

Eye movement biomarkers allow for the definition of phenotypes in Gaucher Disease

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1 **Title Page**

2

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5

6 **Title:** Eye movement biomarkers allow for the definition of phenotypes in Gaucher Disease

7

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23

1 **Abstract**

2 **Background**

3 Neurological forms of Gaucher disease, the inherited disorder of β -Glucosylceramidase caused by bi-
4 allelic variants in *GBA1*, is a progressive disorder which lacks a disease-modifying therapy. Systemic
5 manifestations of disease are effectively treated with Enzyme Replacement Therapy (ERT), however,
6 molecules which cross the blood-brain barrier are still under investigation. Clinical trials of such
7 therapeutics require robust, reproducible clinical endpoints to demonstrate efficacy and clear phenotypic
8 definitions to identify suitable patients for inclusion in trials.

9
10 The single consistent clinical feature in all patients with neuronopathic disease is the presence of a
11 supranuclear saccadic gaze palsy, in the presence of Gaucher disease this finding serves as diagnostic of
12 'type 3' Gaucher disease.

13
14 **Methods**

15 We undertook a study to evaluate saccadic eye movements in Gaucher patients and to assess the role of
16 the EyeSeeCam in measuring saccades. The EyeSeeCam is a video-oculography device which was used to
17 run a protocol of saccade measures. We studied 39 patients with non-neurological Gaucher disease (type
18 1), 21 patients with type 3 (neurological) disease and a series of 35 healthy controls. Mean saccade
19 parameters were compared across disease subgroups.

20
21 **Results**

22 We confirmed the saccadic abnormality in patients with type 3 Gaucher disease and identified an
23 unexpected subgroup of patients with type 1 Gaucher disease who demonstrated significant saccade
24 parameter abnormalities. These patients also showed subtle neurological findings and shared a *GBA1*
25 variant.

26
27 **Conclusions**

28 This striking novel finding of a potentially attenuated type 3 Gaucher phenotype associated with a
29 specific *GBA1* variant and detectable saccadic abnormality prompts review of current disease
30 classification. Further, this finding highlights the broad spectrum of neuronopathic Gaucher phenotypes
31 relevant when designing inclusion criteria for clinical trials.

32
33 **Key Words**

34 rare disease, neuronopathic, saccades, video-oculography, eye tracker, ocular-motor, neurodegenerative
35 disease

36
37

1 **Manuscript Text**

2

3 **Background**

4 Gaucher Disease is a Lysosomal Storage Disorder (LSD) resulting from deficiency of β -
5 Glucosylceramidase (glucocerebrosidase), a lysosomal enzyme which hydrolyses the substrate
6 glucosylceramide; a sphingolipid. Deficiency is secondary to recessively inherited mutations of the
7 *GBA1* gene (OMIM: 606463). The predominant phenotype results in hepatosplenomegaly, bone
8 marrow dysfunction resulting in thrombocytopenia, anaemia and bone disease. Accumulation of
9 substrate in other tissues such as the liver or lungs can result in additional disease morbidity,
10 patients with disease isolated to these systemic tissues are considered to have non-neuronopathic
11 'type 1' Gaucher disease. A clinically more severely effect group of patients have substrate
12 accumulation in the CNS and their disease-course is variable. Those with a rapidly progressive form
13 in the neonatal period and who die within the first two years of life have 'type 2' acute
14 neuronopathic disease and those with a slower, more progressive neurological phenotype have
15 been termed 'type 3' or 'chronic neuronopathic'. 'Neuronopathic Gaucher Disease' has been defined
16 as Gaucher disease with neurological signs or symptoms which cannot be attributed to any other
17 pathology[1] and, more recently, refined by an expert consensus group to be a biochemical and
18 genetic Gaucher disease with the clinical finding of a gaze palsy[2]. A notable exception to the
19 definition are those patients with Gaucher-related Parkinson's Disease (PD) in whom there is clearly
20 neurological feature (PD) however the primary mechanism is associated with *GBA1* mutation rather
21 than CNS Gaucher cell accumulation.

22

23 In the early 1990s treatment for Gaucher Disease was established[3], Enzyme Replacement Therapy
24 (ERT) revolutionised the lives of patients, halting the progression of established systemic disease
25 features and reversing some. Insufficient and ineffective ERT penetration of the blood-brain barrier
26 (BBB) means that central substrate accumulation persists in patients with neuronopathic

1 phenotypes and the neuropathology, although demonstrated[4], remains poorly understood. The
2 clinical features and course of CNS disease is markedly heterogenous.

3

4 In the 1970s, case reports identified a series of patients with neuronopathic disease who had
5 saccadic eye movement abnormalities[5,6] and it is now accepted that saccade initiation failure,
6 followed by slowing of saccades and eventual saccadic palsy are universal clinical features of
7 neuronopathic disease[1,7]. The consistency of this finding has, to date, been limited by the
8 difficulty in measuring eye movements in clinical settings. Furthermore, being able to clinically
9 detect them is a skill requiring experience, particularly in children. Subtle compensatory techniques
10 are often adopted by children, which confirm the presence of the pathology; these include excessive
11 blinking to initiate saccades or 'head thrusting' to aid in moving the eyes towards the target[8].

12

13 The relationship between horizontal saccade abnormalities and the neuropathology of nGD is not
14 well understood. In mouse models of disease, focal microglial activation in the area of the Substantia
15 Nigra Reticulata and the Reticulotegmental Nucleus of the Pons (Nucleus of Bechterew)[9] has been
16 demonstrated. The generation of saccades is within the Paramedian Pontine Reticular Formation
17 (PPRF), part of the reticular formation which runs parallel to the pontine nucleus and extends
18 throughout the brainstem[10]. It is likely that that pathology in this area; as demonstrated by Wong
19 et al.[4] is responsible for the clinical sign but the vulnerability of this region to the disease process
20 has not been explained.

21

22 Normal saccades are fast, *generally* voluntary, conjugate eye movements which enable rapid
23 alteration of fixation[11]. They are best exemplified by the movement of the eyes while reading.
24 Measures of saccadic movement include velocity, gain (a measure of accuracy in generating a
25 desired amplitude of saccade in response to target), latency (the time taken to initiate a saccade in
26 response to the appearance of the target) and duration. Historical methods of measuring

1 oculomotor function have included the invasive, scleral search coil technique[12], infrared light
2 methods[13], video-oculography (VOG) and electrooculography (EOG). EOG involves application of
3 electrodes to skin surrounding the eyes and detects eye movements through electrical impulses
4 generated by eye movements, this method although less invasive, is less accurate and vulnerable to
5 artefact from muscle tension underlying the electrodes[14]. Contemporary video-oculography offers
6 a method which is acceptable to patients and is increasingly being demonstrated to show consistent
7 accuracy.

