Assessment of vigilance and response quality during static automated perimetry

A study using the method of constant stimuli (MoCS)

and

an enhanced presentation rate of catch trials

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Abstract

Purpose

To develop a methodology to monitor and validate vigilance during static automated perimetry.

Methods

The method of constant stimuli (MoCS) was applied to assess the differential luminance sensitivity with the OCTOPUS 900 perimeter (Haag-Streit AG, Koeniz, Switzerland). OPI (Open Perimetry Interface) was used to set up the test algorithms: Stimulus intensity was varied in 13 logarithmic stimulus luminance steps between 0.04 and 160 cd/m^2 at a background luminance of 10 cd/m^2. Goldmann size III (25,7') stimuli were presented 20 times each in three locations (-6.1°,-3.5°), (0°,7°), (6.1°,-3.5°), and a reference stimulus location was added at (0°,0°) with a weight of 0.1 (compared to a weight of 1.0 for all other stimuli locations) as an additional fixation incentive. Stimuli presented at this reference location were excluded from data evaluation. An increased rate of false positive and false negative catch trials was implemented (25% each). Each examination included 1,612 stimuli altogether. Response time was monitored. Pupil data, blink rate and the height of the palpebral fissure were extracted from the built-in camera of the OCTOPUS 900 perimeter. The camera operated with a frequency of 20 fps. Heart rate was recorded with the Ecgmove4 heart rate monitor using a chest strap (movisens, Karlsruhe, Germany). The Epworth Sleepiness Scale (ESS) questionnaire was obtained from all participants and evaluated in accordance with the existing guidelines (see chapter 3.3.7).
Subjects were included if the minimum distant visual acuity (without or with correction) was at least 0.8 (single letter optotypes [numbers], VISUCAT, argus individuell optic GmbH, Ottobrunn, Germany). The maxima of the acceptable ametropia were set to $\pm$8.00 dpt spheric and 2.50 dpt astigmatic ametropia. Ophthalmologic status had to be normal and subjects had to give their informed consent.

Results

Sufficient data were obtained from 48 test subjects (18 males, 30 females, age range 22–78 years, median 47 years) distributed equally among three age groups (21–40, 41–60, 61–80 years).

Twenty-four dominant eyes and 24 non-dominant eyes were examined in randomized order.

No significant correlation was found between the ESS score, age, total number of errors, and onset of sleepiness. No accordance of onset of sleepiness and pathological ESS scores was present (McNemar's test, χ^2 = 16, df = 1, p = $6.33 \cdot 10^{-5}$, statistically significant difference between onset of sleepiness and ESS scores).

Data evaluation was divided into *global* and *individual* analysis. One specific evaluation method per parameter was selected via AUROC (area under receiver operating characteristics curve) evaluation for global analysis and via best median correlation values for individual analysis, respectively as shown in Tab. 0.1.

Table 0.1: Agreement indices (AI) and Spearman correlation coefficients (Spearman's ρ) for agreement with/correlation to the error rate for parameters/evaluation methods included in the study (BRV: blink rate variability, PD: pupil diameter, PDV peaks: peaks in pupil diameter variability, PF: height of the palpebral fissure, PFV: variability of the height of the palpebral fissure, HRVLF: heart rate variability for low frequencies, RTV: response time variability). Parameters/evaluation methods that performed best are highlighted in gray

parameters / evaluation methods	**Global analysis: Agreement indices**		**Individual analysis: Spearman's ρ**	
	median	**maximum**	**median**	**maximum**
BRV	0.08	0.49	0.05	0.50
PD	0.01	0.44		
PDVpeaks			0.05	0.61
PF			-0.05	-0.82
PFV	0.09	0.52		
HRVLF	0.06	0.60	0.06	0.67
RTV	0.14	0.47	0.27	0.61

For *global* analysis, the agreement indices (AI) and for *individual* analysis, the Spearman correlation coefficients were calculated. Tab. 0.1 shows the median and maximum values: Response time variability and the height of the palpebral fissure performed best and are therefore highlighted in gray.

An exemplary artificial prevalence enrichment was simulated for the individual analysis of the pal-pebral fissure height by only considering the five subjects with the highest total number of errors. The median Spearman correlation coefficient for this subgroup increased to -0.60.

Conclusion

Response time variability and the height of the palpebral fissure were identified as the most promising and valid parameters in assessing and quantifying vigilance. An increased number of catch trials turned out as an excellent validation tool for the assessment of failures resulting from reduced vigilance with high temporal resolution.

Keywords

eye tracking, vigilance, perimetry, quality control, catch trials, heart rate, pupil oscillations, palpebral fissure, reaction time, eyelid closure, blink rate, psychometric function, ESS

Zusammenfassung

Ziel

Das Ziel dieser Arbeit war die Entwicklung einer Methode zur Überwachung und Validierung der Vigilanz während statischer, automatischer Perimetrie.

Methodik

Die Methode der konstanten Stimuli (MoCS) wurde angewandt, um die Leuchtdichteunterschiedsempfindlichkeit (LUE) mit dem OCTOPUS 900 Perimeter (Haag-Streit AG, Köniz, Schweiz) zu bestimmen. OPI (Open Perimetry Interface) wurde verwendet, um die Testalgorithmen zusammenzustellen: Die Stimulusleuchtdichte wurde in 13 Schritten zwischen 0,04 und 160 cd/m^2 mit einer Hintergrundleuchtdichte von 10 cd /m^2 variiert. Goldmann-Stimuli der Größe III (25,7') wurden jeweils 20 Mal an drei Orten (-6.1°, -3.5°), (0°,7°), (6.1°, -3.5°) gezeigt und ein Referenzort (0°, 0°) wurde hinzugefügt. Der Referenzort wurde mit 0,1 gewichtet (während alle anderen Stimulusorte mit 1,0 gewichtet wurden) und war als zusätzlicher Fixationsanreiz gedacht. Jedoch wurden am Referenzort präsentierte Stimuli von der weiteren Datenauswertung ausgeschlossen. Die Untersuchung umfasste insgesamt 1.612 Stimuli. Die Reaktionszeit wurde überwacht.

Es wurde eine erhöhte Rate falsch-positiver und falsch-negativer Fangfragen eingestreut (jeweils 25%). Die Pupillendaten, die Lidschlussrate und die Lidspaltenhöhe wurden über die eingebaute Kamera des OCTOPUS 900 Perimeter mit einer Frequenz von 20 Hz bestimmt.

Die Herzfrequenz wurde mit dem Ecgmove4-Herzfrequenzsensor und Brustgurt (movisens, Karlsruhe, Deutschland) aufgezeichnet. Der Epworth Sleepiness Scale (ESS)-Fragebogen wurde von allen Teilnehmern ausgefüllt und entsprechend der bestehenden Richtlinien (siehe Kapitel 3.3.7) ausgewertet.

Die Probanden wurden in die Studie eingeschlossen, wenn die Mindestfernsehschärfe (ohne oder mit Korrektion) mindestens 0,8 betrug (Einzeloptotypen [Zahlen], VISUCAT, argus individuell optic GmbH, Ottobrunn, Deutschland). Die akzeptable Ametropie wurde auf maximal $\pm$8,00 dpt Sphäre und maximal 2,50 dpt Zylinder festgelegt. Der augenärztliche Status musste normal sein, und die Probanden mussten ihre Einwilligung nach Aufklärung erteilen.

Ergebnisse

Suffiziente Daten wurden von 48 Testpersonen (18 Männer, 30 Frauen, Alter 22–78 Jahre, Median 47 Jahre) erhoben, die gleichmäßig auf drei Altersgruppen (21–40, 41–60, 61–80 Jahre) verteilt waren. 24 dominante und 24 nicht dominante Augen wurden in zufälliger Reihenfolge untersucht.

Table 0.2: Übereinstimmungsindices (AI) und Spearman-Korrelationskoeffizienten (ρ) für die Übereinstimmung/Korrelation zur Fehlerrate für die in die Studie einbezogenen Parameter/Bewertungsmethoden (BRV: Variabilität der Lidschlussrate, PD: Pupillendurchmesser, PDVpeaks: Variabilität der Pupillendurchmesserspitzen, PF: Lidspaltenhöhe, PFV: Variabilität der Lidspaltenhöhe, HRVLF: Variabilität der Herzrate für niedrige Frequenzen, RTV: Variabilität der Reaktionszeit

Parameter/ Bewertungs-methoden	**Globale Analyse: Übereinstimmungsindices**		**Individuelle Analyse: Spearman-Korrelations-koeffizienten ρ**	
	Median	Maximum	Median	Maximum
BRV	0.08	0.49	0.05	0.50
PD	0.01	0.44		
PDVpeaks			0.05	0.61
PF			-0.05	-0.82
PFV	0.09	0.52		
HRVLF	0.06	0.60	0.06	0.67
RTV	0.14	0.47	0.27	0.61

Es trat keine signifikante Korrelation zwischen ESS-Wert, Alter, Gesamtfehlerzahl und Zeitpunkt des Einsetzens von Schläfrigkeitsperioden auf. Ein McNemar Test ergab, dass ebenfalls keine Übereinstimmung zwischen dem Vorhandensein von Schläfrigkeitsperioden und einem pathologischen ESS-Wert vorlag (χ^2 = 16, df = 1, p = $6.33 \cdot 10^{-5}$, statistisch signifikanter Unterschied zwischen dem Vorhandensein von Schläfrigkeitsperioden und ESS-Werten).

Die Datenauswertung erfolgte in *globaler* und in *individueller* Form. Eine spezifische Bewertungsmethode pro Parameter wurde über die Bewertung der Fläche unter der ROC (receiver operating characteristics)-Kurve (AUROC) für die globale Analyse bzw. über die besten Median-Korrelationswerte für die individuelle Analyse ausgewählt, wie in Tab. 0.2 ersichtlich.

