neurological disorders and also from clinical studies devoted to EM biomarker research.

Previous studies have evaluated saccadic performance in healthy populations, but few have performed a systematic evaluation including a large number of parameters in the same study [39], [40]. Our results are in line with the findings of these studies but we believe that the evaluation of saccadic performance as a whole is also a significant contribution of our work, that is needed to the development of a systematic approach to assess saccadic performance.

The evaluation of saccadic performance has been pointed out by several types of studies as a valid approach to ageing and likely, for neurodegenerative disorders. Saccadic performance is sustained by a complex neural network that changes in adaptation to ageing [41]–[43]. This neurobiological substrate highlights the importance of saccadic performance as a tool to approach brain function. Moreover, several studies have demonstrated a correlation between several saccadic parameters and cognitive function, both in aging and neurodegenerative disorders [43].

Considering the different groups of age that we had established a priori, we believe that subjects form group A and group B shows similar eye movements performance due to the absence of significant differences between them. This implies that the saccadic performance remains nearly constant from 18 to 45 years of age. In contrast, the groups of subjects older than 45 years show significant changes

TABLE 15. Visually Guided Saccade Test. Comparison among groups.

Measured Variables	Group A M. values ± SEM	Group B M. values ± SEM	Group C M. values ± SEM	Group D M. values ± SEM	Groups A vs B P-Value	Groups C vs D P-Value	Groups AB vs CD P-Value	ANOVA One-way P-value
HORIZONTAL VISUAL SACCADES								
Latency (ms)	197.6±7	198.6±10	226.1±8	236.2±6	ns	ns	< 0.001	< 0.001
Gain	1.02±0.01	1.02±0.01	1.04±0.01	1.05±0.01	ns	ns	< 0.05	ns
Peak of velocity (º/mseg)	334±26	332±36	362±27	332±16	ns	ns	ns	ns
Positive error[a] (º)	0.52±0.06	0.53±0.09	0.52±0.06	0.8±0.06	ns	ns	ns	ns
Negative error[a] (º)	-0.489±0.09	-0.29±0.12	-0.46±0.06	-0.60±0.09	ns	ns	ns	ns
Blinks[a]	2±0.7	3.4±0.9	5±0.7	12±1.0	ns	< 0.05	< 0.001	< 0.001
Anticipated saccades	0.23±0.13	0.36±0.23	0.31±0.18	0.36±0.27	ns	ns	ns	ns
Back latency	186.5±5	186±10	220±8	227±5	ns	< 0.05	< 0.001	< 0.001
Back Peak of velocity	337±29	344±44	345±29	326±18	ns	ns	ns	ns
VERTICAL VISUAL SACCADES								
Latency	211.7±6	221±10	239±6	259±6	ns	< 0.05	< 0.001	< 0.001
Gain	1.04±0.02	1.04 ±0.02	1.02±0.02	1.03 ±0.01	ns	ns	ns	ns
Peak of velocity	262±15	266±26	262±18	251±11	ns	ns	ns	0.04
Positive error[a]	0.53±0.08	0.52±0.08	0.43±0.05	0.71±0.06	ns	ns	ns	ns
Negative error[a]	-0.28±0.03	-0.27±0.03	-0.37±0.03	-0.57±0.05	ns	ns	ns	ns
Blinks[a]	1.7±0.2	2.1 ±0.7	3±0.9	8±0.6	ns	< 0.005	< 0.005	< 0.05
Anticipated saccades[a]	0.05±0.05	0.65±0.30	0.59±0.20	0.36±0.14	ns	ns	ns	ns
Back latency	188±5	202±9	218±6	242 7±5	ns	< 0.005	< 0.001	<0.001
Back Peak of velocity	276±233	271±30	280±16	260±11	ns	ns	ns	0.04

TABLE 16. Memory Guided Saccade Test. Comparison among groups.