8

9 Interest in saccadic eye movements in Gaucher disease has gained increasing attention as our
10 understanding of Gaucher disease is changing. The aforementioned unexplained relationship
11 between variants of *GBA1* and Parkinson's Disease[15] has encouraged further evaluation of the
12 spectrum of Gaucher phenotypes. Furthermore, as more detailed phenotyping is undertaken and
13 increasing numbers of international cohorts of patients are being described, the spectrum of
14 neurological involvement in Gaucher disease is expanding[16].

15

16 The greatest interest in oculomotor function in Gaucher disease is the pursuit of quantifiable
17 outcome measures for therapeutic trials for neuronopathic disease. Given the variability in clinical
18 features and rate of disease progression, a good biomarker is required to demonstrate efficacy of
19 novel drugs. To date, no robust biochemical or clinical measure has been identified. As saccadic
20 function is impaired in all patients with nGD, it is the single clinical feature which has potential to be
21 measured and which has been previously used as measure in interventional trials[17].

22

23 Here we report on the experience in the UK of measuring saccadic eye movements using video-
24 oculography (EyeSeeCam) in Gaucher Patients with type 1 and type 3 disease. We evaluated 60
25 patients and 29 healthy controls with a view to replicating the previously reported slowing of
26 saccadic movements in patients with neuronopathic disease[18], evaluating the role of longitudinal

1 analysis for disease monitoring and outcome measure development and examining the role of such
2 a device in supporting diagnosis of neuronopathic disease.

3

4

5 **Methods**

6

7 Participants

8

9 A total of 60 Patients with Gaucher disease were recruited from seven specialist centres in the UK
10 and underwent video-oculographic assessment (for details of the protocols, see Recordings of eye
11 movements). For inclusion, patients were at least five years of age at enrolment and had a
12 biochemical and genetic diagnosis of Gaucher disease[19,20]. All participants consented to study
13 procedures according to full ethical approvals (UK research ethics committee approval 16/WA/0129;
14 Wales NHS REC Bangor; IRAS 192163) and provided their written and informed consent.

15

16 Although examination was undertaken in 21 patients with type 3 Gaucher disease, only 14 were
17 adequate for comprehensive analysis; similarly, 39 patients with GD-T1 were examined and only 36
18 were suitable for inclusion (total analysed Gaucher cohort; $n=50$). Analysis was made difficult in the
19 presence of significant strabismus, excessive compensatory blinking or such profound palsy that no
20 saccadic movement was recordable clinically. The patients with nGD excluded from comprehensive
21 analysis had the most profound saccadic impairments.

22

23 The Gaucher cohort ($n=50$, median age 32 years, range 5—77 years) comprised two groups of
24 patients that were included in the final statistical analysis: (GD-T1) Patients with a clinical diagnosis
25 of ‘type 1’ Gaucher disease ($n=36$, age 38 years, range 5—77 years), and (nGD) patients with ‘type 3’
26 Gaucher disease ($n=14$, age 23 years, range 17—33 years). The patient classification was provided by

1 the clinician caring for the patient (all experts in LSD management) and was consistent with the
2 traditional phenotypic approach to categorisation of GD-T1 as Gaucher disease ‘with lack of early
3 onset central nervous system (CNS) involvement’[2]. Diagnosis of nGD typically requires the
4 presence of a saccadic gaze palsy as the earliest manifestation of CNS involvement in GD with
5 subsequent development of other neurological features, given the expertise of the clinical teams
6 caring for these patients the clinical categorisation used to manage the patients care was adopted
7 for the purposes of this study. Patient screening for the study consisted of confirmation of
8 biochemical and genetic diagnosis of Gaucher disease; the clinical examination and phenotypic
9 categorisation was not part of the screening process.

10

11

12 For comparison, healthy controls ($n=35$, age 40 years, range 23—59 years) were recruited from a
13 single research centre. None of the healthy volunteers had any clinically significant medical or
14 psychiatric condition. All participants underwent a clinical examination of saccadic eye movements
15 prior to video-oculographic recordings in order to define the eye providing the ‘better quality’ in the
16 presence of strabismus or palsy. Any clinically detectable (on examination) abnormality of saccadic
17 movements was recorded during this time and, as later discussed, had not been previously reported
18 for some patients in the GD-T1 group by the caring clinician at time of screening; they therefore
19 remained in the disease type group for the duration of the study, no reclassification of disease was
20 made during the study period.

21

22 Recording of eye movements

23 Measurements took place in an acoustically shielded and softly lit environment. Participants were
24 seated with their head stabilised by an adjustable chin rest facing a specially dedicated computer
25 screen at an eye-to-screen distance of $d=60\text{cm}$. Some children did not tolerate the chin rest and
26 stabilised their heads with their hands. Monocular eye movements were video-oculographically

1 recorded using the headmounted EyeSeeCam® device (EyeSeeTec GmbH, Munich, Germany)
2 operating at temporal sampling rate of 220Hz[21] . The room lighting was dimmed to maximise both
3 patient' focus and video recording of the pupillary motion. Patients were instructed to keep their
4 head as motionless as possible and attentive focus on the series of target spot motion on the screen.

5

6 The stimulus protocol was adapted from Bremova-Ertl and colleagues[18] and comprised a
7 calibration sequence followed by visually-guided reflexive prosaccades. All participants were
8 instructed to re-fixate to the new target spot as rapidly and as accurately as possible and to withhold
9 any unwanted gaze shifts. Verbal encouragement was offered to track the target motion and to
10 minimize head movement and blinking where possible.

11

12 Prosaccades were pseudo-randomly elicited in vertical and horizontal direction by presenting target
13 spots ($d=1.33^\circ$) at the screen. Vertical saccades were elicited by target steps of $\pm 10^\circ$ and $\pm 20^\circ$ within
14 a target range of $\pm 10^\circ$ with respect to the central position. Horizontal saccades were elicited by
15 target steps of $\pm 15^\circ$ and $\pm 30^\circ$ within a target range of $\pm 15^\circ$ with respect to the central position.

16 Targets for both vertical and horizontal direction were presented for a pseudo-random duration
17 ranging from 2.5s—3.0s. Each target step was repeated seven times in order to increase the
18 probability of measuring a number of saccades that is sufficient for statistical analysis in patients
19 with difficulties in performing saccades. The overall protocol lasted at most five minutes.

20

21 Analysis of eye movements

22 An interactive MATLAB®-based software package as shipped with the EyeSeeCam® device was used
23 for the analysis of eye movement traces. Prior to event detection in the recordings, noise reduction,
24 deletion of artefacts such as blinks was performed. The recordings obtained from the calibration
25 sequence was used to map the 'raw' signal to the 'true' orthogonalized eye position. An
26 acceleration-based saccade detection algorithm for search coil data was used and adapted to

1 automatically extract 1) saccade amplitude, 2) saccade peak velocity, 3) duration, and 4) reaction
2 time from the eye tracker data with respect to the stimulus amplitude. All cases were visually
3 inspected for proper saccade detection. In case for incorrect automatic saccade detection, the onset
4 and offset of the respective saccades was manually performed. Slow saccades that did not meet
5 detection criteria were manually selected.