Für die *globale* Analyse wurden Übereinstimmungsindizes (AI) und für die *individuelle* Analyse wurden Spearman-Korrelationskoeffizienten berechnet. Tab. 0.2 zeigt den Median und die Maxima/Spitzenwerte an: Die Reaktionszeitvariabilität und die Lidspaltenhöhe zeigten die beste Eignung und sind daher grau hervorgehoben.

Exemplarisch wurde für die individuelle Analyse der Lidspaltenhöhe eine künstliche Prävalenzanreicherung simuliert, indem lediglich die fünf Testpersonen mit der höchsten Gesamtfehlerzahl betrachtet wurden. Für diese ergab sich im Median ein Spearman-Korrelationskoeffizient von -0,60.

Fazit

Die Variabilität der Reaktionszeiten und die Lidspaltenhöhe wurden als vielversprechendste und valide Parameter zur Beurteilung und Quantifizierung der Vigilanz identifiziert. Eine erhöhte Anzahl an Fangfragen erwies sich als ein hervorragendes Validierungsinstrument mit hoher zeitlicher Auflösung zur Beurteilung von Fehlern, die auf eine verringerte Vigilanz zurückzuführen sind.

Schlüsselwörter

Vigilanz, Perimetrie, Qualitätskontrolle, Fangfragen, Herzrate, Pupillenoszillationen, Lidspaltenhöhe, Reaktionszeit, Lidschlussrate, psychometrische Funktion, ESS

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I want to express my deepest gratitude to Prof. Dr. med. Ulrich Schiefer for co-supervising this Dissertation and for being my first point of contact concerning this work. Thank you for numerous fruitful discussions on data presenting, for substantial input concerning theoretical understanding, for sharing your wide experiences in experimental work and for crucial support in matters of paper writing. Beyond that, it is my concern to thank you for your advice in all respects and for lending me both an open ear and a helping hand, whenever I needed one – not only with regard to my dissertation but to any possible issue.
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I also want to thank Dr. Michael Wörner for “computer science support”, whenever needed. Your tremendous commitment in developing an algorithm for determining the height of the palpebral fissure and for improving an algorithm for the determination of the pupil diameter as well as your tireless and prompt assistance at any time in any regard were more than helpful and I am really grateful.

I would like to thank Prof. Dr. Yvonne Weber for her help with regard to EEG measurement and evaluation as well as for giving me the opportunity to carry out experiments at the EEG lab of the University Hospital in Tübingen, Department of Neurology and Epileptology. Many thanks to the whole team of the EEG lab for their support, especially to Barbara Wörner.

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Many thanks also go to Gustavo Vergani Dambros for a test evaluation of my data with algorithms developed by him.

Finally, I thank all my colleagues for the great, friendly working atmosphere which has made the last few years really pleasant.

This dissertation was financially supported by the Ministry of Science, Research and Arts Baden-Württemberg as part of the “HAW-Prom” program. Many thanks to all those, who were responsible for the selection and consideration of my work.

Statutory Declaration

I declare that I have authored this thesis independently, that I have not used other than the declared sources, and that I have explicitly marked all material which has been quoted either literally or by content from the used sources.

Aalen, July 2020

Judith Ungewiß

Contents

List of Figures

List of Tables

List of Abbreviations

a	lowpass filtered signal (with regard to wavelet analysis)
ADHD	attention deficit hyperactivity disorder
AGIS	Advanced Glaucoma Intervention Study
a.m.	ante meridiem (before noon)
AI	agreement index
App.	Appendix
approx.	approximately
ARAS	ascending reticular activation system
AUROC	area under receiver operating characteristics (curve)
BCI	Brain Computer Interface
bpm	beats per minute
BR	blink rate
BRV	blink rate variability
C	central (with regard to EEG)
cd	candela
CFF	critical flicker fusion
CIGTS	Collaborative Initial Glaucoma Treatment Study
cm	centimeter(s)
CT	catch trial(s)
d	highpass filtered signal (with regard to wavelet analysis)
d10	specific highpass filtered signal (with regard to wavelet analysis)
d10V	variability of specific highpass filtered signal (with regard to wavelet analysis)
dB	decibel
df	degrees of freedom
DLS	differential luminance sensitivity
E	sensation difference (according to Fechner's law)
ECP	evoked cognitive potential(s)
EEG	electroencephalography / electroencephalogram
e.g.	exempli gratia (meaning "for example")
EOG	electrooculography / electrooculogram

ESS	Epworth Sleepiness Scale
etc.	et cetera
F	frontal (with regard to EEG)
FFT	Fast Fourier Transformation
FHWA	US Federal Highway Administration
Fig.	Figure
fn	false negative
FOS	frequency of seeing
fp	false positive
fps	frames per second
HF	high frequencies
HFA	Humphrey Field Analyzer
HR	heart rate
HRV	heart rate variability
HRVHF	heart rate variability (high frequency band)
HRVLF	heart rate variability (low frequency band)
Hz	Hertz
ICA	Index of Cognitive Activity
ID	identification number
i.e.	id est (meaning ”that is”)
IEC	International Electrotechnical Commission
IPS	Imaging and Perimetry Society
L	luminance
LASSO	least absolute shrinkage and selection operator
LF	low frequencies
m	meter
max	maximum
med	median
min	minute(s)
mm	millimeter(s)
MoCS	method of constant stimuli
ms	millisecond(s)
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
n	number

NHTSA	US National Highway Traffic Safety Administration
no.	number
O	occipital (with regard to EEG)
OHTS	Ocular Hypertension Treatment Study
OPI	Open Perimetry Interface
OSAS	obstructive sleep apnea syndrome
p	p value (significance level)
P	parietal (with regard to EEG)
p.m.	post meridiem (after noon)
PD	pupil diameter
PDV	pupil diameter variability
PDVpeaks	peaks of the pupil diameter variability
perc.	percentile
PERCLOS	percentage of eyelid closure
PF	height of the palpebral fissure
PFV	variability of the palpebral fissure height
PNS	parasympathetic nervous system
POAG	primary open angle glaucoma
PSD	power spectral density
PST	Pupillographic Sleepiness Test
PUI	Pupillary Unrest Index
PVT	Psychomotor Vigilance Task
px	pixel(s)
RAM	random access memory
ROC	receiver operating characteristics
RT	response time
RTV	response time variability
s	second(s)
sens.	sensitivity
SITA	Swedish Interactive Thresholding Algorithm
SNS	sympathetic nervous system
spec.	specificity
SSL	slope steepness
SSS	Stanford Sleepiness Scale
SVR	support vector regression

T	temporal (with regard to EEG)
Tab.	Table
TAP	Test: Alertness Program
TEPR	Task-Evoked Pupillary Responses
TOP	Tendency-Oriented Perimetry
VF	visual field
z	midline sagittal plane (with regard to EEG)

1 Preliminary remarks

This work builds partly on the author's master thesis. For this reason, parts of the Introduction and Background chapters have already been used in a similar form in this master thesis:

> Ungewiss J. 2015. Parameters for Vigilance, Attention and Cognitive Workload within Eye Tracking Recordings. Master thesis, Aalen University of Applied Sciences.

This does not affect the results or research process of this dissertation.

In addition, a review-paper on the fundamentals of perimetry has been published. However, neither scientific data nor results of this dissertation are included in this work. The publication has no relation to the research process in the context of this dissertation but does only summarize previously known facts.
Only parts of the Background chapter of this work have been used in a similar form in this publication (wherever this was done, it is marked by appropriate citation):

> Ungewiss J, Schiefer U. 2018. Perimetrie in der neuroophthalmologischen Funktionsdiagnostik. Indikation – Methoden – Topodiagnostik. Klin Monatsbl Augenheilkd 235:1218–1228.

In addition, partial results of the present work have been published in advance:

> Ungewiss J, Kübler T, Mallot HA, Schiefer U. 2016. Monitoring quality and vigilance during automated static perimetry. 22nd International Visual Field and Imaging Symposium, Udine.

The publication took place as a poster presentation and affiliated abstract. No manuscript or scientific paper was published or written. Although, a detailed declaration of the proportions in which all co-authors were involved, is prepared. As this declaration refers to parts of different chapters (Study design and methodology, Results, and Discussion as well as App. E – only with regard to *pilot study 1*, respectively), it is included at this point:

Author	**Author position**	**Scientific ideas %**	**Data generation %**	**Analysis & interpretation %**	**Paper writing %**
Ungewiss J	1	50	100	80	90
Kübler T	2	only preliminary work			
Mallot HA	3	10	0	0	5
Schiefer U	4	40	0	20	5
Title of paper		Monitoring quality and vigilance during automated static perimetry			
Status in publication process		published as abstract and poster (2016)			

Parts of this dissertation were submitted in the form of an abstract for the Annual Meeting of the Deutsche Ophthalmologische Gesellschaft (DOG) in 2020:

> Ungewiss J, Mallot HA, Schiefer U. 2020. Die Reaktionszeit und deren Variabilität als Prädiktor der individuellen Antwortqualität während statischer, automatischer Perimetrie. *Abstract submitted and accepted for the DOG 2020.*

No manuscript or scientific paper was published or written. Although, a detailed declaration of the proportions in which all co-authors were involved, is prepared. As this declaration refers to parts of different chapters (Study design and methodology, Results, and Discussion, respectively), it is included at this point:

Author	**Author position**	**Scientific ideas %**	**Data generation %**	**Analysis & interpretation %**	**Paper writing %**
Ungewiss J	1	60	100	80	90
Mallot HA	2	10	0	0	5
Schiefer	3	30	0	20	5
Title of paper		Die Reaktionszeit und deren Variabilität als Prädiktor der individuellen Antwortqualität während statischer, automatischer Perimetrie			
Status in publication process		abstract submitted and accepted (2020-06-19)			

During the course of this dissertation, several algorithms have been used, that were not developed by the author. As parts of different chapters (Background, Study design and

methodology, Results, and Discussion) refer to these algorithms, a detailed declaration is given at this point:

Algorithm	**Developer**	**Explanation**	**Status in publication process**
Determination of the pupil diameter (initial algorithms)	Müller M	see chapter 3.4.4.1	Master thesis (Müller 2013), Publication (Müller et al. 2014)
Determination of the pupil diameter (improved algorithm)	Wörner M	see chapter 3.4.4.1	not published, no manuscript written
Determination of the height of the palpebral fissure	Wörner M	see chapter 3.4.4.2	not published, no manuscript written
Prediction of false responses by EEG and pupil data	Vergani Dambros G	see chapter 3.4.3	Bachelor thesis (Vergani Dambros 2017)

The author was not involved in the development of the algorithms at all.
The developers of the algorithms were not involved in scientific ideas, data generation, analysis & interpretation and paper writing in any other way than by the development of the algorithms.

