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*Published in:*  
Clinical Parkinsonism and Related Disorders

*DOI:*  
[10.1016/j.prdoa.2022.100170](https://doi.org/10.1016/j.prdoa.2022.100170)

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2022

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Grillini, A., Koens, L. H., Lizaitiene, G., Lange, F., Cornelissen, F. W., & Tijssen, M. A. J. (2022). Measuring saccades in patients with Niemann-Pick type C: A comparison between video-oculography and a novel eye tracking test based on continuous psychophysics. *Clinical Parkinsonism and Related Disorders*, 7, Article 100170. <https://doi.org/10.1016/j.prdoa.2022.100170>

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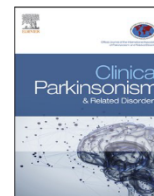
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## Short Communications

## Measuring saccades in patients with Niemann-Pick type C: A comparison between video-oculography and a novel eye tracking test based on continuous psychophysics

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## ARTICLE INFO

## Keywords:

Eye movement disorders  
Vertical supranuclear gaze palsy  
Niemann-Pick type C  
VOG  
SONDA

## ABSTRACT

**Introduction:** Vertical supranuclear gaze palsy is a key feature of Niemann-Pick type C (NP-C) and is commonly quantified using video-oculography (VOG). VOG requires sitting still for long times and performing specific tasks, thus it can be challenging or impossible for patients severely affected by movement disorders or cognitive impairment. To overcome this limitation, we measure saccades of NP-C patients using a fast eye tracking test based on continuous psychophysics and compare it to VOG.

**Methods:** Saccades of six NP-C patients and six age-matched controls were assessed using VOG and Standardized Oculomotor and Neuro-ophthalmic Disorders Assessment (SONDA). In SONDA, participants continuously track a semi-randomly moving dot on a computer screen while their gaze is being tracked. For both assessments, saccades were quantified using four conventional measures: amplitude, gain, latency, and peak velocity. Furthermore, SONDA's continuous measures were quantified with several novel spatio-temporal properties.

**Results:** In the NP-C patients, both methods revealed reduced amplitude, gain, peak velocity, and increased latency of vertical saccades compared to horizontal saccades and compared to healthy controls. Effect sizes obtained with SONDA were overall larger than those for VOG. SONDA's spatio-temporal properties showed similar trends.

**Conclusion:** SONDA reveals a deterioration of vertical saccades in NP-C patients that is consistent with VOG. SONDA's measures based on continuous psychophysics are consistent with traditional saccadic parameters and can potentially provide complementary information. SONDA shows larger effect sizes than VOG, suggesting that it provides robust and clinically relevant outcomes with a more intuitive task and shorter testing time.

### 1. Introduction

Niemann-Pick disease type C (NP-C) is an autosomal recessive lysosomal lipid storage disorder, caused by mutations in the *NPC-1* or *NPC-2* gene. The incidence of NP-C is estimated to be 1 in 100,000 live births

but is likely under-diagnosed in adults [1,2].

The clinical presentation of NP-C is very heterogeneous, with an age of onset ranging from infancy until adult age. The adult-onset manifestation includes gelastic cataplexy, movement disorders (mainly ataxia, myoclonus, and dystonia), cognitive impairment, or psychosis [1–4].

**Abbreviations:** VOG, Video-oculography; SONDA, Standardized Oculomotor and Neuro-ophthalmic Disorders Assessment; NP-C, Niemann-Pick type C; VSGP, Vertical supranuclear gaze palsy.