6

7 Saccade performance parameters

8

9 Saccade performance is expressed in four saccade parameters including 1) reaction time, 2) saccade
10 duration, 3) peak saccade velocity, and 4) saccade gain for each stimulus direction, i.e. left, right, up,
11 and down resulting in a total of 4x4=16 parameters.

12

13 The *reaction time* is almost independent of the saccade trajectory properties (duration, velocity,
14 etc.) and is therefore provided as the average value.

15

16 The *saccade duration* D increases as a function of eye amplitude A and can be adequately modelled
17 within a restricted range for $5^\circ < A < 50^\circ$ as

18

$$D(A) = D_0 + k \cdot A$$

19 with linear model parameters D_0 and k to be estimated for each individual [22].

20

21 *Peak saccade velocity* increases nonlinearly as a function of saccade amplitude. The exponential
22 relationship

23

$$V_{\text{peak}}(A) = V_{\text{max}} \left(1 - e^{-\frac{A}{A_c}} \right)$$

24 produces very satisfactory fits [23] where A_c denotes an individual amplitude constant and V_{max}

25 indicates the individual saturation velocity at large amplitudes ($A \rightarrow \infty$).

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Saccades are frequently dysmetric and commonly undershoot the target for amplitudes $A > 10^\circ$. The mismatch between Target T and saccade amplitude A can be expressed as the error amplitude $\epsilon = T - A$ which is an approximately linear function of the target distance:

$$\epsilon(T) = d \cdot (T - T_0)$$

The slope d is the rate of error amplitude increase and T_0 a ‘neutral’ target distance were saccades are on average hit the target[22]; both parameters vary across individuals. Targets $T > T_0$ commonly undershoot the target. A common measure of target-saccade amplitude mismatch is the *saccade gain* G which is the proportion between saccade amplitude A and target distance T and can therefore be expressed as a function of the error amplitude as follows:

$$G(T) = 1 - \frac{\epsilon(T)}{T}$$

All saccade trajectory characterising parameters, i.e. saccade duration, saccade peak eye velocity, and saccade gain, are computed for each individual and stimulus direction as the readout from the respective fit at 20° and finally subjected to the statistical analysis (see Statistical Analysis section below).

Computing reference ranges for healthy controls

Reference ranges were computed from the healthy control cohort ($n=29$) in order to quantitatively appreciate the VOG measurement in the patient cohorts. The 95% prediction intervals (PI) were calculated by assuming a normal distribution for the respective parameter as follows:

$$PI_{95\%} = mean \pm t_{0,975,n-1} \cdot sd \cdot \sqrt{(n+1)/n}$$

Statistical Analysis

SPSS 23 (Version 23.0.0.0, 2015; IBM Corporation, Armonk, New York) was used for statistical data analysis. Data on participants’ demographic features and eye movement parameters were provided

1 as median (interquartile range). Non-parametric inference statistics were used for hypothesis testing
2 between groups as the values for patients' groups cannot be assumed to be normally distributed.
3 Fisher's exact test was applied for categorical variables and Kruskal-Wallis analysis of variances or
4 Wilcoxon- Mann-Whitney-*U*-test on ranks for continuous variables. In case of comparing three or
5 more groups, Kruskal-Wallis analysis of variances on ranks was followed in the event of significance
6 ($p < 0.05$) by Dunn's multiple comparison test for pairwise post-hoc contrasts. Spearman's rank order
7 correlation coefficient was used to describe the relationships between different scores. All statistical
8 tests were 2-sided with $p < 0.05$ indicating statistical significance; p -values were adjusted for multiple
9 testing using family-wise error correction when contrasts were not driven by a specific hypothesis.

10

11 **Results**

12 Reference ranges from healthy controls

13 Out of a total of 35 healthy controls (HC), data was considered suitable for the final statistical
14 analysis in 29. In those who it was considered 'unsuitable' this was a result of poor or incomplete
15 saccade recordings caused by eye makeup which generated excessive artefact, participants falling
16 asleep during the task, significant head movement artefact or technical failures of the recording.

17

18 Saccade parameters for left and right (mean values arithmetically averaged) were not statistically
19 related to age as indicated by Spearman rank order correlations with (1) peak saccade velocity as
20 obtained by a readout from the non-linear fit of the main sequence for an amplitude of 30° ($\rho = -0.04$;
21 $p = 0.86$), (2) mean saccade gain ($\rho = -0.08$; $p = 0.71$), (3) mean saccade duration ($\rho = -0.19$; $p = 0.37$), and
22 (4) response time ($\rho = 0.40$; $p = 0.059$). It is of note, that correlation between age and response time
23 revealed a clear (but not significant) trend for increasing response time across the lifespan.

24

25 In order to investigate saccade performance in Gaucher disease, reference ranges for controls were
26 computed. Table 1 summarises the reference ranges (95% prediction interval) for the control cohort

1 ($n=29$) for each of the investigated oculomotor parameters. In addition, **Figure 1a—4a** show the
 2 reference range for the main sequence which was obtained by computing the reference range for
 3 readouts at given amplitudes (i.e., 0° , 1° , 2° , ...) from the individual's non-linear ($V_{max}-V_{max}*\exp(-A/A_c)$)
 4 fit along their main sequence.

5
 6 *Table 1*

	Mean value	reference range
<u>Response time¹</u>		
left / ms	205	144—267
right / ms	213	149—277
up / ms	197	147—246
down / ms	213	145—281
<u>Saccade duration²</u>		
left / %	99	76—122
right / %	98	74—123
up / %	113	58—167
down / %	118	75—161
<u>Saccade peak velocity³</u>		
left (10°) / ($^\circ/s$)	325	244—405
left (20°) / ($^\circ/s$)	448	338—556
right (10°) / ($^\circ/s$)	312	240—385
right (20°) / ($^\circ/s$)	447	342—552
up (10°) / ($^\circ/s$)	316	236—397
up (20°) / ($^\circ/s$)	443	293—594
down (10°) / ($^\circ/s$)	310	238—382
down (20°) / ($^\circ/s$)	398	299—497
<u>Saccade gain⁴</u>		
left / %	94	85—103
right / %	90	80—101
up / %	88	70—105
down / %	97	80—116

7 **Table 1: Reference ranges.** Data are provided as the population mean and the 95% prediction
 8 interval as computed for the healthy control cohort ($n=29$). ¹Time duration from target onset to
 9 saccade onset. ²Time duration from saccade onset to saccade end obtained from readouts of the
 10 linear amplitude –saccade duration fit at 20° for each individual. ³Peak saccade velocity obtained
 11 from readouts at 10° and 20° from the individual's fit along the main sequence. ⁴Ratio of saccade

1 amplitude and target amplitude obtained from readouts of the target distance—gain fit at 20° for
2 each individual.

3
4

5 Quantitative analysis of saccade performance in Gaucher disease

6

7 Saccade performance in patients with Gaucher disease (Type 1 and Type 3) was compromised in all
8 aspects, i.e. response time, saccadic duration, peak eye velocity, and saccadic gain.