2 Introduction

The eyes are the only human sense organs that - as an upstream part of it - allow for a direct insight into the human brain. For example, the visual field examination does not only allow for an examination of the eye, but can also provide additional information about the entire visual pathway right through to the processing procedures of the visual cortex. For this reason, perimetry is an important tool, especially in the (neuro)ophthalmological context. For example, perimetry allows for non-invasive studies of certain types of tumors, as well as for follow-up of various eye disorders (such as the glaucoma) associated with visual field loss. Treatment procedures are based on these investigations, which in the worst case, in turn, can decide whether the eyesight of a patient is preserved. Validity of the results of visual field examinations is therefore a decisive prerequisite to be able to make informed decisions.

2.1 Exposure of the Research Issue

Perimetric sessions nowadays can take up to 15 minutes per eye. The only activity patients are forced to practice during that time is to fixate a target and to press a response button in case of perception of visual stimuli. Visual field examinations in general are as boring as monotonous and exhausting. Thus it is difficult to keep up with concentration and vigilance during the entire perimetric session.

On the other hand, for the examiner, it is vital that patients' concentration is kept at a continuously high and constant level in order to perform well during perimetry. Visual fields can only be seen as valid, if patients do not produce errors unintentionally. Thus it is necessary that patients are vigilant, attentive and focused. Otherwise, incorrect answers are generated, that reflect the attentive status of a subject rather than his or her visual field capabilities. Therefore, it is vital to monitor the according status of patients during visual field examinations. The quality with regard to the validity of perimetric results can be improved by terminating a perimetric session *before* its considerable contamination due to vigilance- or concentration-related issues.

2.2 Research Objectives

The purpose of this work was to develop a methodology to monitor and validate vigilance during static automated perimetry.

A considerably enhanced presentation rate of catch trials was applied during a static automated perimetric examination using the method of constant stimuli (MoCS) over an extended examination time. Therefore, patients' vigilance was challenged in order to identify the onset of vigilance-related problems in a standardized manner with high temporal resolution. Additional parameters such as eyelid closures (blinks), the pupil diameter, the height of the palpebral fissure, heart rate and response time were investigated in order to cross-correlate their results with the manifestation of false responses to catch trials and therefore the occurrence of vigilance deficits. As a result, simple and valid parameters were searched for as a replacement for the time-consuming use of an enhanced presentation rate of catch trials.

2.3 Organization of this Research Project

This dissertation starts with a theoretical background of the research topic in order to unfold terminology, physiological definitions, and an illustration of the algorithms applied. The state of the art in vigilance monitoring during perimetry is displayed.

Study design and methodology are shown: This work contains two pilot studies, which were necessary for the establishment of the final methodology of the main study.

The original data and derived measures are presented. The performance of the selected parameters named above is being assessed and discussed - not only for perimetric examinations, but also in the context of further thinkable application fields such as nighttime driving experiments or examinations on the immediate consequences of drug or alcohol abuse.

3 Background

To start with, the relevant background issues for this study are constituted and the state of the art in science and technology is displayed in order to provide an estimation of the potential of different parameters with regard to vigilance and quality monitoring in the context of perimetry.

3.1 Perimetry and the visual field

The *visual field* (VF) is defined as the totality of all visual sensory input that can be perceived when looking straight ahead at a fixation object, with the eye still and without head or trunk movements (Traquair 1938). The differential luminance sensitivity (DLS, see chapter 3.1.1) is a measure of the local position-related function within the visual field. The DLS is highest at the center and drops towards the periphery. Locations of identical DLS are connected by so-called isopters. The outer visual field limits are determined by individual anatomical conditions (eye position, upper eyelid, eyebrows, nose) and are temporally at approx. 100°, below at approx. 70° and nasally and above at approx. 50° (Traquair 1938) (Glaser 1967) (Schiefer et al. 2005a), as cited in (Ungewiss and Schiefer 2018).

The visual field can be examined with regard to its external borders or to circumscribed lesions within the visual field borders. Visual field examinations are relevant for various reasons. The most common reasons are

1. to detect a pathology affecting any part of the visual pathway
2. to evaluate a disease status
3. for follow-up of pathologies over time for progression analysis
4. to assess the efficacy of a treatment
5. for visual ability testing (Racette et al. 2017)

3.1.1 Basic psychophysics

Weber's law (1846) puts the luminance difference (i.e. the contrast), which can just be perceived (ΔL), in relation to the surrounding luminance (L) (Weber 1846):

$$\frac{\Delta L}{L} = const. \tag{3.1}$$

This law was extended by the Fechner law (1860) to the description of identical sensation differences (ΔE) (Fechner 1860).

$$\Delta E = \frac{\Delta L}{L} \tag{3.2}$$

With these laws, relations are represented, since the interrelation between subjective sensitivity and physically measurable stimulus intensity cannot be adequately represented by looking at differences alone.
The specified unit is the Bel, which is used to identify the decimal logarithm of the ratio of two similar energy or power quantities. The more common unit is the decibel [dB], which denotes the tenth part of a Bel and thus denotes two sizes in a ratio of $10^{0.1}$ = 1.259. In perimetry, the maximum luminance that a perimeter can represent is generally used as a reference and is therefore set to 0 dB. Larger dB values describe an attenuation of the presented luminance levels (Lachenmayr and Vivell 1992). The luminance at which a stimulus can be perceived by the patient with a probability of 50% is referred to as differential luminance sensitivity (DLS). The boundary between stimuli seen and not seen by a subject is not reached abruptly, but there is a transition area, which means that the associated psychometric function follows a sigmoid course (Aulhorn and Harms 1972) (Greve 1973) (Bebie et al. 1976a) (Johnson 1998) (Schiefer et al. 2003), as cited in (Ungewiss and Schiefer 2018).

3.1.2 Perimetric methods

In principal, there are two main perimetric methods: kinetic and static perimetry.

3.1.2.1 Kinetic perimetry

In kinetic perimetry, stimuli of different sizes and luminance levels (see Fig. 3.1), according to (Goldmann 1945a) are moved from the non-seeing area to the seeing area of the patient

(Harms 1940) (Goldmann 1945b). The outer visual field boundaries and scotoma are thus determined (Anderson 1987) (Schiefer et al. 2005b).