Measured Variables	Group A M. values ± SEM	Group B M. values ± SEM	Group C M. values ± SEM	Group D M. values ± SEM	Groups A vs B P-Value	Groups C vs D P-Value	Groups AB vs CD P-Value	ANOVA One-way P-value
HORIZONTAL MEMORY-GUIDED SACCADES								
Latency	249.5±15	270.4±26	262.5±12	355±16	ns	< 0.001	< 0.005	< 0.001
Gain	1.01±0.03	1.06±0.05	1.10±0.03	1.04±0.03	ns	ns	ns	ns
Peak of velocity[a]	353.6±23	365±46	355±29	3137±16	ns	ns	ns	ns
Positive error[a]	1.07±0.2	1.77±0.35	1.8±0.3	1.7±0.1	ns	ns	ns	ns
Negative error[a]	-0.9±0.1	-1.33±0.4	-0.8±0.2	-1.4±0.2	ns	ns	ns	ns
Flickers[a]	5.5±1.3	11.7±1.8	11.7±2.2	24±2.5	ns	ns	ns	ns
Anticipated saccades[a]	4.3±0.5	3.1±0.5	2.4±0.4	3±0.7	ns	ns	ns	ns
Correct saccades[a]	11.6±0.2	11.4±0.3	11.5±0.5	10±0.9	ns	< 0.01	< 0.01	< 0.01
Rate of correct saccades[a]	96.9±2	95.9±3	95.8±4	84.2±3	ns	< 0.01	< 0.01	< 0.01
Return latency	246.9±13	319±32	3053±20	352±16	ns	ns	< 0.05	< 0.05
Return Peak of velocity	359.5±32	365±53	371±33	315±17	ns	ns	< 0.05	< 0.05
VERTICAL MEMORY-GUIDED SACCADES								
Latency	252.1±14	264±28	276.4±14	350±18	ns	< 0.05	< 0.01	< 0.05
Gain	0.94±0.03	1.01±0.04	0.98±0.03	1.01±0.02	ns	ns	ns	
Peak of velocity	243.14±19	245.0±25	244±19	241±12	ns	ns	ns	ns
Positive error[a]	0.7±0.09	0.9±0.2	1.02±0.1	1.3±0.08	ns	ns	ns	ns
Negative error[a]	-0.9±0.11	-0.9±0.05	-0.8±0.07	-1.2±0.1	ns	ns	ns	ns
Flickers[a]	3.6±0.7	4.3±1.8	8±1.6	17±1.6	ns	< 0.005	< 0.001	< 0.001
Anticipated saccades	3.3±0.3	3.2±0.6	2±0.6	2 ±0.5	ns	ns	< 0.001	< 0.001
Correct saccades[a]	7.8±0.2	8±0.5	7.8±0.7	6.6±0.7	ns	ns	< 0.005	< 0.005
Rate of correct saccades[a]	99.6±2	99.4±2	98.6±3	82.6±9	ns	ns	ns	ns
Return latency	239.5±12	267.8±26	279±16	340±16	ns	< 0.05	< 0.001	< 0.001
Return Peak of velocity	238.5±18	237.5±38	228±19	220±13	ns	ns	ns	ns

TABLE 17. Antisaccade Test. Comparison among groups.

Measured Variables	Group A M. values ± SEM	Group B M. values ± SEM	Group C M. values ± SEM	Group D M. values ± SEM	Groups A vs B P-Value	Groups C vs D P-Value	Groups AB vs CD P-Value	ANOVA One-way P-value
HORIZONTAL ANTISACCADES								
Latency	310.6±10	349.6±17	380.8±23	483±12	ns	ns	< 0.005	< 0.001
Latency of reflexive saccades	407±14	442±19	514.3±37	586±18	ns	ns	< 0.001	< 0.001
Duration of reflexive saccades	135.3±11	160.7±19	341±34	237±17	ns	< 0.05	< 0.001	< 0.001
Positive error[s]	2.4±0.27	2.8±0.66	2.33±0.44	3.0±0.25	ns	ns	ns	ns
Negative error	-2.52±0.31	-2.51±0.43	-2.36±0.49	-3.53±0.4	ns	ns	ns	ns
Number of correct antisaccades	6.72±0.74	6.3±0.84	4.2±0.48	3.04±0.21	ns	ns	< 0.001	< 0.001
Success rate (%)	56±7.4	55±7.3	35.3±4.9	25.3±3.9	ns	ns	< 0.001	<0.001
Error rate(%)	0.8±1.3	0.8±1.1	0.8±1.7	4.5±2	ns	ns	ns	ns
Corrected antisaccades rate (%)	41±6.7	45±6.3	57.7±6.3	57.7±7.5	ns	ns	ns	ns
Anticipated antisaccad. rate (%)	1.3±4.6	2.9±4.1	3.4±3.7	10.3±3.7	ns	ns	< 0.05	< 0.05
VERTICAL ANTISACCADES								
Latency	336.7±10	444.5±21	390±24	439.4±12	ns	ns	< 0.005	< 0.001
Latency of reflexive saccades	428±15	139.75±27	516±42	594±14	ns	ns	< 0.001	< 0.001
Duration of reflexive saccades	138±11	135.75±18	183.5±33	227±13	ns	< 0.05	< 0.001	< 0.001
Positive error	1.29±0.17	2.02±0.4	1.43±0.3	1.95±0.15	ns	ns	ns	ns
Negative error	-1.93±0.20	-2.03±0.38	-2.03±0.41	-3.05±1.68	ns	ns	ns	ns
Number of correct antisaccades[a]	4.3±0.45	3.9±0.46	2.5±0.27	1.8±0.26	ns	ns	< 0.001	< 0.001
Succes rate (%)	54±6	52±6	31±4	23±3	ns	ns	< 0.001	<0.001
Error rate(%)[a]	2.4±1.7	2.6±0.9	2.6±8	6.8±6	ns	ns	ns	ns
Corrected antisaccades rate (%)	38.3±5	40.5±6	60±7	39±7	ns	ns	ns	< 0.05
Anticipated antisaccad. rate (%)	2.0±1.3	0.9±2.8	3.5±3.1	7.68±4	ns	ns	< 0.05	< 0.05