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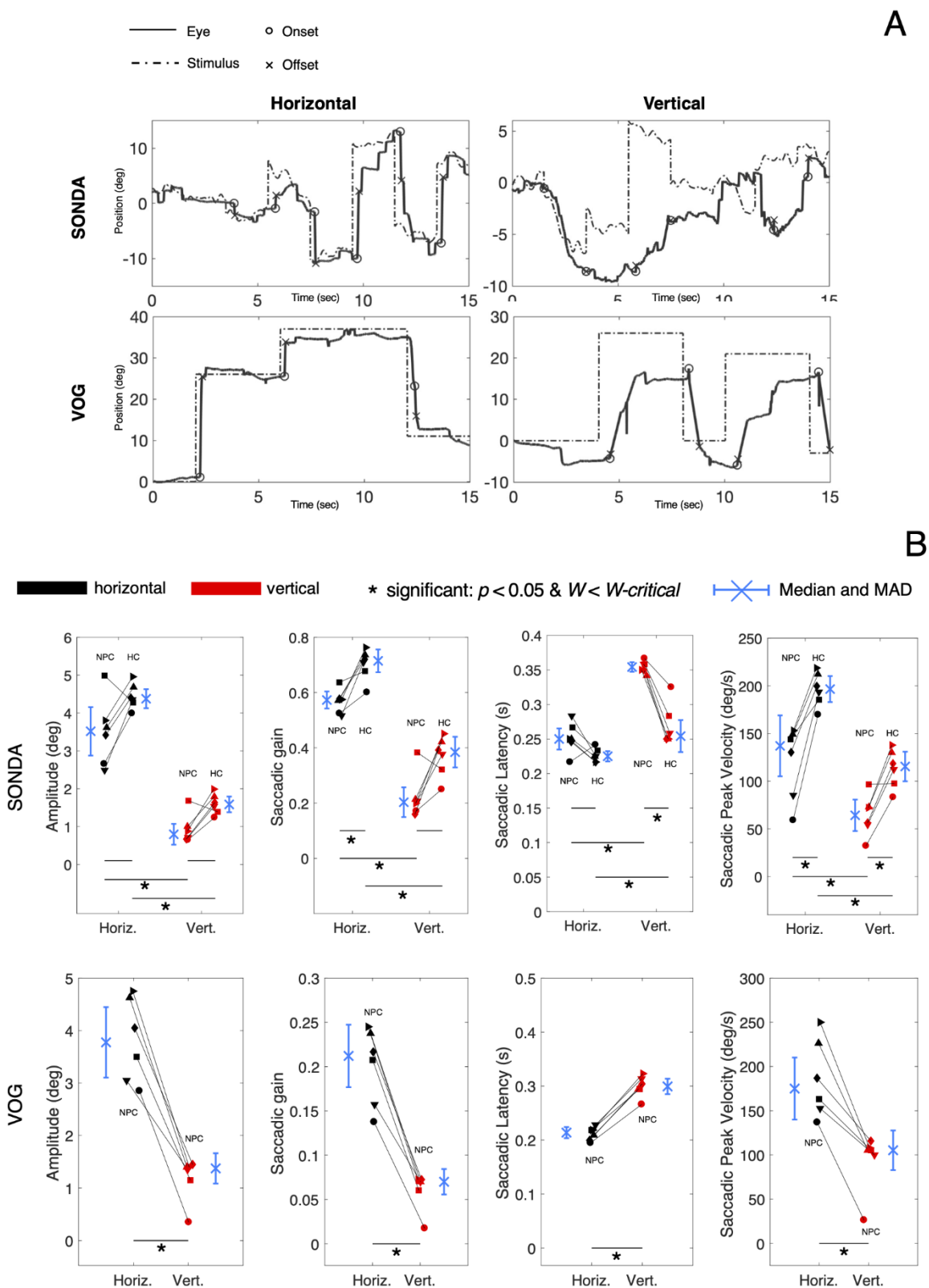
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<https://doi.org/10.1016/j.prdoa.2022.100170>

Received 9 June 2022; Received in revised form 29 September 2022; Accepted 23 October 2022

Available online 26 October 2022

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**Fig. 1.** Conventional saccadic parameters (amplitude, gain, latency, and peak velocity) in SONDA and VOG. A. Time-series of gaze data obtained with SONDA (upper panel) and VOG (lower panel). The stimuli had comparable spatial ranges, leading to saccades with amplitudes prevalently between 0 deg and 20 deg. Both methods showed a robust identification of visually evoked saccades. B. Comparisons of conventional saccadic parameters between NP-C patients and age-matched controls, and between horizontal and vertical saccades, measured with SONDA and VOG. On each scatterplot, the blue X mark is the median, the error bars are the Mean Absolute Deviations. The black horizontal lines indicate the pair-wise comparisons used for statistical testing. Each age-matched patient-control pair is indicated by connected dots with matching symbols. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Furthermore, vertical supranuclear gaze palsy (VSGP) is a key feature. It is detected in 66 % of the patients with NP-C [4], although this might be an underestimation as it is frequently overlooked [5].