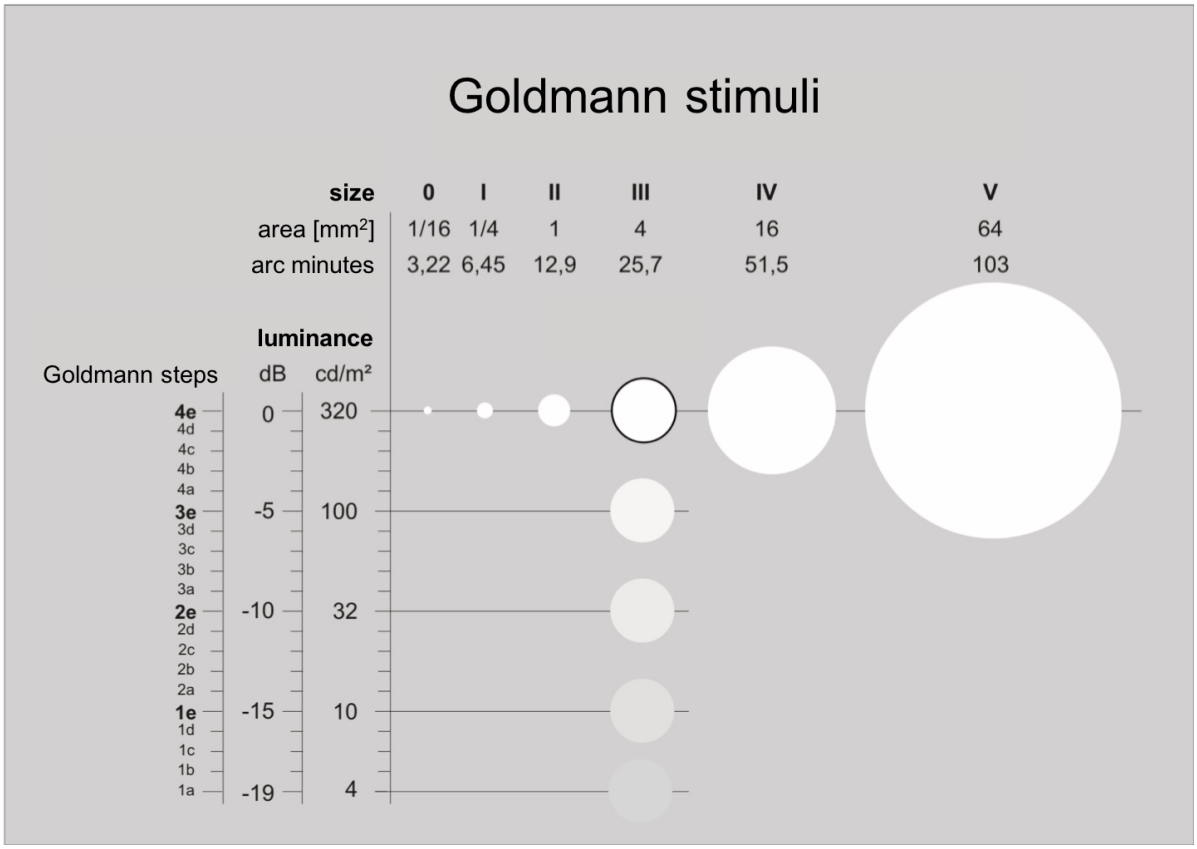

Figure 3.1: Size and luminance levels of the Goldmann stimuli according to (Goldmann 1945a). The mark III4e, which is determined in Germany as relevant to the expert opinion, corresponds to a stimulus diameter of 25.7' and a stimulus luminance of 320 cd/m^2. The increase in stimulus area by one step corresponds to the same perception effect as the increase in stimulus luminance by 5 dB (Figure modified from Wilhelm Durst, published in (Schiefer et al. 2003), as cited in (Ungewiss and Schiefer 2018))

Since the stimulus moves in the time interval between perception and response (response latency), this method results in a systematic shift of the scotoma boundaries in the direction of the stimulus movement. For manually driven stimuli (for example with Goldmann perimetry), there is no possibility to monitor the angular velocity (Flammer 1993). In contrast, semi-automated kinetic perimetry offers the possibility of determining vectors with origin, direction of stimulus movement and constant angular velocity (Schiefer et al. 2003). So-called response time measurement vectors can then be used to correct scotoma for

the patient's response latency (Schiefer et al. 2005b) (Vonthein et al. 2007), as cited in (Ungewiss and Schiefer 2018).

3.1.2.2 Static perimetry

In static perimetry, fixed, i.e. non-moving stimuli are presented (mostly independent of the examiner) in a grid of pre-defined test locations with defined luminance levels. Particular importance is attributed to the selection of the examination strategy, the examined visual field extension and the number of stimuli presented (Harms 1969) (Bebie et al. 1976b). The distribution of defined test locations within the visual field results in a grid that sets the local resolution for local differences in the DLS. An age-correlated standard value must be available as a reference for each tested location (Anderson 1987).

A clear statement about the local DLS should be made with as few queries per test location as possible. The stimuli are randomly presented across the examination area. Several strategies are available according to (Bebie et al. 1976b). With the threshold-related, supra-threshold strategy, the stimulus is initially presented at each test location a little above threshold (i.e. with a higher luminance than the age-correlated standard value). If this stimulus is recognized, the examination at this test location is ended. If the stimulus is not recognized, the stimulus is presented at this test location with maximum luminance in the further course of the examination. With this 2-phase strategy, defects can be divided into three classes: normal, relative defect, absolute defect. In the case of a relative defect, the slightly above-threshold stimulus is not recognized, but the maximum stimulus is perceived. As part of a 3-phase strategy, relative defects can be described more precisely by means of a bracketing procedure or by querying pre-defined fixed levels of luminance (Johnson et al. 1992). A disadvantage of this strategy is the difficult detection of early scotoma stages, with visual field defects being more shallow than the supra-threshold level chosen by the algorithm. Since this strategy does not allow for numerical values, but rather for an assignment to defect classes, progression analysis is difficult (Schiefer et al. 2005a), as cited in (Ungewiss and Schiefer 2018). By means of the threshold-determining strategy, a stimulus of pre-defined (e.g. 4 dB supra- or infra-threshold) luminance (starting luminance) is presented, which, depending on the patient's response, is raised or lowered in 4 dB steps until a response reversal from "seen" to "not seen" or vice versa occurs. After this response reversal, the luminance is increased or decreased in 2 dB steps until another response reversal takes place (4-2 dB input, according to (Bebie et al. 1976b)).

The local DLS is then determined from this sequence (Schiefer et al. 2005a), as cited in (Ungewiss and Schiefer 2018). In addition to these basic strategies, there are various ”fast strategies” (such as SITA: Swedish Interactive Threshold Algorithm (Bengtsson et al. 1997) or TOP: Tendency-Oriented Perimetry (Maeda et al. 2000)) that were designed to reduce patient fatigue and stress. Interstimulus interval times adapted to patient reaction times or luminance start levels are determined from already known DLS values from adjacent test locations. Ultimately, such ”fast strategies” are often a black box with non-accessible algorithms. In addition, these strategies lead to different threshold results than the conventional methods, which is why a switch to a different strategy should be avoided in the course of follow-up studies (Schiefer et al. 2005a) as cited in (Ungewiss and Schiefer 2018).

As an alternative to the methods described above, the method of constant stimuli (MoCS) (Urban 1910) can be used. A defined number of stimuli per defined luminance level is shown at each pre-defined location in randomized order. This enables to achieve very precise results, even with associated frequency of seeing (FOS) curves (Hegelmaier 1852). However, this method is very time-consuming and therefore at best suitable for studies that allow for intense examinations, but not for common clinical use.

3.1.3 Definition of quality and validity with regard to visual field examinations

Validity is the main *quality* criterion for a diagnostic method that is fulfilled, if the method measures the feature that it is supposed to measure or pretends to measure with sufficient accuracy (Wirtz 2013).
Quality in the context of visual field testing is usually defined by steadiness of a central fixation of the patient combined with the proportion of false responses to catch trials (for more information, see 3.1.4) (Schiefer et al. 2006). Quality can also be defined by the retest reliability, i.e. deviations in the local DLS within the scope of repeated visual field examinations. A distinction is made between ”short-term fluctuation” (deviations within one perimetric session) and ”long-term fluctuation” (deviations for different perimetric sessions that were carried out at intervals of weeks or months) (Chauhan et al. 1993) (Demirel and Vingrys 1994) (Schiefer et al. 2006).

Therefore, *valid* perimetric results by means of sufficient accuracy of the method used can only be achieved if the *quality* of a visual field examination is sufficient.

3.1.4 Quality monitoring during perimetry

The quality of a perimetric examination can be investigated by observing the patient's fixation via an infrared videocamera, as a fundamental requirement for a visual field examination is a steady central fixation of the patient (Demirel and Vingrys 1994). In addition, so called *catch trials* are used (Anderson 1987) (Demirel and Vingrys 1995) (Vingrys and Demirel 1998). Due to time constraints, catch trials are usually interspersed in a very limited number (about 3 - 5% of all stimuli presented). In the case of *false negative* catch trials, a stimulus with a very high luminance is presented at a test location, at which a stimulus was previously perceived. If the response button is not pressed, the response is considered false negative. In patients with many false negative responses, the DLS is determined too low, and visual field defects are falsely detected or falsely increased (Demirel and Vingrys 1995) (Vingrys and Demirel 1998). In the case of *false positive* catch trials, the perimeter produces the mechanical noise that is customary for a stimulus presentation, but no stimulus is presented. If the response button is pressed anyway, the response is considered false positive. In "trigger-happy" patients with many false positive responses, the DLS is determined too high, and local defects can be overlooked or artificially reduced (Demirel and Vingrys 1994) (Schiefer et al. 2006) as cited in (Ungewiss and Schiefer 2018).

The problem with visual field quality is, that the central DLS fluctuates strongly: It is initially often very high, but can vary considerably during the course of an examination due to a decrease of vigilance and attention (see 3.2) (Johnson et al. 1988) (Schiefer et al. 2006) as cited in (Ungewiss and Schiefer 2018).
Therefore, the quality of visual field examinations is directly linked to vigilance and attention.

3.2 Vigilance and attention – definition and scope

The terms *vigilance* and *attention* are often used synonymously in colloquial language although there are noticeable differences. Therefore, it is necessary to define these terms right at the beginning.

Vigilance is a derivation from the Latin word “vigilantia”. It can be translated as wakefulness. Vigilance, as a technical term, primarily refers to the level of central nervous activation that enables a subject to adapt to the current environment (Head 1923).
In general medicine, vigilance is understood as a physiological state that is directly related to central nervous activation (Canisius and Penzel 2007).
Central nervous activation is understood as the general neuronal willingness of the central nervous system to respond to internal and external stimuli (Posner and Rafal 1987). Different levels of alertness are attributed to diurnal fluctuations in the tonic excitation system (e.g. sleep-wake rhythm). The ARAS (ascending reticular activation system) of the brain stem is believed to play a central role in both tonic and phasic components of central nervous activation. Thus, particular emphasis is being placed on the locus coeruleus, which is is located in the posterior area of the rostral pons in the lateral floor of the fourth ventricle (Posner and Petersen 1990) as cited in (Weeß et al. 1998). Central nervous activation and the level of vigilance underlie physiological daytime variation. In the morning and in the afternoon, central activation is in general higher than at nighttime (Wilhelm et al. 2001). For that, indicators used to monitor vigilance also vary during the day (Kraemer et al. 2000).
Decreased vigilance – taking into account the current state of scientific knowledge – is called daytime sleepiness (Weeß et al. 1998) as cited in (Endres 2009).