9

10 Compared to controls, nGD patients presented considerably longer response times in all directions
11 (Kruskal-Wallis $p < 0.0035$, post-hoc $p < 0.0051$, family-wise error corrected) whereas response times
12 between Gaucher subtype 1 and 3 did not statistically differ (post-hoc $p > 0.124$). GD-T1 patients
13 presented longer response times than controls, an effect that was significant for leftwards (post-hoc
14 $p = 0.0044$) and upwards (post-hoc $p < 0.0001$) gaze.

15

16 Saccade duration was statistically different across groups (Kruskal-Wallis $p < 0.038$). Saccades in nGD
17 vs. controls were significantly prolonged in all directions (post hoc $p < 0.031$, family-wise error
18 corrected). Post-hoc testing for nGD vs GD-T1 revealed prolonged saccade duration for horizontal
19 saccades ($p < 0.0007$) but not in vertical direction ($p > 0.099$). Post-hoc testing indicated prolonged
20 saccades between GD-T1 and controls for horizontal ($p < 0.032$) but not for vertical saccades
21 ($p = 0.585$).

22

23 As expected, main sequence analysis of peak saccade velocity readout from the main sequence
24 function at the amplitude of 20° indicated a significant difference between nGD (Type 3) and
25 controls (Kruskal-Wallis $p < 0.0007$, post-hoc Dunn's test, $p < 0.0013$). Surprisingly, however, there was
26 a significant difference in peak saccade velocity also between GD-T1 and controls (post-hoc,
27 $p < 0.017$, family-wise error corrected), with the exception of downward peak velocities ($p = 0.267$).

28

1 Saccade gain analysis revealed hypometric saccades in nGD vs. controls (Kruskal-Wallis $p < 0.034$,
 2 post-hoc leftwards and downwards, $p < 0.0025$, family-wise error corrected), but was similar in GD-T1
 3 and controls ($p > 0.123$).

4
 5

6 Subgroup saccade analysis in type 1 Gaucher disease (GD-T1)

7

8 To further investigate the difference in patients with type 1 Gaucher disease relative to controls
 9 (which was not expected), their peak eye velocities were compared with the reference range (for
 10 definition see below) at the individual level. Abnormal peak saccade velocities (velocities below the
 11 reference range according to Table 1) were demonstrated in 19 (56%) patients with type 1 Gaucher
 12 disease (of $n = 36$). In five patients the velocity was slowed in two or less measures of vertical gaze,
 13 which is less specifically relevant to saccade abnormalities in Gaucher disease. An examination of the
 14 clinical characteristics of the fourteen GD-T1 patients who had abnormality of saccade velocities in
 15 three or more measures was therefore undertaken with a view to identifying unifying features; see
 16 Table 2.

17
 18 *Table 2*

Age	Age Dx	Age at ERT	Genotype	Spleen	Gaucher Related Co-morbidities	Number of velocity measures abnormal	Direction of abnormality	Clinical Saccade Abnormality
53	5	32	R463C/RecNcil	S	Liver Disease	4	Left & Right	Y
49	19	37	R463C/RecNcil	S		6	All	Y
55	47	47	R262G/RecNcil		Abnormal Neurology	4	Left, right, down	Y
48	4	25	R463C/IVS2+1	S	Liver Disease & Lung Disease	6	Left, right, down	Y
77	56	57	R463C/L444P		Lung Disease	6	Left, right, up	Y
15	8	8	R463C/R257Q			8	All	
70	6	54	R463C/G377R	S	Lung Disease	5	All	Y
64	6	46	R463C/RecNcil	S	Cognitive Impairment	6	Left, right, down	Y

18	3	3	R463C/N462K		4	Left & down	
73	48	56	R463C/L444P	S	6	All	Y
31	5	6	R463C/L444P		8	All	Y
43	2	27	R463C/L444P	S	8	All	
16	3	3	R463C/RecNcil		3	Right & down	
12	11mo	1	H311R/R359Q		4	Left & Right	Y

1 *Dx: Diagnosis; Age given in years; Genotype: Traditional GBA1 variant nomenclature used; R463C (p.Arg502Cys); RecNcil*
2 *(recombinant consisting of multiple pseudo-gene derived point mutations); L444P (p.Leu483Pro); IVS2+1 (Splice site variant*
3 *c.115+1G>A); G377R (p.Gly416Arg); R262G (p.Arg301Gly); R257Q (p.Arg296Gln); N462K (p.Asn501Lys).*

4 *S: Splenectomised; Y: Yes/Present *Genotype documented but not confirmed*

5
6 The striking shared feature is presence of the *GBA1* variant p.Arg502Cys (c.1504C>T; traditional
7 nomenclature: R463C) in 12 of 14 of these patients. When correlated with clinical examination, a
8 very subtle defect of eye movements (clinical saccade slowing or delayed initiation) was identifiable
9 in most patients.

10
11 The identification of a fourth subgroup (Gaucher Type 1 with an R463C mutation) enabled us to
12 refine the cohorts and re-perform the statistical analysis for saccade parameters across all groups.
13 The Gaucher cohort ($n=50$) comprised three groups of patients that were included in a second
14 statistical analysis: GD-T1; patients with a clinical diagnosis of 'type 1' Gaucher disease without
15 R463C mutation ($n=18$); R463C patients with type 1 Gaucher disease and a single allele with an
16 R463C mutation ($n=18$) and (nGD) patients with 'type 3' Gaucher disease ($n=14$). Saccade
17 performance in patients with Gaucher disease with the refined subgroups is comprehensively
18 summarized in **Figure 1—4**. Kruskal-Wallis analysis on ranks for mean saccadic eye movement
19 parameters (i.e., peak eye velocity, saccadic gain, saccadic duration, and response time) across these
20 four groups (GD-T1, R463C, nGD, controls) revealed statistically significant differences for each
21 parameter in left (**Figure 1**), right (**Figure 2**), up (**Figure 3**), and down (**Figure 4**) direction ($p<0.0043$)
22 with an exception of right saccade gain (**Figure 2b**) and response time (**Figure 2d**), and upward

1 saccade gain (**Figure 3b**). Relative to controls, post-hoc testing using Dunn's test followed by family
2 wise error correction revealed that saccade performance was impaired in all patient groups (reduced
3 peak velocities, hypometric saccades, prolonged saccade duration and response times).

4
5
6 **Figure 1: Saccade performance left.** (a) Main sequence with individual's data points and 95% prediction
7 interval (red solid lines) with statistics of peak saccade velocities obtained from readouts at given eye
8 amplitudes (left and right lower panel) from the individual's non-linear ($V_{max} \cdot \exp(-A/A_c)$) fit along the
9 main sequence. (b) Saccade gain computed as the ratio of saccade amplitude and target amplitude. (c) Time
10 duration from saccade onset to saccade end. (d) Response time as the time difference from target onset to
11 saccade onset. Provided p -values resulted from Kruskal-Wallis analysis on ranks across groups, i.e. controls,
12 Gaucher disease type 1 (GD-T1), Gaucher disease type 1 with R463C mutation (R463C), and Gaucher Disease
13 type 3 (NGD). Statistically significant differences of post-hoc Dunn's test are indicated by * $p < 0.05$; ** $p < 0.01$;
14 *** $p < 0.001$. All p -values are adjusted for multiple comparisons using the family-wise error rate.