VSGP is characterized by a paralysis of voluntary and reflexive vertical saccades, especially downward, whereas smooth pursuit is initially spared [6]. When patients attempt to make a vertical saccade, a so-called “round-the-houses” phenomenon can be found in which the eyes do not move directly up or down, but in a lateral arc instead. Histopathological examination in NP-C patients shows neuronal loss in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) with sparing of the interstitial nucleus of Cajal and oculomotor neurons, leading to VSGP [6]. When the disease progresses, the paramedian pontine reticular formation (PRRF), involved in horizontal saccades, gets also affected. Cerebellar atrophy is correlated to reduced gain, and impairment of the frontal lobes influences the initiation of voluntary saccades and suppression of unwanted reflexive saccades [7].

In patients with NP-C, quantifying eye movements, and in particular saccadic abnormalities, is important to follow-up disease progression and to evaluate the effect of treatment [8]. In clinical practice, video-oculography (VOG) is used to measure eye movements, using a camera that tracks the pupils during various tasks, including saccades, smooth pursuit, optokinetic reflexes, and vestibulo-ocular reflexes. A VOG can be challenging for patients who are severely affected by movement disorders or cognitive impairment, which is often the case for patients with Niemann-Pick type C. The video goggles can be weighty or uncomfortable, it requires sitting still for 30–45 min, and patients have to perform specific tasks [9]. This makes that a VOG cannot be performed in patients who are severely affected by NP-C, as results may not be reliable.

To overcome this limitation, we assess saccades of NP-C patients using a continuous psychophysics-based approach and compare it to VOG. Continuous psychophysics measures the perception of an observer by modeling behavioral responses as time-varying signals (e.g., the gaze position in the function of time), instead of repeating the presentation of a stimulus with discrete trials, like in traditional psychophysics.

The continuous psychophysics approach is used in the Standardized Oculomotor and Neuro-ophthalmic Disorders Assessment (SONDA), a test developed by our group and partially based on the Eye-Movement Cross-correlogram [10]. It provides a novel way to quantify eye movements. A camera tracks the pupil of an individual who continuously tracks a semi-randomly moving dot on a computer screen. The advantage of this test is that it takes less than three minutes and does neither require stable fixation nor manual motor responses. SONDA was used before in patients with other neurological conditions and showed characteristic patterns of spatio-temporal properties (STP) of oculomotor behavior per disorder [11]. These properties can assume different patterns depending on the neurological condition of the patients, and it has been shown to measure aspects of saccades that can go undetected by conventional measures, such as the main sequence (the relationship between saccadic amplitude and peak velocity) [11].

In this pilot study, we compare the results of saccadic eye movement measurements in patients with NP-C and age-matched controls acquired with conventional VOG and SONDA to assess whether these results correspond.

## 2. Methods

We assessed six patients with genetically confirmed NP-C and six healthy, age-matched controls. Every participant gave their informed consent. The study followed the tenets of the Declaration of Helsinki and was approved by the Medical Ethical Committee of the University Medical Center Groningen.

The SONDA data were acquired using an eye-tracker “Eyelink Portable Duo” (SR-Research, Ontario, Canada) at a sampling rate of 120 Hz, while VOG data were acquired at a sampling rate of 100 Hz. The SONDA task consisted of six trials of 20 s each, where the participant had

to follow with their gaze a small dot (~0.5 deg) moving in a smooth random-walk path with interleaved displacements in a random direction every 2 s. This relatively slow pace ensures that each saccade can be completed before another stimulus displacement is initiated. Calibration took approximately 90 s.

The VOG task consisted of a standard battery of tests, including saccades, smooth pursuit, and optokinetic reflexes, and was performed as part of the regular clinical follow-up of the patients. For this study, we did only use the measurements of the saccadic movements in which the stimulus was displaced alternatively in horizontal, vertical, and diagonal directions, also with intervals of 2 s between each displacement. The VOG took approximately 10 min for settling the patient and calibration, and 5 min for testing the saccades.

To make the two methods directly comparable, the raw gaze recordings of both methods were analyzed using an identical algorithm to selectively detect the saccades evoked by the stimulus. For both methods, the algorithm classifies the first event where the ocular velocity exceeds 30 deg/s occurring within one second from the stimulus displacement onset as the start of a visually evoked saccade. Then, a saccadic event is considered over when the ocular velocity returns below 30 deg/s. In both methods, for each visually evoked saccade, we measured its amplitude, peak velocity, gain (computed as the ratio between its amplitude and the amplitude of the stimulus displacement), and latency in regard to the stimulus.