Sleepiness accords to the level of vigilance where a characteristic reduction of the central nervous activation and inhibition of the Edinger-Westphal nuclei sets in. In addition, cerebral structures of the posterior hypothalamus are involved. Usually, sleepiness is caused by a decrease of quantity or quality of sleep during the night and can be characterized by falling asleep as soon as possible (Weeß et al. 2000) as cited in (Endres 2009) and (Ungewiss 2015).
In addition to the term sleepiness, there is also the term *fatigue*, which is defined as a difficulty in initiating or sustaining voluntary activities (Chaudhuri and Behan 2004). The state of fatigue cannot be measured objectively, but only described subjectively (Weeß

et al. 2000).
Fatigue and sleepiness are often seen and applied synonymously (Shapiro et al. 2002). Both conditions often appear together, and “sleepy” and “fatigued” can feel quite similar and be at times hard to distinguish. Although, fatigue and sleepiness arise from different physiological scales.

There are miscellaneous definitions of the term *attention*, that have been improved over time (Carrasco 2011).
William James already stated in his *Principles of Psychology* in 1890 (James 1890):

> “Everyone knows what attention is. It is taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration, of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others, and is a condition which has a real opposite in the confused, dazed, scatterbrained state which in French is called distraction, and Zerstreutheit in German.”

Bleuler expounded in 1916, that attention was the allocation of limited awareness resources to awareness contents, for example to the perception of the environment or of one’s own behavior and action as well as thoughts and emotions (Bleuler 1916 / 1983).
The substance of that is that attention can be directed, whereas vigilance, fatigue and sleepiness are global terms. Attention can change fast while sleepiness is a slow process.

In summary, it can be said that the terms vigilance, sleepiness and fatigue describe a *general state* of arousal. In contrast, the terms attention, abstraction and distraction can be described as *directable*. Figure 3.2 illustrates the antagonisms.

In the present study, perimetric measurements are analyzed. A perimetric session should generally be terminated before reduced vigilance has a negative impact on the results.
It is not clear a priori, which of the above-mentioned terms is relevant with regard to visual field testing. However, it can be assumed that inattention and sleepiness rather than fatigue may be factors in this regard, and consequently concentration may also be vital. For this reason, various physiological parameters are included, which are used as correlates for inattention and for both, sleepiness and fatigue (see chapter 3.3).

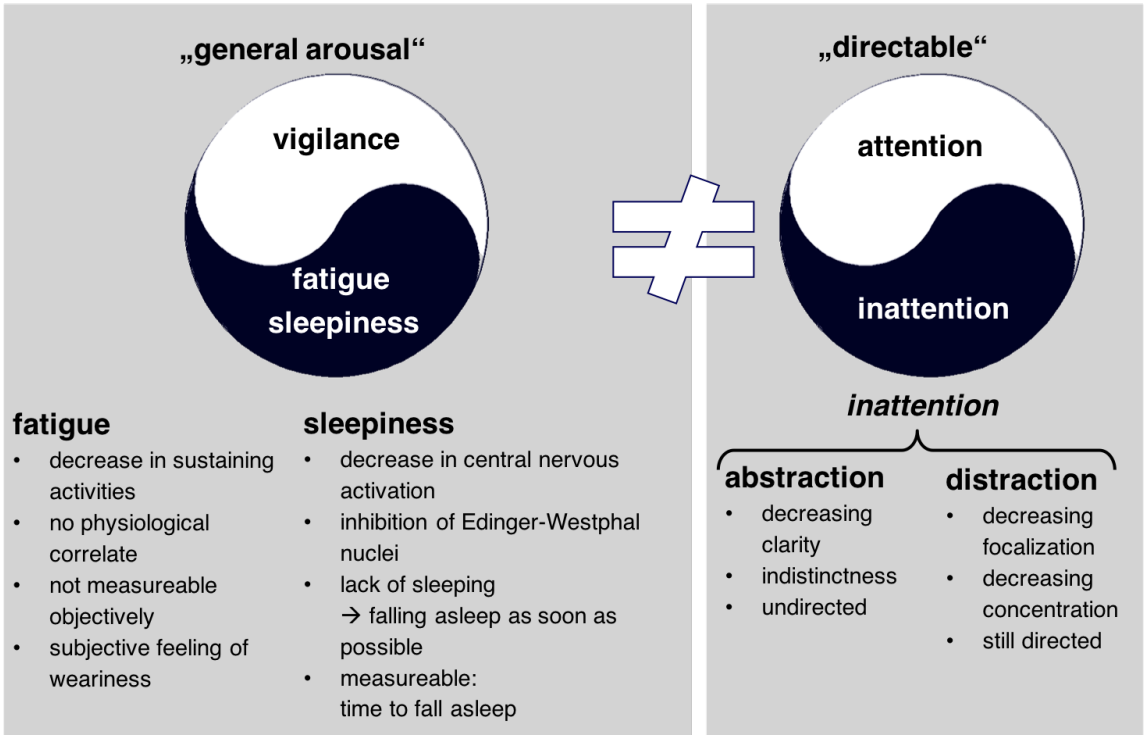

Figure 3.2: Comparison of the antagonisms vigilance, sleepiness, fatigue and attention, inattention, abstraction, distraction

3.3 Parameters corresponding to perimetric quality

There are various physiological parameters that are associated with sleepiness, fatigue or distraction - and therefore, in turn, with perimetric quality as described above. These can be measured in order to draw conclusions about the vigilance level of subjects (see chapter 3.2). The parameters are presented in detail below.

3.3.1 Blink rate

A blink is a fast, often automatic and involuntary closure and opening of the eyelids. It provides bearing up the precorneal film for a permanent moistening of the cornea and therefore protects the eye from drying-out. Additionally, small particles can be removed from the eye in this way.

Normal eye blink rates range from 10 to 15 times per minute, that corresponds to one blink every four to six seconds (Moses 1981). Several recent studies figured out quite equal values for the eye blinking rate (Bentivoglio et al. 1997) (Barbato et al. 2000) (Ziemssen et al.

2005).
With an increase in fatigue, the eye blink rate increases as well (De Padova et al. 2009).

3.3.2 Pupillary oscillations

The diameter of a physiological pupil ranges from 1.5 mm under photopic conditions to 8 mm under scotopic conditions. Under average photopic conditions, the pupil diameter ranges from about 2 mm to about 6 mm. The pupil diameter is age-related and decreases by about 0.4 mm per decade. For that reason, the pupil diameter of elderly people ranges from about 4 mm to about 5 mm (Joos et al. 2003).

Pupillary oscillations under constant environmental conditions arise, as permanent change of the pupil diameter constantly has to correct the retinal illuminance level. Therefore, the pupil shows physiological unrest. Pupillary oscillations are the result of this feedback loop, especially under varying photopic conditions. With less attenuation of the feedback loop (which may occur due to increasing fatigue and/or sleepiness), pupillary oscillations increase (Grünberger et al. 1994).
The term *hippus* is a synonym for psychophysiological pupillary oscillations. It is sometimes also applied for the excrescence of pupillary oscillations (Beatty and Lucero-Wagoner 2000). A novel definition says, that a hippus is an inconstant, spontaneous, bilateral, synchronous, rhythmic constriction and dilatation of the pupil with a large amplitude. Specifically in sleepy people, the size change can be observed. Such large changes in pupil diameter are called fatigue waves (Wilhelm et al. 1999) as cited in (Ungewiss 2015).
The terms of pupil diameter and pupillary oscillations are often found in the context of vigilance, fatigue and sleepiness. The sleepier a person is and the less sleep suppression is strived for, the shorter the time of initial mydriasis is and the higher and more frequent the resulting pupillary oscillations that can be detected in healthy and vigilant persons under *scotopic conditions* are. These waves consist of two components:

- Waves of dilatation and constriction lasting from 4 to 40 seconds with amplitudes of up to 0.5 mm.
- Superposed fast and inextended oscillations, i.e. constrictions and re-dilatations of a duration of 0.5 to 1 seconds with amplitudes of 0.1 to 0.3 mm.

These waves show central nervous activation (Lowenstein et al. 1963) as cited in (Ungewiss 2015).

Another theory trying to establish a relation between hippus and vigilance states that a characteristic hippus with a mean frequency of 2 to 3 Hz and amplitudes of many fluctuations up to over 1 mm can be observed in sleepy persons. The origin of these oscillations is unknown (Korczyn 1987).

3.3.3 Palpebral fissure

The eyelid morphology is influenced by age, race, ethnic group, and surrounding facial anatomy. The height of the palpebral fissure ranges from approximately 9 to 12 mm and decreases with increasing age (senile ptosis) (Iliff and Pacheco 2001).
When sleepy, inattentive and exhausted, the upper eyelid is lowered. In contrast, in the state of vigilance or attention it is rather raised. The Müller muscles (Musculi tarsales) adjust the position of the upper eyelid and therefore the height of the palpebral fissure. They are innervated by sympathetic nerve fibers with alpha endings and therefore indicate the degree of arousal (Records 1979). In slow drift-off phases (which means falling asleep slowly over a long time period), as can be observed in exhausted people, there is an increasing decoupling of voluntary eyelid closure and height of the palpebral fissure (Galley 2001).

3.3.4 Heart rate

The heart rate is defined as the speed of the heartbeat measured by the number of contractions (beats) of the heart per minute (bpm). Normal resting heart rates range from 60 to 100 bpm. Bradycardia is defined as a resting heart rate below 60 bpm. However, heart rates from 50 to 60 bpm are common among healthy people and do not necessarily require special attention. Tachycardia is defined as a resting heart rate above 100 bpm (Mason et al. 2007).
The heart rate is varying due to the body's physical needs and activities (for instance physical exercise, sleep, anxiety, or stress). The heart rate is regulated by sympathetic and parasympathetic input to the sinoatrial node (Schmidt-Nielsen 1997).