with age, overall in parameters from antisaccade tests. This observation seems to be coherent with previous studies and taking into account the neurobiology of antisaccade tests, we believe it may be reflecting a decline in the functionality of areas related to executive functions that are found in normal ageing. The practical consequence of this fact while evaluating saccadic movements in clinical practice or research is that controlling by age effect is extremely relevant for patients older than 45 years, which is the age range in which disorders affecting eye movements found their highest incidence.

We have also evaluated parameters from the saccade that returns the fovea to the original position. Interestingly, this saccade has differences with the prosaccade that targets to a new target in visually guided saccades. In the horizontal and vertical back saccades, latencies tend to be lower but increase more with aging. We hypothesize this is reflecting that the subject has previous information about the origin position and that ageing is influencing the ability of the subject to control eye movement according to this information. This fact is also confirmed in the latency of memory saccade where the subject knows where he/she must fix the gaze.

Finally, in this paper, we found parameters independent from the age. Any alteration in these ocular variables would

be due to potential neurological disease and this analysis is particularly interesting from a clinical or research point of view.

VII. CONCLUSION

In this article, we presented a systematic procedure to measure eye movements and data analysis for healthy adults. In order to consider eye movements a biomarker for normal ageing and thus assist in the diagnosis of neurodegenerative diseases, it is necessary to define a standard such as we presented in this article.

The results delivered show that the performance of the eye movements decreases with age and values for the main variables were presented. Most of the parameters show there are linear variations with the age, except duration and latency of the reflexive saccades in the antisaccade test.

This systematic procedure is going to be used with patients with different types of neurodegenerative disorders such as Alzheimer's dementia, frontotemporal dementia, Parkinson's disease, and parkinsonisms to get an easy-to-use and non-invasive biomarker to assist in the diagnosis of these diseases.

The next step is to research on eye movement patterns in different neurodegenerative diseases that improve the actual process of diagnosis in a faster and more reliable way.

REFERENCES

[1] O. V. Acuna, P. Aqueveque, and E. J. Pino, "Eye-tracking capabilities of low-cost EOG system," in *Proc. 36th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.*, Chicago, IL, USA, Aug. 2014, pp. 610–613.

[2] D. A. Robinson, "A method of measuring eye movement using a scleral search coil," *IEEE Trans. Bio-Med. Electron.*, vol. BME-10, no. 4, pp. 137–145 Oct. 1963.

[3] S. Aungsakun, A. Phinyomark, P. Phukpattaranont, and C. Limsakul, "Robust eye movement recognition using EOG signal for human-computer interface," in *Software Engineering and Computer Systems*, vol. 180, J. M. Zain, W. M. Wan Mohd, and E. El-Qawasmeh, Eds. Berlin, Germany: Springer, 2011, pp. 714–723.

[4] C. Atmaji, A. E. Putra, and A. Hanif, "Sliding window method for eye movement detection based on electrooculogram signal," in *Proc. Int. Conf. Inf. Commun. Technol. (ICOIACT)*, Yogyakarta, India, Mar. 2018, pp. 628–632.