In addition, for SONDA, the spatio-temporal properties (STP) of eye movements were computed as described earlier by Grillini et al. 2020 [11]. The STP in this study are 4 parameters that describe different aspects of continuous visual tracking performance: *lag* (between stimulus and ocular velocity), *uncertainty* (computed as the standard deviation of the gaussian fit to the cross-correlation between stimulus and ocular velocity), *error spread* (computed as the standard deviation of the distribution of tracking errors) and *dissimilarity* (computed as 1 minus the cosine similarity between stimulus and eye positions). We compared each STP between horizontal and vertical saccades, and between NP-C patients and age-matched controls.

To account for small sample sizes (unavoidable due to the extremely low prevalence of NP-C), the possible presence of outliers, and non-normal data distributions, all statistical comparisons are performed with Wilcoxon Signed Rank (a non-parametric test for paired data), with Bonferroni correction for multiple comparisons. Given the small samples, the p-values alone cannot be reliably used to established statistical significance, which in this case is determined also using the *W* value of the Wilcoxon Signed Rank test (see [Table 2 Supplementary Information](#)). Effect size is computed with equation:

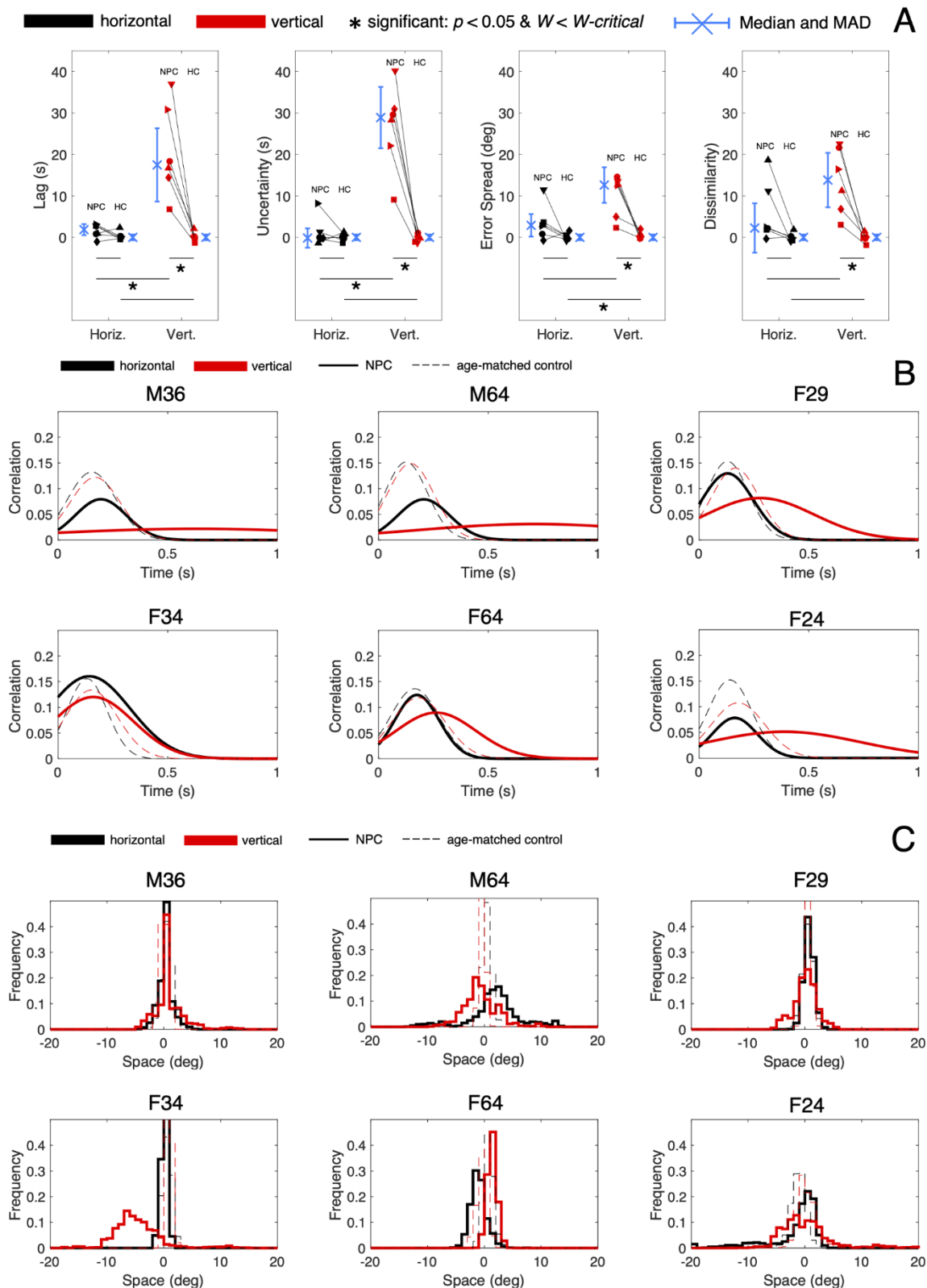
$$effectsize = Z_{val}/\sqrt{N}$$

Comparisons with p-values smaller than 0.05, *W* values equal to 0, and effect size larger than 0.8, are considered to be statistically significant and clinically relevant.

## 3. Results

The NP-C patients (two males, four females, age 24–64 years) all showed VSGP and movement disorders during neurological examination. Five of them had cognitive impairment. Patient characteristics can be found in [Table 1 in the Supplementary Information](#).

[Fig. 1-A](#) shows examples of gaze recordings obtained with SONDA (upper panel) and VOG (lower panel). Both methods have a sampling rate sufficiently high to allow for automatic classification of visually evoked saccades, which onsets and offsets are indicated in the plots by respectively circles and crosses. [Fig. 1-B](#) shows conventional saccadic parameters: amplitude, gain, latency, and peak velocity compared with horizontal (in black) and vertical (in red) axes, and with NP-C patients (NPC) and healthy controls (HC). Both VOG and SONDA show statistically significant differences between vertical saccades of NP-C patients