The heart rate variability (HRV) is defined as the fluctuation in the time intervals between adjacent heartbeats. The HRV is necessary to be able to adapt to environmental and psychological challenges. An optimal HRV is associated with health and self-regulatory capacity as well as adaptability or resilience. Stable higher levels of HRV are linked to the performance of executive functions like attention (Shaffer and Ginsberg 2017).

HRV can be differentiated into different time domains: Long-term (24 h), short-term (about 5 min) and ultra-short-term ($<$5 min) HRV. Only ultra-short term HRV seems to be suitable for experiments aiming at highly time-resolved results (such as vigilance monitoring during a visual psychophysical examination) (Shaffer and Ginsberg 2017).

It is also possible to divide the HRV into components of different frequency ranges by a Fast Fourier Transformation (FFT):
The low frequency (LF) band includes frequencies from 0.04 to 0.15 Hz and reflects the sympathetic nervous system (SNS).
The high frequency (HF) band, on the other hand, ranges from 0.15 to 0.40 Hz. It is said to reflect the activity of the parasympathetic nervous system (PNS).
The LF/HF ratio is intended to estimate the ratio between SNS and PNS activity. Therefore, it acts as an indicator if the sympathetic or the parasympathetic part of the nervous system is dominant (Shaffer and Ginsberg 2017).

It has to be stated, that there are various further HRV metrics. However, it is not possible to cover all existing methods in the course of this work. At least the basic and most promising methods have been addressed.

3.3.5 Response time

There are different factors affecting reaction time or response time. One of the main parameters – beneath the type of task applied – is the state of attention. Response time is fastest with an intermediate degree of arousal, and increases when a subject is too relaxed or too tense (Freeman 1933) (Broadbent 1971) (Welford 1980).
Response time also depends on age. Already a study from Galton (1890) reported that reaction times for teenagers (15–19 years) were 187 ms (mean value) for simple reaction time tasks with light stimuli. Reaction time shortens from infancy to the 20s, then slowly

increases until the 60s, and then, in turn, decreases from the 70s and beyond (Galton 1890). In contrast to intuitive belief, adolescents may probably react slower than adults (Riddervold et al. 2008) (Van Damme and Crombez 2009).
Welford (1980) examined the impact of fatigue on response times. It was found that response time gets slower when a subject is less vigilant, while Singleton (1953) observed that especially sleepiness has a high effect on response times (Singleton 1953).
An experiment designed to link response times directly to vigilance showed that response times are directly correlated to vigilance (Surwillo and Quilter 1964).

3.3.6 Electroencephalography (EEG)

Electroencephalography (EEG) is defined as a method of medical diagnosis and neurological research to measure the electrical activity of the brain by recording the voltage fluctuations on the surface of the head.
Therefore, EEG is suitable for measuring the degree of central nervous activation electrophysiologically. The electroencephalogram (EEG) is the only physiological signal that has been shown to accurately reflect shifts in attention (Berka et al. 2007).
EEG evaluation is traditionally carried out by pattern recognition of a trained evaluator, sometimes supported by software algorithms. Typical wave forms are stated in Tab. 3.1. Alpha waves are of particular clinical importance with regard to sleepiness. According to Weeß, changes in the clinically relevant alpha rhythm only appear when the state of sleepiness becomes so massive that attention and consciousness losses and pseudohallucinations already begin (Weeß et al. 1998).

It has to be stated, that alpha waves as well as their desynchronisation due to sleepiness can only be measured with closed eyes, whereas perimetric tasks require open eyes. In

Table 3.1: Typical EEG wave forms according to (Pschyrembel 2013)

wave form	**frequency**	**state**
delta	0.5 – 3.5 Hz	dreamless deep sleep phase
theta	4 – 7 Hz	light sleep phases
alpha	8 – 13 Hz	relaxed alertness/vigilance
beta	14 – 30 Hz	attention, arousal
gamma	31 – 70 Hz	strong concentration

the latter case, alpha waves usually change into beta waves. However, beta waves are not specific with regard to sleepiness, as they also occur as a standard variant in some subjects and are also visible when a muscle is constantly tensed or when active concentration is used (Zschocke and Hansen 2012) (Schorner and Lopes da Silva 2018).
Broughton stated that the shape and amplitude of evoked potentials are dependent on vigilance and thus allow for conclusions to be drawn about the degree of vigilance (Broughton et al. 1988). However, these experiments were not performed in a way, in which EEG measurement took place simultaneously to other tasks that required visual attention.

In the recent past, there have been additional approaches to not only investigate alpha waves (in their form and/or rhythm), but also to examine the alpha power via its spectral density, which describes, how the power (i.e. the amount of energy converted per time unit) of a signal is distributed over frequency.
According to Wascher et al., alpha power is said to decrease with the allocation of attention (Herrmann and Knight 2001) and with increasing demands for the working memory (Klimesch 2012) (Wascher et al. 2018). Thus, high alpha power may be related to withdrawal of attention or task disengagement (Wascher et al. 2014) (Wascher et al. 2016) that becomes predominant when boring tasks have to be performed (Borghini et al. 2014). Therefore, alpha power may reflect mind-wandering when perceptual demands are reduced, e.g. during monotonous situations.

3.3.7 Questionnaires

Due to their nature, questionnaires for the subjective assessment of subject's vigilance cannot be time-matched. They only serve as an "overall" parameter that can be used to estimate in advance or retrospectively whether vigilance restrictions could occur during an examination or activity. A large number of such questionnaires is available, the best known of which are the Stanford Sleepiness Scale (SSS) (Hoddes et al. 1973) and the Epworth Sleepiness Scale (ESS) (Johns 1991). To the author's knowledge, the latter questionnaire is the only one that has been validated in German language. Test subjects rate the likelihood of falling asleep in eight typical everyday situations on a scale from 0 (not at all) to 3 (high). The individual results are summed up to a total score between 0 and 24 (Johns 1991) (Weeß et al. 2000) (Sauter et al. 2007).

A German version of the ESS, taken from the Website of the German Sleep Society (Deutsche Gesellschaft für Schlafforschung und Schlafmedizin (DGSM) 2007), that was used within this study is attached in App. D.

3.4 State of the art

Subsequently, the state of the art in vigilance and response quality monitoring in the context of ophthalmologically relevant psychophysical examination methods is described.

3.4.1 Vigilance monitoring

In the recent past, several efforts have been made to monitor vigilance, in part by means of pupillography, which are mentioned subsequently.

3.4.1.1 Monitoring vigilance with pupillography

The company AMTech licensed the Pupillographic Sleepiness Test (PST) (Wilhelm et al. 1998) in 1997. It is based on infra-red video-pupillography and intended for specifically *scotopic* conditions. The pupil diameter of subjects is determined by an implemented algorithm, even with disturbing factors such as eye movement or eyelid closure. The pupillary oscillation is recorded, averaged and described as Pupillary Unrest Index (PUI) in millimeters per minute [mm/min]. The PST was the first test that verified Lowenstein's assumption, according to which the occurrence of fatigue waves was related to sleep deprivation (Lowenstein et al. 1963). Therefore, the PST made a quantification of fatigue and objective statements about vigilance possible. Today, it is seen as the gold standard in examining sleepiness under scotopic conditions (Endres 2009).

A quite similar test has been implemented first into a campimetric device by Henson and Emuh (Henson and Emuh 2010). Examinations took place under low *photopic* conditions. Henson and Emuh found that pupillary fatigue waves became more evident with test duration, and the probability of stimulus perception was higher when the amplitude of the pupillary fatigue waves was low. However, exclusively supra-threshold stimuli were used

and only a small group of patients (n = 13) with a limited age range (51–88 years), all of whom were glaucoma patients or glaucoma suspects, but not further stratified, were examined for a time period of 10 minutes.

Müller implemented an algorithm for vigilance monitoring by pupillography into a conventional perimeter, operating under low photopic conditions as well, in 2013 (Müller 2013) (see chapter 3.4.4.1). This algorithm has been refined (Müller et al. 2014) and validated by proof-of-concept studies. However, validation by a larger sample size study has not taken place until now.

3.4.1.2 Monitoring vigilance with other methods

There are also combinations of different methods to monitor vigilance, that are mentioned for a comprehensive state of the art, as listed subsequently according to Weeß et al. (2000) as cited in (Ungewiss 2015).

- Multiple Sleep Latency Test (MSLT)
  The MSLT measures latencies of falling asleep and REM phases under polysomnographic conditions. Latency of falling asleep is reduced with increasing fatigue (Carskadon and Dement 1977).

- Maintenance of Wakefulness Test (MWT)
  The MWT is a modification of the MSLT. It is an electro-physiological examination method, test criteria are latency of falling asleep and REM phases as well (Mitler 1993).

- Critical Flicker Fusion Test (CFF-Test)
  The CFF-Test is used to determine the visual fusion threshold. It depends on the observation, that intermitting light in a range of frequency lower than 20 Hz is percepted as a flicker signal. By increasing the frequency, the impact of constant light appears continuous upon central nervous activation from a certain, critical frequency on (Aufdembrinke 1982).

- Evoked Cognitive Potentials (ECP)
  Today, this method creates the possibility of illustrating specific reactions of neural structures to a stimulus. Thus, central nervous activation can be assessed (Weeß et al. 2000).

- Test: Alertness Program (TAP)
  The TAP is a measurement of reaction time with a warning signal. Via subtest alertness of the TAP, both tonic and phasic components of the central nervous level of activation can be captured by a computer-based examination (Fimm 1989).

- Questionnaires
  There are several questionnaires available, such as the Stanford Sleepiness Scale (SSS) (Hoddes et al. 1973) and the Epworth Sleepiness Scale (ESS) (Johns 1991). These are, as described in chapter 3.3.7, methods of self-assessment.