15
16
17 **Figure 2: Saccade performance right.** (a) Main sequence, (b) saccade gain, (c) time duration, and (d) response
18 time. See Caption Figure 1 for details.

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23 **Figure 3: Saccade performance up.** (a) Main sequence, (b) saccade gain, (c) time duration, and (d) response
24 time. See Caption Figure 1 for details.

25
26 **Figure 4: Saccade performance down.** (a) Main sequence, (b) saccade gain, (c) time duration, and (d) response
27 time. See Caption Figure 1 for details.

28 29 **Discussion**

30 This study was undertaken to evaluate the use of video-oculography as a tool to measure saccadic
31 eye movement parameters in Gaucher Disease. We have replicated the previously reported data
32 showing lower peak velocity in horizontal and vertical saccadic eye movements in nGD patients
33 versus a control cohort[13,18,24,25]; although the specific values in the cohort are slightly higher
34 than those reported by Bremova-Ertl et al.[18] the difference between the values is consistent. The
35 ability to replicate data findings between disease states is supportive of a role for such a device for

1 clinical use. However, the lack of a large cohort study showing normative values in healthy controls
2 is a limitation of implementation.

3
4 Saccadic eye movements in the context of Gaucher disease are becoming increasingly important.
5 Defects in saccade initiation are thought to be the earliest sign of CNS involvement in Gaucher
6 disease and are eagerly pursued at time of diagnosis to help offer patients and families prognosis.
7 However, as we enter an era in Gaucher disease with increasing treatment options and clinical trials,
8 determination of disease categorisation is becoming ever more important[26,27]. Therapeutic
9 strategy and eligibility for interventional trials is determined, in part, by which disease 'type' a
10 patient has been categorised as.

11
12 In this series we have been able to show, using this non-invasive quick test and measuring just a few
13 parameters, that patients with different disease types (and now also different genotypes) can be
14 differentiated on the basis of saccadic parameters. However, we also were *unable* to report
15 objectively on the saccadic movements of several patients with known, profound defects.
16 Furthermore, we only successfully examined six patients aged 12 years and younger; the youngest
17 two patients were aged five years at time of recording, one with type 1 disease and one with type 3
18 disease; a six-year-old with type 3 disease also underwent examination but the quality of the
19 recordings (due to severity of abnormality) limited detailed analysis. A further two patients with
20 profound type 3 disease weren't approached for examination in view of their difficulties in
21 cooperating with instructions and ability to remain still for the duration of testing. This inability to
22 use the EyeSeeCam in all settings raises questions about its utility in diagnosing saccadic eye
23 movement problems. However, for those with profound deficits or profound Gaucher-related
24 neurology which prevents examination, there generally is no diagnostic uncertainty, therefore the
25 role for the EyeSeeCam in confirming diagnostic category is with the patients in whom the clinical

1 findings are subtle or equivocal, typically a group of patients who are able to cooperate and tolerate
2 this examination.

3

4 The most striking finding in this study was a cohort of patients who had been phenotypically
5 categorised as having type 1 Gaucher disease but who have significantly slower saccadic eye
6 movements than healthy controls and generally more severe systemic phenotypes than would be
7 expected of type 1 Gaucher disease. Some such patients also had subtle additional neurological
8 features which hadn't previously been explained. Although these findings were all subtle and hadn't
9 provoked the attention of their caring physician (which suggests minimal functional impact), it
10 prompts consideration of each individual's future prognosis which in the current environment of
11 pursuit of CNS-penetrant therapy they may be excellent candidates for. We also have not examined
12 the saccadic eye movements of patients with Parkinson's disease in this study or patients with
13 Gaucher-related Parkinson's disease, the neuropathophysiology of which, remains elusive. Slowing
14 of saccades may be indicative of such evolving pathology[28]. Many historical reports exist of varying
15 neurological features in type 1 Gaucher disease which have yet to be truly untangled in their
16 relationship to both Gaucher disease and Gaucher-related Parkinson's disease[29–33].

17

18 The unifying feature of these patients with GD-T1 and saccadic abnormalities, was the presence of a
19 *GBA1* variant, p.Arg502Cys (R463C), most frequently seen here associated with a second 'severe' or
20 previously described 'neuronopathic' variant on the opposing allele. This variant has been previously
21 implicated in neuronopathic disease and specifically in the development of saccadic slowing[34].

22 R463C is also present in three of the patients in the type 3 cohort examined, all who had an adult
23 diagnosis of type 3 disease. Although in many other rare diseases, clinical assessment of phenotype
24 has been superseded by genotype evaluation; genotype: phenotype correlations in Gaucher disease
25 is incomplete and continues to be disputed. This in part reflects the vast number of variants (>400
26 reported to date) but also the marked phenotypic heterogeneity displayed. It is thought that

1 multiple environmental and genetic modifiers are implicated in explaining the spectrum of disease
2 encountered[30,35–37]., Only very few *GBA1* pathogenic mutations have shown consistent
3 phenotype correlation [44] and therefore clinical evaluation remains the primary source of such
4 prediction. As more detailed methods of characterising the *GBA1* variants in the disease are
5 established, larger cohorts are reported, and more detailed longitudinal phenotyping is undertaken,
6 we may see that a greater relationship between genotype and phenotype exist which offers
7 opportunities for therapeutic stratification.

8

9 The study also aimed to evaluate the role of the EyeSeeCam as an outcome measure for clinical and
10 trial purposes. Correlation with markers of disease severity in this setting is particularly difficult,
11 given the lack of other robust biomarker of neuronopathic disease. The modified Severity Scoring
12 Tool (mSST)[38] was designed and implemented as a clinical tool for this purpose and has shown
13 utility, however a component of the tool includes saccadic eye movement deficits and the cohort
14 presented here with objective measures with neuronopathic disease was small. Correlation has been
15 demonstrated with vertical saccade duration and mSST previously[18,24] but a larger cohort study is
16 required and ideally a more detailed scoring tool or biomarker to demonstrate CNS involvement.