**Fig. 2.** Spatio-temporal properties analysis. A. Comparisons of spatio-temporal properties (STP) between NP-C patients (circles) and age-matched controls (triangles), and between horizontal and vertical saccades, measured with SONDA. The STP are normalized as z-scores computed using the age-matched parameters as normative values. The blue X marks are the group medians of NP-C and age-matched controls, respectively; error bars represent MAD. The black horizontal lines indicate the pair-wise comparisons used for statistical testing. Each age-matched patient-control pair is indicated by connected dots with matching symbols. B. Normalized correlograms obtained from the cross-correlation between stimulus velocity and ocular velocity. Each plot represents an NP-C patient coupled with their age-matched control. The code on top of each plot indicates sex and age. C. Probability density distributions of tracking errors, computed as the difference between stimulus position and gaze position. Each plot represents an NP-C patient coupled with their age-matched control. The code on top of each plot indicates sex and age. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and controls, for all parameters in exam.

Analogously, in Fig. 2-A, the STP of SONDA show a statistically significant deterioration of tracking performance of NP-C patients compared to their age-matched controls, only when tracking along the vertical axis. Using SONDA spatio-temporal analysis, the differences can be better examined at an individual level as well. Fig. 2-B shows the cross-correlograms between stimulus and ocular velocity that are used to compute the STP lag and uncertainty. The code above each plot indicates sex and age. In all but one case, the vertical component of the cross-correlogram of the NP-C patient is flatter, indicating higher uncertainty in tracking, and is delayed compared to their control counterpart. Participant F34 is the exception, where the cross-correlogram is flatter, but not delayed. Fig. 2-C shows the distribution of tracking errors that are used to compute the STP error spread and dissimilarity. Again, in most cases, the vertical component shows wider distributions (indicating lower spatial precision, e.g., F29), offset distributions (indicating lower spatial accuracy, e.g., F64), or both (e.g., F34).

#### 4. Discussion

In this study, we compare different ways to measure saccades in patients with NP-C. Conventionally, VOG is used to quantify VSGP, however, this can be difficult for NP-C patients with movement disorders or cognitive disturbances. In this paper, we show that measuring saccades with SONDA gives analogous results to VOG about the impairment of vertical saccades.

VSGP was demonstrated in both VOG and SONDA, showing vertical saccades that are smaller, slower, and less precise than their horizontal counterparts and their age-matched controls. These differences are captured by all parameters in exam (saccadic parameters: amplitude, gain, latency, peak velocity and spatio-temporal properties: lag, uncertainty, error spread, dissimilarity) in both VOG and SONDA. The differences showed are substantial for both methods tested.