3.4.2 Monitoring attention and cognitive workload

Hess and Polt suggested in 1964, that task-evoked pupillary responses (TEPRs) might provide a dynamic neurophysiological index of momentary information processing load. Pupil size was measured in five subjects, while they had to mentally calculate the product of two small numbers in four different challenges of varying difficulty. Their results showed very clearly, that the pupil of each subject dilated as each calculation was mentally performed. The extent of the observed calculation was almost monotonically related to the difficulty of the announced calculation (Hess and Polt 1964).
Today, TEPRs are used to show subject's cognitive state concerning perception, memory, and responding as well. Pupil dilatation can be used for monitoring information processing load and also refers to attention and concentration. For that reason, they can also be used as an indicator for attention (Beatty and Lucero-Wagoner 2000) as cited in (Ungewiss 2015).

There is a method providing an objective psychophysiological measurement of cognitive workload, which is called the *Index of Cognitive Activity* (ICA). The ICA is able to estimate the levels of cognitive effort of subjects (Marshall 2000). It is based on changes in pupil size that occur from the interaction between subjects and visual displays. The ICA measures abrupt discontinuities in the pupil diameter signal. As long as cognitive processing is effortful, the pupil response occurs rapidly with a reflex reaction of dilatation. Simultaneously, the pupil shows a reflex reaction to light changes. The ICA separates light reflex and dilation reflex.
The index is computed as the number of times an abrupt discontinuity in the pupil signal is detected per second (Marshall 2002).
The effect of cognitive workload can be observed during perimetry: Mental workload

reduces subject's visual field areas, with heavy workload leading to a higher reduction than light workload (see Figure 3.3) (Rantanen and Goldberg 1999) as cited in (Ungewiss 2015).

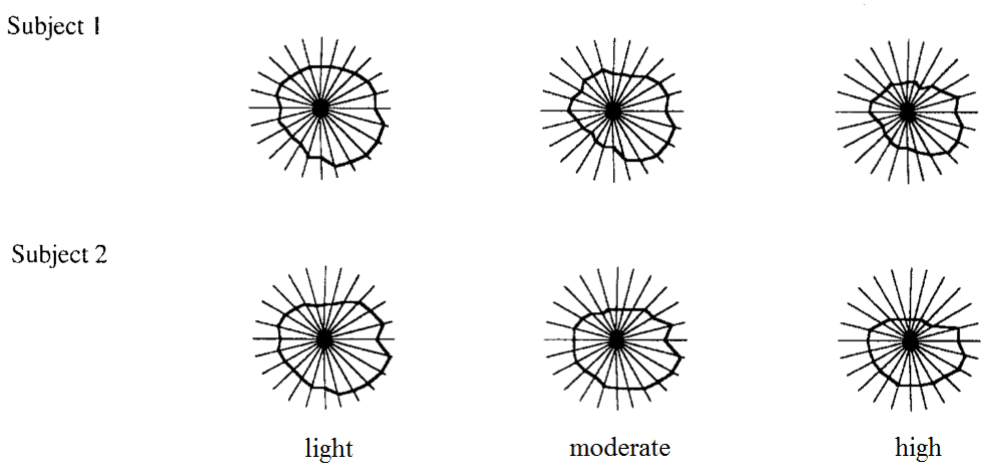

Figure 3.3: The effect of light, moderate and high cognitive workload on the visual fields of two subjects. The vertices extend 90° from the point of fixation. A Goldmann perimeter for kinetic perimetry with stimulus III 4e was used (Rantanen and Goldberg 1999)

3.4.3 Response quality monitoring

Previously, it has been tried to predict the error rate (as a correlate of fatigue) of subjects during a visual experiment. A 40 minutes campimetric task was carried out, during which the test subjects had to detect visual stimuli of different contrast levels. It was found that pupillographic measures can be used to train a machine learning model to predict the error rate of a user with an average correlation of 0.72 ± 0.17 (Vergani Dambros et al. 2017). However, correlations were not stable between the subjects, whereas for some, positive and for other subjects, negative correlation coefficients occurred. Moreover, only nine young test subjects (age range 20–32 years), that were not stratified or ophthalmologically pre-examined in any way, were included (Vergani Dambros et al. 2017).

Additionally, EEG data (especially with regard to their alpha power) were evaluated together with pupillary data with regard to their ability to predict false responses to catch trials. Therefore, Dambros developed specific machine learning algorithms (Vergani Dambros

2017).
Data was analyzed by an SVR (support vector regression) as well as by a LASSO (least absolute shrinkage and selection operator) algorithm. For more information on these algorithms, see (Vergani Dambros 2017). Correlations of predicition and actual errors were assessed.

3.4.4 Algorithms

There have been various studies to monitor vigilance in the recent past. Therefore, algorithms to determine basic indicators for vigilance do already exist. Subsequently, two particular algorithms used to determine the pupil diameter and the height of the palpebral fissure are described, as these algorithms seem very helpful to monitor vigilance especially in examinations based on visual attention. Wavelet transformation is additionally used to extract fatigue waves out of pupil diameter recordings and thus is mentioned.

3.4.4.1 Determination of the pupil diameter and definition of eyelid closures (blinks)

Pupillography can be used to – generally spoken – determine the pupil diameter. For that, the term pupillography is used to describe all methods to record and evaluate pupil activity by means of changes in the pupil diameter. Continuous recordings of the pupil diameter are carried out over a defined period.

To determine the pupil diameter by pupillography during perimetric examinations, an algorithm has been released by Müller in 2013 (Müller 2013). This algorithm has been extended and improved for the application within this dissertation by Michael Wörner (no specific publication available). The pupil diameter is recorded during the perimetric session. This is practically realized by the infrared camera integrated in the OCTOPUS 900 perimeter (Haag-Streit AG, Koeniz, Switzerland). A maximum frame rate of 20 frames per second (fps) can be achieved. Resolution is 320x240 pixels (px) in grayscale.
Since the pupil is black and the surroundings are relatively bright, it can in principle be assumed that the lowest luminance values found lie within the pupil. An exception to this can only occur if the near-glass mount of the perimeter is used. To differentiate between the pupil and the near-glass mount, a check is made as to whether the lowest values found

are located within an ellipse or an ellipse section. If this is the case, it can be assumed that the pupil is annotated.

As described, the pupil detection algorithm was improved in the course of this study. This occurred between the conduct of the pilot studies and the main study. The reason for this was, that a precise analysis of the annotated pupils showed, that in some cases of eyelid closure, the pupil sizes detected were too small. This occurred due to the fact that the initial algorithm was designed to recognize ellipses (including circles). The algorithm was revised in a way that with the aid of a machine learning algorithm instead of ellipses, it was now also possible to recognize circle or ellipse *sections*. Thus, pupil sizes could be calculated more realistically (see Fig. 3.4).

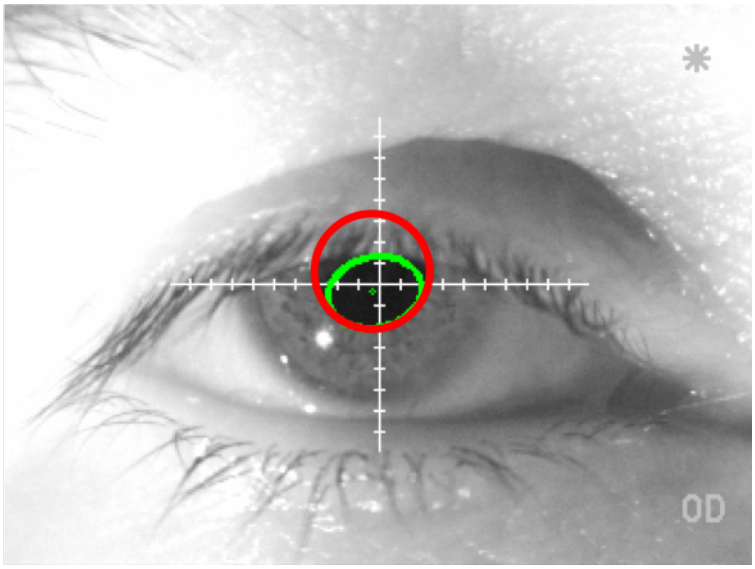

Figure 3.4: Illustration of the different pupil sizes detected by the different versions of the pupil detection algorithm. The green circle shows the pupil detected by the initial algorithm (ellipse recognition), the red circle shows the pupil detected by the improved algorithm (circle or ellipse section recognition)

In addition, a neural network has been implemented that does not only determine the pupil diameter based on the preconditions stated above, but also gives a confidence value of the probability that the detected part of the image is the real pupil or if no pupil is visible, for instance during a blink.
It is decided, whether a blink is occurring in a specific video frame or not depending on the confidence value of the pupil recognition taking into account the previous detection. According to this definition, on the one hand an eyelid closure can be reliably recognized

and on the other hand the height of the palpebral fissure can be detected without generating a bias due to eyelid closures.

3.4.4.2 Determination of the height of the palpebral fissure

The algorithm for the determination of the height of the palpebral fissure including its description was released by Michael Wörner for the purposes of this study.
The procedure for determining the height of the palpebral fissure is based on a paper by Kazemi and Sullivan on the shape detection of faces (Kazemi and Sullivan 2014). *Shape* is understood as a multitude of points that trace the contours of the chin, nose, eyes, etc. of a face. A *shape detection* places such points within a given image based on the approximate position and extent of a face determined by automatic facial recognition. The method of Kazemi and Sullivan starts with a medium shape, which is gradually changed by a variety of intensity comparisons between pixel pairs of the present image so that it approximates the actual facial contours. Which pairs of pixels are compared in each step and which changes in the current shape are made depending on the difference in intensity are trained beforehand as part of a machine learning process using a number of appropriately annotated images.
To determine the palpebral fissure height, this procedure was adapted so that the shape to be found does not describe a whole face, but eight points along the upper and lower edge of the eyelid. For this shape, the recognition was trained on 373 manually annotated images from the present study, so that these eight points for describing the contour of the eyelids could then also be found in unknown perimeter images. A center point could then be determined for each eyelid from the four points on the upper and lower eyelid. The distance between the upper and lower center finally results in the height of the palpebral fissure.