17

18 *Limitations*

19 A larger cohort of control data confirming any subtle differences in saccade parameters by age
20 would be of value. Observations from this cohort of controls may not have been adequately
21 powered to demonstrate significant statistical difference by age; however previous studies (using
22 various devices to measure saccadic movements) have shown that with increasing age, peak saccade
23 velocity is reduced[39]. Saccade latency is also determined partly by specific areas in the cerebral
24 cortex and is therefore vulnerable to greater variability, even in children, latency changes with age in
25 some studies[40]. The lack of Paediatric controls is a limitation to interpretation, previous studies
26 have shown that saccade velocities are stable throughout the paediatric age groups and match those

1 of adult cohorts[40,41]. The saccadic slowing identified in the GD-T1 group however would not be
2 thought to reflect age-related saccadic changes given the significant number of young adults they
3 were found in. Other potential confounders; fatigue, caffeine intake or mental health diagnoses
4 which may affect oculomotor function were not controlled for in either healthy controls or disease
5 groups; these should be considered in future studies as they have potential to impact oculomotor
6 parameters[42,43].

7

8 **Conclusion**

9 This study showed that a subgroup of patients with type 1 Gaucher disease and a shared *GBA1*
10 mutation all had significantly slowed saccades suggestive of a greater phenotypic spectrum of
11 Gaucher disease than previously described.

12

13 Video-oculography devices such as the EyeSeeCam have utility in objectively measuring eye
14 movements in patients with mild to moderate defects or in cases where clinical examination is
15 inconclusive. This is useful in the context of Gaucher disease, where presence of oculomotor
16 abnormalities determines disease categorisation and may indicate prognostic differences and
17 therefore alter therapeutic strategies. Given the rarity of the disease and delays in expert
18 assessment, objective methods of measuring consistent clinical features to support such
19 categorisation is essential and even greater in the setting of interventional clinical trials; larger
20 datasets are needed to establish this as part of standard clinical assessments and to define the
21 pathological thresholds of the various oculomotor parameters.

22

23 This study has highlighted a broader spectrum of type 3 Gaucher disease, indicating that features of
24 neuronopathic disease may not be discernible until later in life, future studies and evaluation of
25 these patients over time will aid in understanding the clinical relevance of this for these patients.

26 These findings also highlight the need for repeated clinical assessment of patients following

1 diagnosis. Although not a focus of the reported data, the high burden of non-neurological Gaucher
2 disease complications in the GD-1 R463C cohort was noted and may reflect the greater systemic
3 disease experienced by patients with nGD. Furthermore, these observations raise the question of
4 the utility of current phenotypic categorisation of Gaucher disease for patients where the disease
5 descriptions are becoming increasingly heterogeneous.

6

7 **Abbreviations**

8 LSD : Lysosomal Storage Disorder

9 CNS : Central Nervous System

10 ERT : Enzyme Replacement Therapy

11 BBB : Blood Brain Barrier

12 nGD : Neuronopathic Gaucher Disease

13 VOG : Video-Oculography

14 EOG : Electro Oculography

15 HC : Healthy Control

16

17 **Declarations**

18

19 **Ethics approval and consent to participate**

20 This study was undertaken with UK research ethics committee approval (REC: 16/WA/0129; Wales NHS
21 REC Bangor; IRAS 192163) and was therefore undertaken in accordance with the ethical standards laid
22 down in the 1964 Declaration of Helsinki and its later amendments. All participants provided informed
23 written consent prior to study inclusion.

24

25 **Consent for publication**

26 All participants provided informed written consent prior to study inclusion which included consent for
27 publication.

28

29 **Availability of data & material**

30 The datasets used and/or analysed during the current study are available from the corresponding author
31 on reasonable request.

32

33 **Competing interests**

34 No authors have any conflicts of interest with the study sponsors.

35 ES is general manager and shareholder of EyeSeeTec GmbH.

36

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39 Association (registered charity: 1095657) and Manchester Foundation Trust Willink Research Unit.

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41 A Donald (first author) was funded through an MRC grant on the study GAUCHERITE.

42

43 **Authors Contributions**

44 AD: Conceived, designed and undertook all study procedures. Analysed data collected and author of
45 manuscript.

46 MG: Saccadic data analysis and manuscript writing

1 CYT; AC; DAH; RS; DC: equally contributed patient data, supported study recruitment and offered
2 manuscript review.
3 SB: Saccadic data analysis
4 SAJ: Study design and contributed significantly to contextual interpretation of results
5 ES: Saccadic data analysis and manuscript writing.
6
7