[5] M Penhaker, T Štula, and M Cerny, "Automatic ranking of eye movement in electrooculographic records," in *Proc. 2nd Int. Conf. Comput. Eng. Appl.*, Bali, Island, 2010, pp. 456–460.

[6] N. M. M. Noor and M. Q. Bin Kamarudin, "Study the different level of eye movement based on electrooculography (EOG) technique," in *Proc. IEEE EMBS Conf. Biomed. Eng. Sci. (IECBES)*, Kuala Lumpur, Dec. 2016, pp. 792–796.

[7] J. Park, Y. Kong, and Y. Nam, "A low-cost video-oculography system for vestibular function testing," in *Proc. 39th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. (EMBC)*, Seogwipo, South Korea, Jul. 2017, pp. 4078–4081.

[8] J. Naruniec, M. Wieczorek, S. Szlufik, D. Koziorowski, M. Tomaszewski, M. Kowalski, and A. Przybyszewski, "Webcam-based system for video-oculography," *IET Comput. Vis.*, vol. 11, no. 2, pp. 173–180, Mar. 2017.

[9] R. Wierts, R. Wierts, R. Wierts, M. J. A. Janssen, M. J. A. Janssen, M. J. A. Janssen, H. Kingma, H. Kingma, H. Kingma, and H. Kingma, "Measuring saccade peak velocity using a low-frequency sampling rate of 50 Hz," *IEEE Trans. Biomed. Eng.*, vol. 55, no. 12, pp. 2840–2842, Dec. 2008.

[10] C. E. G. Cena, "Device for synchronized measure of ocular and cephalic movements," Europe Patent EP 3 241 488 A1, Nov. 8, 2017.

[11] R. J. Leigh and D. S. Zee, *The Neurology of Eye Movements*, 5th ed. New York, NY, USA: Oxford Univ. Press, 2015.

[12] R. Dodge, "Five types of eye movement in the horizontal meridian plane of the field of regard," *Amer. J. Physiol.-Legacy Content*, vol. 8, no. 4, pp. 307–329, Jan. 1903.

[13] P. Termsarasab, T. Thammongkolchai, J. C. Rucker, and S. J. Frucht, "The diagnostic value of saccades in movement disorder patients: A practical guide and review," *J. Clin. Movement Disorders*, vol. 2, no. 1, pp. 2–14, Dec. 2015.

[14] N. Noiret, N. Carvalho, É. Laurent, G. Chopard, M. Binetruy, M. Nicolier, J. Monnin, E. Magnin, and P. Vandel, "Saccadic eye movements and attentional control in Alzheimer's disease," *Arch. Clin. Neuropsychol.*, vol. 33, no. 1, pp. 1–13, Feb. 2018, doi: 10.1093/arclin/acx044.

[15] Q. Yang, T. Wang, N. Su, S. Xiao, and Z. Kapoula, "Specific saccade deficits in patients with Alzheimer's disease at mild to moderate stage and in patients with amnestic mild cognitive impairment," *Age*, vol. 35, no. 4, pp. 1287–1298, Aug. 2013.

[16] E. Petregiani and L. M. Optican, "Eye movement in Parkinson's disease and inherent Parkinsonian syndromes," *Frontiers Neurol.*, vol. 8, pp. 1–7, 2017, Art. no. 592.

[17] Y. Terao, H. Fukuda, Y. Ugawa, and O. Hikosaka, "New perspectives on the pathophysiology of Parkinson's disease as assessed by saccade performance: A clinical review," *Clin. Neurophysiol.*, vol. 124, no. 8, pp. 1491–1506, Aug. 2013.

[18] C. Meyniel, S. Rivaud-Pèchoux, P Damier, and B Gaymard, "Saccade impairments in patients with fronto-temporal dementia," *Neurol. Neurosurg. Psychiatry*, vol. 76, pp. 1581–1584, 2005, doi: 10.1136/jnnp.2004.060392.

[19] R. A. Armstrong, "Visual signs and symptoms of progressive supranuclear palsy," *Clin. Experim. Optometry*, vol. 94, no. 2, pp. 150–160, Mar. 2011.

[20] K. Holmqvist, N. Nystrom, R. Andersson, R. Dewhurst, H. Jarodzka, and J. Van de Weijer, *Eye Tracking: A Comprehensive Guide to Methods and Measures*. Oxford, U.K.: Oxford Univ. Press, 2011.