Furthermore, the SONDA method allows for the measurement of eye movement spatio-temporal properties (STP). Previous studies showed that, when combined with each other, the STP can discriminate between different neurological conditions [11]. Here, we showed that the STP can be used to also detect a selective deterioration of vertical tracking performance that is congruent with measurements done using conventional saccadic parameters. Unlike the conventional saccadic parameters which highlighted differences across most comparisons, the STP showed to be more selective in detecting VSGP (i.e. a specific deterioration of vertical eye movement of NP-C patients compared to an age-matched healthy control). This can potentially indicate a promising clinical relevance. However, the VOG records not only saccades and smooth pursuit but also other modalities of eye movements that are affected in NP-C patients, such as optokinetic reflexes and vestibulo-ocular reflexes, which is not the case for SONDA at present.

A potential benefit of using the STP based on continuous psychophysics instead of (or together with) conventional saccadic parameters, is that STP capture different aspects of the visual processing that elicit saccades. The conventional saccadic parameters are the result of repeated discrete measures of individual saccades, while the STP are computed as an aggregated measure of continuous tracking over time. Therefore, the STP can account for physiological and perceptual abnormalities that progress on completely different time scales than that of individual saccades [12], while not requiring a large number of repetitive trials to obtain robust results.

As new treatments for NP-C are expected, there is a need for an easy and robust method to follow-up disease progression and the effect of treatment. At the moment, VOG is used for this purpose, but this is not suitable for severely affected patients. We show that SONDA is a patient-friendly method to quantify eye movements in these patients and that it can provide several robust saccadic parameters, complementary to the conventional ones, in a short time.

This small pilot, although with limitations, shows promising

preliminary results regarding the application of the SONDA method in clinical practice. However, further research is needed to evaluate whether SONDA and VOG can be used interchangeably or in complement to each other: follow-up studies could include more extensive saccadic characterization (e.g. with separate analysis for saccades of different amplitudes or by fitting the main sequence) and, if possible, given the low prevalence of NP-C, increase the sample size.

#### CRediT authorship contribution statement

**A. Grillini:** Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. **L.H. Koens:** Conceptualization, Formal analysis, Investigation, Methodology, Writing – original draft. **G. Lizaitiene:** Conceptualization, Writing – original draft. **F. Lange:** Conceptualization, Writing – review & editing. **F.W. Cornelissen:** Conceptualization, Writing – review & editing. **M.A. J. Tijssen:** Conceptualization, Writing – review & editing.

#### Declaration of Competing Interest

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

#### Acknowledgments

We thank the Niemann-Pick type C patients and healthy controls for participating in this study. M.A.J.T is a member of the European Reference Network for Rare Neurological Diseases - Project ID No 739510."

#### Disclosures

LHK and FL report no disclosures.

AG is the majority shareholder of REPERIO B.V., a private company that develops ophthalmic and neurological tests based on eye movements. AG is listed as inventor on the European patent application Grillini, A., Hernández-García, A., Renken, J. R. (2019). Method, system and computer program product for mapping a visual field. EP19209204.7 which is partially based on the content of this manuscript.

GL was supported by a Research Experience Fellowship for 2020 from the European Academy of Neurology.

FWC reports grants from the European Union's Horizon 2020 research and innovation programme (Marie Skłodowska-Curie(grant agreement No 641805 "NextGenVis")), NOVUM, Programmaraad Visuele Sector, Uitzicht (collaborating funds), Graduate School Medical Sciences (GSMS), University of Groningen.

MAJT reports grants from the Netherlands Organisation for Health Research and Development ZonMW Topsubsidie (91218013), the European Fund for Regional Development from the European Union (01492947), and the province of Friesland, Dystonia Medical Research Foundation, from Stichting Wetenschapsfonds Dystonie Vereniging, from Fonds Psychische Gezondheid, from Phelps Stichting, and an unrestricted grants from Actelion and AOP Orphan Pharmaceuticals AG.

#### Ethical Compliance Statement

The authors confirm that the approval of an institutional review board was obtained (METc 2018/593 and METc 2016/16). Every participant signed informed consent.

#### Financial Disclosure/Conflict of Interest concerning the research related to the manuscript

AG is the majority shareholder of REPERIO B.V., a private company

that develops diagnostic tests for Glaucoma based on eye movements. AG is listed as inventor on the European patent application Grillini, A., Hernández-García, A., Renken, J. R. (2019). Method, system, and computer program product for mapping a visual field. EP19209204.7 which is partially related to the technique presented in this manuscript.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.prdoa.2022.100170>.

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