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14 Donald.
15
16

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Figures

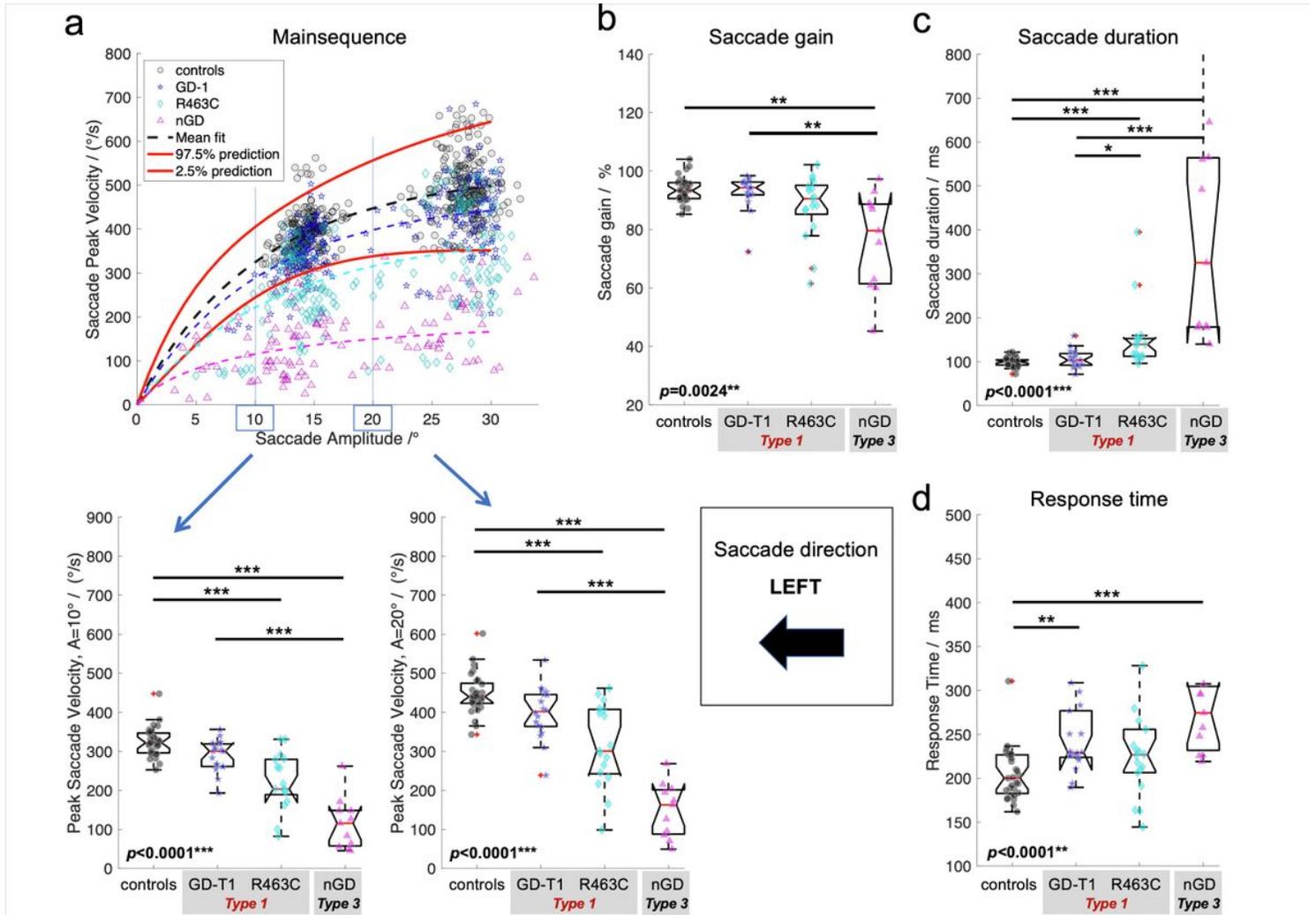


Figure 1

Saccade performance left. (a) Main sequence with individual's data points and 95% prediction interval (red solid lines) with statistics of peak saccade velocities obtained from readouts at given eye amplitudes (left and right lower panel) from the individual's non-linear ($V_{max}-V_{max} \cdot \exp(-A/A_c)$) fit along the main sequence. (b) Saccade gain computed as the ratio of saccade amplitude and target amplitude. (c) Time duration from saccade onset to saccade end. (d) Response time as the time difference from target onset to saccade onset. Provided p-values resulted from Kruskal-Wallis analysis on ranks across groups, i.e. controls, Gaucher disease type 1 (GD-T1), Gaucher disease type 1 with R463C mutation (R463C), and Gaucher Disease type 3 (NGD). Statistically significant differences of post-hoc Dunn's test are indicated by * $p<0.05$; ** $p<0.01$; *** $p<0.001$. All p-values are adjusted for multiple comparisons using the family-wise error rate.

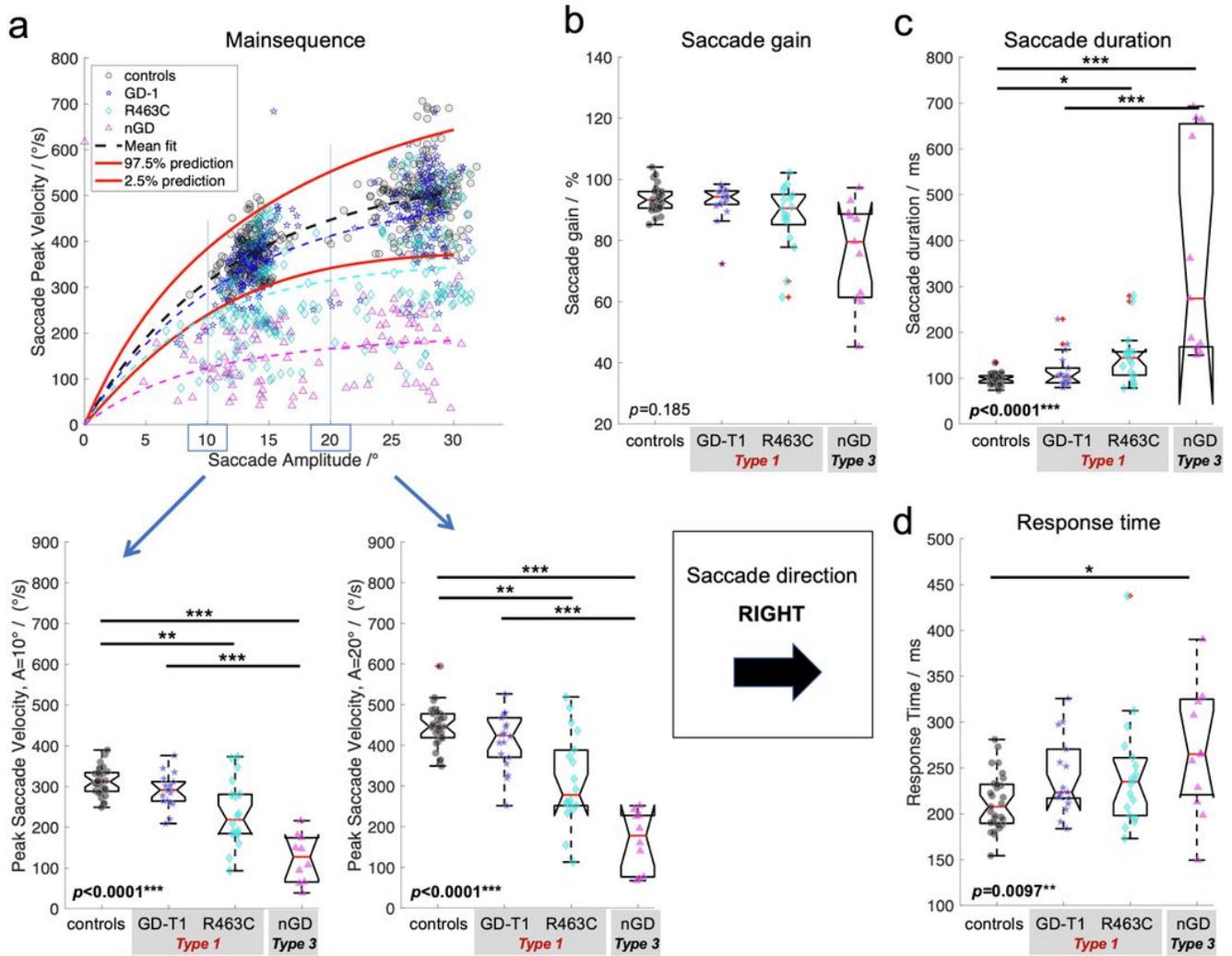


Figure 2

Saccade performance right. (a) Main sequence, (b) saccade gain, (c) time duration, and (d) response time. See Caption Figure 1 for details.