[21] N. Catz and P. Their, "Neural control of saccadic eye movements," *J. Dev. Ophthalmol.*, vol. 40, pp. 52–75, Feb. 2007.

[22] R. Levy and P. S. Goldman-Rakic, "Segregation of working memory functions within the dorsolateral prefrontal cortex," *Exp. Brain Res.*, vol. 133, no. 1, pp. 23–32, 2000.

[23] C. Antoniades, U. Ettinger, B. Gaymard, I. Gilchrist, A. Kristjánsson, C. Kennard, R. John Leigh, I. Noorani, P. Pouget, N. Smyrnis, A. Tarnowski, D. S. Zee, and R. H. S. Carpenter, "An internationally standardised antisaccade protocol," *Vis. Res.*, vol. 84, pp. 1–5, May 2013.

[24] C. Pierrot-Deseilligny, R. M. Müri, T. Nyffeler, and D. Milea, "The role of the human dorsolateral prefrontal cortex in ocular motor behavior," *Ann. New York Acad. Sci.*, vol. 1039, no. 1, pp. 239–251, Apr. 2005.

[25] K. Johnston, M. J. Koval, S. G. Lomber, and S. Everling, "Macaque dorsolateral prefrontal cortex does not suppress saccade-related activity in the superior colliculus," *Cerebral Cortex*, vol. 24, no. 5, pp. 1373–1388, May 2014.

[26] L. Selemon and P. Goldman-Rakic, "Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: Evidence for a distributed neural network subserving spatially guided behavior," *J. Neurosci.*, vol. 8, no. 11, pp. 4049–4068, Nov. 1988.

[27] C. Pierrot-Deseilligny, R. M. Müri, C. J. Ploner, B. Gaymard, S. Demeret, and S. Rivaud-Pechoux, "Decisional role of the dorsolateral prefrontal cortex in ocular motor behaviour," *Brain*, vol. 126, no. 6, pp. 1460–1473, Jun. 2003.

[28] E. Hernández, S. Hernández, D. Molina, R. Acebrón, and C. G. Cena, "OSCANN: Technical characterization of a novel gaze tracking analyzer," *Sensors*, vol. 18, no. 3, p. 522, Feb. 2018, doi: 10.3390/s18020522.

[29] A. J. Larrazabal, C. E. García Cena, and C. E. Martínez, "Video-oculography eye tracking towards clinical applications: A review," *Comput. Biol. Med.*, vol. 108, pp. 57–66, May 2019.

[30] B. H. Anderton, "Ageing of the brain," *Mech. Ageing Develop.*, vol. 123, no. 7, pp. 811–817, Apr. 2002.

[31] R. I. Scahill, C. Frost, R. Jenkins, J. L. Whitwell, M. N. Rossor, and N. C. Fox, "A longitudinal study of brain volume changes in normal aging using serial registered magnetic resonance imaging," *Arch. Neurol.*, vol. 60, no. 7, pp. 989–994, Jul. 2003.

[32] F. M. Gunning-Dixon and N. Raz, "Neuroanatomical correlates of selected executive functions in middle-aged and older adults: A prospective MRI study," *Neuropsychologia*, vol. 41, no. 14, pp. 1929–1941, Jan. 2003.

[33] R. Cabeza, "Cognitive neuroscience of aging: Contributions of functional neuroimaging," *Scandin. J. Psychol.*, vol. 42, no. 3, pp. 277–286, Jul. 2001.

[34] R. M. Eenshuistra, K. R. Ridderinkhof, and M. W. V. D. Molen, "Age-related changes in antisaccade task performance: Inhibitory control or working-memory engagement?" *Brain Cognition*, vol. 56, no. 2, pp. 177–188, Nov. 2004.

[35] T. J. Crawford, E. S. Smith, and D. M. Berry, "Eye gaze and aging: Selective and combined effects of working memory and inhibitory control," *Frontiers Hum. Neurosci.*, vol. 11, p. 563, Nov. 2017.

[36] C. Klein, F. Foerster, K. Hartnegg, and B. Fischer, "Lifespan development of pro- and anti-saccades: Multiple regression models for point estimates," *Develop. Brain Res.*, vol. 160, no. 2, pp. 113–123, Dec. 2005.