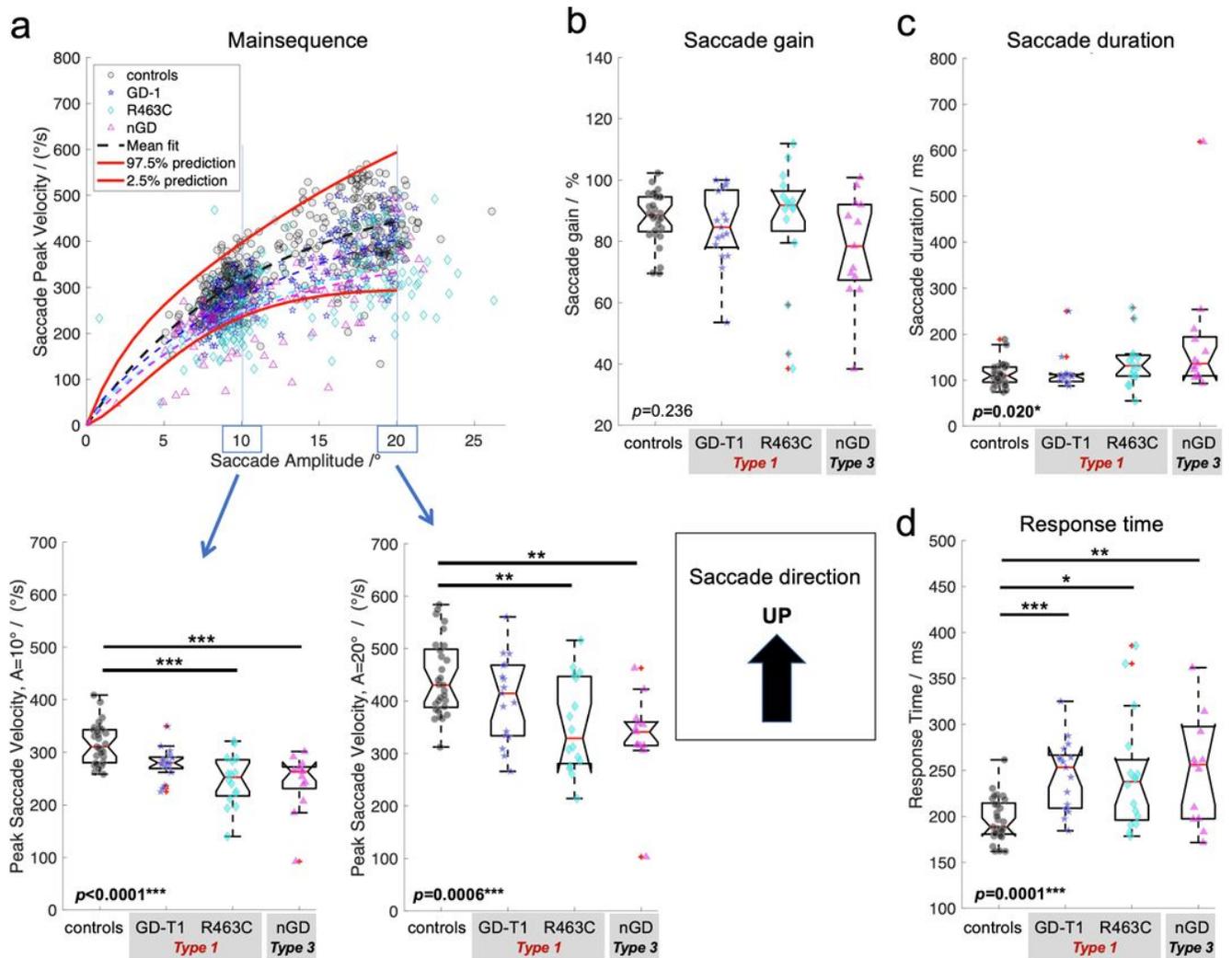


Figure 3

Saccade performance up. (a) Main sequence, (b) saccade gain, (c) time duration, and (d) response time. See Caption Figure 1 for details.

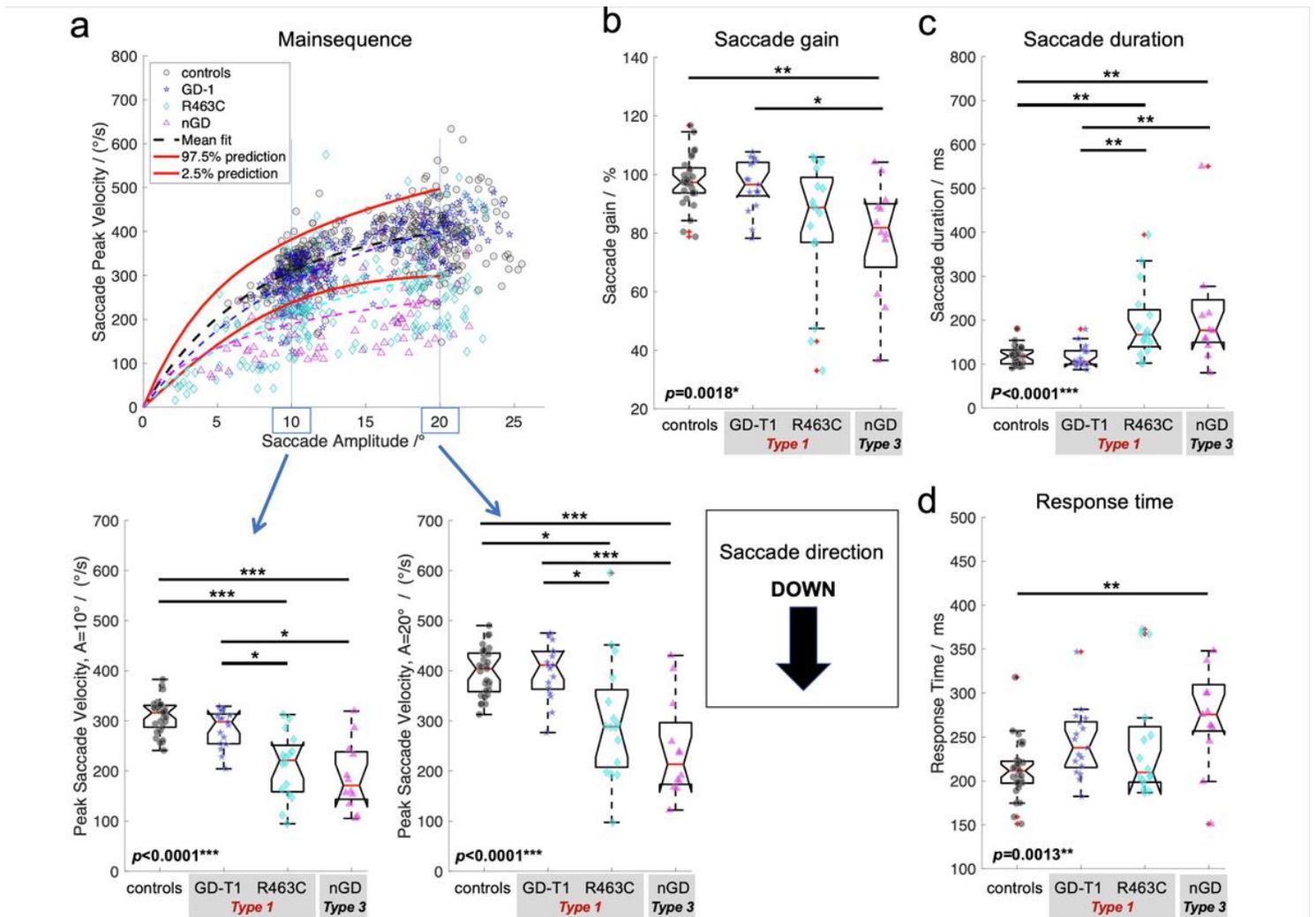


Figure 4

Saccade performance down. (a) Main sequence, (b) saccade gain, (c) time duration, and (d) response time. See Caption Figure 1 for details.