[37] A. Peltsch, A. Hemraj, A. Garcia, and D. P. Munoz, "Age-related trends in saccade characteristics among the elderly," *Neurobiol. Aging*, vol. 32, no. 4, pp. 669–679, Apr. 2011.

[38] J. Fernandez-Ruiz, A. Peltsch, N. Alahyane, D. C. Brien, B. C. Coe, A. Garcia, and D. P. Munoz, "Age related prefrontal compensatory mechanisms for inhibitory control in the antisaccade task," *NeuroImage*, vol. 165, no. 165, pp. 92–101, Jan. 2018.

[39] P. L. Chen and L. Machado, "Age-related deficits in voluntary control over saccadic eye movements: Consideration of electrical brain stimulation as a therapeutic strategy," *Neurobiol. Aging*, vol. 41, pp. 53–63, May 2016.

[40] A. C. Bowling, E. A. Hindman, and J. F. Donnelly, "Prosaccade errors in the antisaccade task: Differences between corrected and uncorrected errors and links to neuropsychological tests," *Exp. Brain Res.*, vol. 216, no. 2, pp. 169–179, Jan. 2012.

[41] J. B. Mirsky, H. W. Heuer, A. Jafari, J. H. Kramer, A. K. Schenk, I. V. Viskontas, B. L. Miller, and A. L. Boxer, "Anti-saccade performance predicts executive function and brain structure in normal elders," *Cognit. Behav. Neurol.*, vol. 24, no. 2, pp. 50–58, Jun. 2011.

[42] N. Noiret, B. Vigneron, M. Diogo, P. Vandel, and É. Laurent, "Saccadic eye movements: What do they tell us about aging cognition?" *Aging, Neuropsychol., Cognition*, vol. 24, no. 5, pp. 575–599, Sep. 2017.

[43] J. Hellmuth, J. Mirsky, H. W. Heuer, A. Matlin, A. Jafari, S. Garbutt, M. Widmeyer, A. Berhel, L. Sinha, B. L. Miller, J. H. Kramer, and A. L. Boxer, "Multicenter validation of a bedside antisaccade task as a measure of executive function," *Neurology*, vol. 78, no. 23, pp. 1824–1831, Jun. 2012.

DAVID GÓMEZ ANDRÉS received the M.D. and Ph.D. degrees. In his Ph.D. project, he applied data mining techniques to gait data in cerebral palsy. His training was in Hospital Universitario La Paz and Universidad Autónoma de Madrid. He works as a Child Neurologist and a Researcher with the Child Neurology Department, Hospital Universitari Vall d'Hebron, a well-known reference center in Barcelona, Spain. He is currently a Child Neurologist and a Neuroscientist. Moreover, he is a Co-Founder of Aura Innovative Robotics. He holds one patent registered internationally and has authored over 100 international scientific publications. Apart from gait analysis, his research has been oriented to rare neurological disorders, especially in neuromuscular disorders.

CECILIA E. GARCíA CENA was a Visiting Professor with Universidad Carlos III (UC3M), Madrid, Spain. She is leading the robotics medical applications with the Robots and Intelligence Machine Research Group, Centre for Automation and Robotics (CAR). She has been the Head Director of National Research and Development Projects and a Research Member of European Projects. Since 2016, she has been an Expert Evaluator for European Commission in Robotics topics. Since 2015, she has been strongly involved in the development of medical devices with clinical and social applications. She is currently an Assistant Professor of automation and robotics with the Universidad Politécnica de Madrid (UPM), Madrid, and a Visiting Professor with Ecoles Universitaries Gimbernat, Cantabria, Spain. She has authored over 60 international scientific publications. She holds four patents, two of them registered internationally.

IRENE PULIDO VALDEOLIVAS received the degree in medicine from the Universidad Autónoma de Madrid, in 2010, and the Ph.D. degree in neuroscience *(summa cum laude)* from Universidad Autónoma de Madrid. In her Ph.D. project, using new data analysis tools, she analysed the different gait patterns of patients with hereditary spastic paraplegia. She completed her training as a Neurologist with University Hospital La Paz, Madrid. She is currently a part of the Visual Pathway Laboratory inside the Group of Pathogenesis and New Therapies, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). Moreover, she is a Co-Founder of Aura Innovative Robotics. Her clinical tasks are focused on adults with multiple sclerosis and other immune-mediated central nervous system disorders. She holds one patent registered internationally.

• • •