3.4.4.3 Wavelet Transformation

Wavelet transformation uses wavelike functions in different shapes, that are described as wavelets. Wavelets can be used to transform a signal into another representation which shows the signal information in a more useful form. This transformation of the signal is called the *wavelet transform*. Mathematically, the wavelet transformation is a convolution of the wavelet function with the original signal.

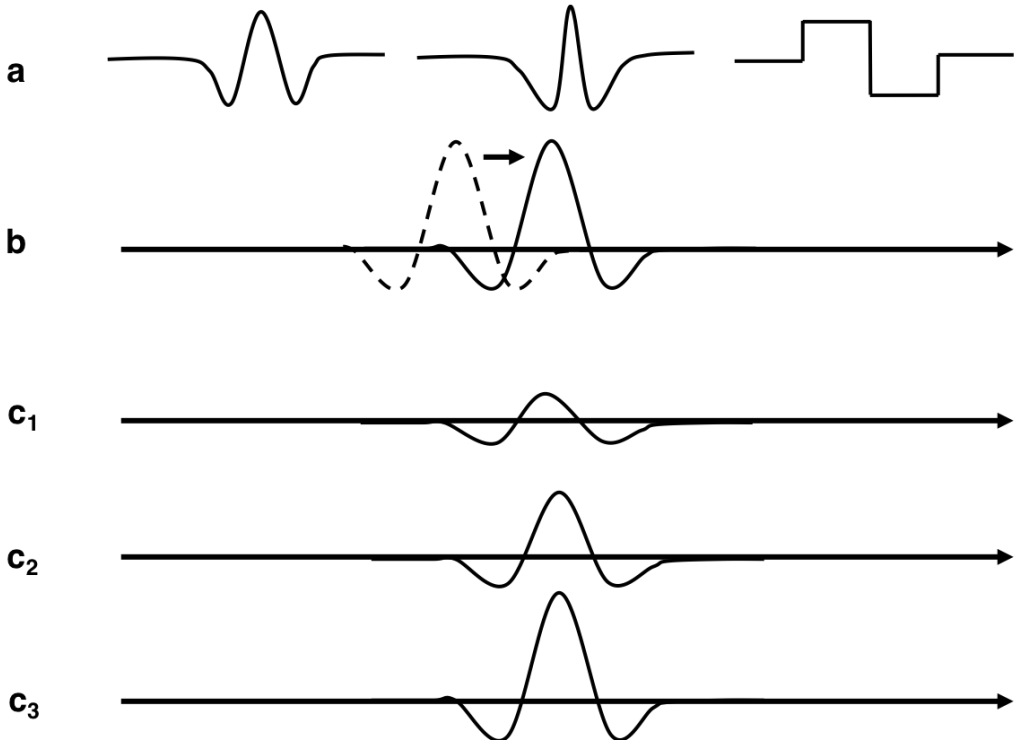

Figure 3.5: Wavelets, **a** some wavelet shapes, **b** location, $\mathbf{c_1}$, $\mathbf{c_2}$, $\mathbf{c_3}$ scale

A wavelet can be manipulated in two ways: it can be moved to different locations on the original signal and it can be stretched (see Figure 3.5) (Addison 2002) as cited in (Ungewiss 2015).

The wavelet transform is based on a pair of filters: One filter is a lowpass filter that takes over the task of a scaling function, while the other is a highpass filter. The lowpass filter produces an average signal (a) and the highpass filter produces a detail signal (d) (Weeks 2011) as cited in (Ungewiss 2015).

Wavelet transformation has, for instance, been used by Henson and Emuh in their study on fatigue waves during a campimetric examination (see chapter 3.4.1.1) (Henson and Emuh 2010).

4 Study design and methodology

4.1 Basics of the methodology

This chapter presents the methodology of this study. It should first be noted that this work is divided into two pilot studies and one main study. Basically, various physiological and non-physiological parameters related to the vigilance of subjects during perimetry were examined. These parameters were compared to the proportion of incorrect responses to catch trials as a gold standard.

The pilot studies were needed to obtain a first rough estimate of the expected effects of the study, which in the main study could be evaluated quantitatively.

For comparison between different test subjects, all physiological parameters mentioned were evaluated relatively and thus normalized to a value range between 0 and 1 by forming the ratio of the respective individual parameter values and the individual, parameter-related maximum for each parameter for each subject.
Frame rate of the pupillographic recordings was set to 20 frames per second (fps). However, due to hardware limitations, the recording software was programmed to lower frame rate or skip single frames in order to maintain the recording procedure also in cases where there were bottlenecks in data processing in connection with the available RAM memory. For this reason, all data were synchronized before the evaluation and resampled and smoothed to an artificial final frame rate of 20 fps.

In addition to the physiological parameters described in chapter 3.3, the frequency of seeing curve (FOS curve) was determined for each subject.

All data were analyzed using MatLab Release 2018a (The MathWorks Inc., Natick, USA).

4.2 Study design and methodology of *pilot study 1*

The first pilot study involved in this work has already been published as a poster with an associated abstract at the IPS Meeting in Udine, Italy in 2016 (Ungewiss et al. 2016). For this reason, only a course description is given for this pilot study at this place. The poster and associated abstract are attached to this work in App. E.

4.2.1 Experimental setup and subject sample for *pilot study 1*

The method of constant stimuli (MoCS) was applied to assess the differential luminance sensitivity with the OCTOPUS 900 perimeter (Haag-Streit AG, Koeniz, Switzerland, see Fig. 6.1).

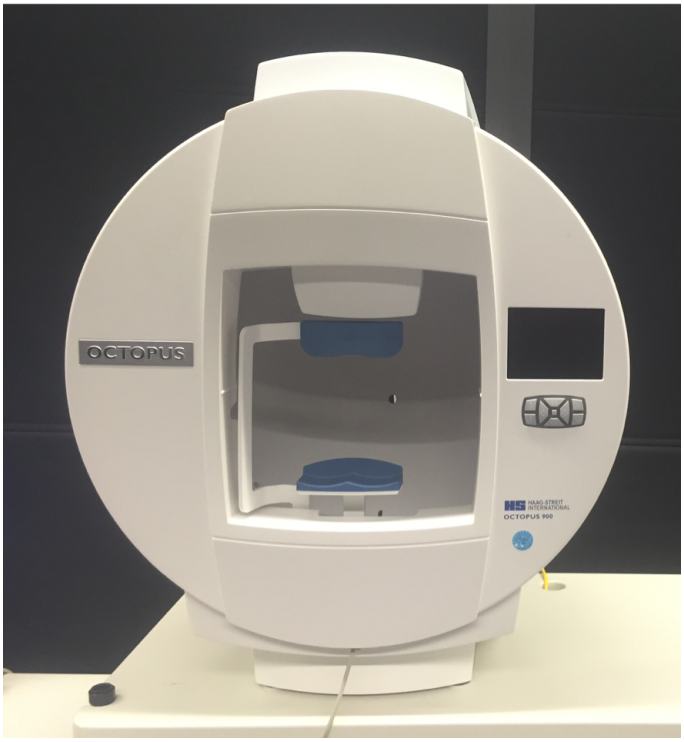

Figure 4.1: OCTOPUS 900 perimeter (Haag-Streit AG, Koeniz, Switzerland)

OPI (Open Perimetry Interface) (Turpin et al. 2012) was used to put together the test algorithms: Stimulus luminance was varied in 13 logarithmic steps (3 dB each) between 0.04 and 160 cd/m^2 at a background luminance of 10 cd/m^2. Goldmann size III (25,7') stimuli

were presented eight times each in three locations (-5°,+5°), (0°,0°), (3°,-6°): Altogether, 1,560 stimuli were presented within approximately 45 minutes. An increased rate of false positive and false negative catch trials was implemented (40% each). Pupil data were extracted from the built-in camera of the OCTOPUS 900 perimeter, which operated with a frequency of 20 fps. Heart rate was recorded with the H7 heart rate monitor using a chest strap (Polar Elektro GmbH, Buettelborn, Germany). Response times (i.e. the time intervals between stimulus presentation and the subjects' confirmation of its recognition by pressing the response button) were evaluated. Five test subjects were included in the *pilot study 1*.
Subjects were in general included if minimum distant visual acuity (without or with correction) was at least 0.8 (single letter optotypes [numbers], VISUCAT, argus individuell optic GmbH, Ottobrunn, Germany). The maxima of the acceptable ametropia were set to $\pm$8.00 dpt spheric and 2.50 dpt astigmatic ametropia. Ophthalmologic and general status had to be normal according to the exclusion criteria listed in chapter 4.4.2.2 in Tab. 4.1.

4.2.2 Data evaluation for *pilot study 1*

The quality of visual field testing was defined by the response behavior to catch trials. An *agreement index* (AI) was determined, relating periods with increased variabilities of

1. pupil diameter variability (see chapter 4.2.2.1)
2. heart rate variability (see chapter 4.2.2.2) and
3. reaction time variability (see chapter 4.2.2.3)

to periods with increased number of false responses to catch trials (see Fig. 4.2).
Parameters were selected with regard to relations found in previous work (Müller 2013) (Müller et al. 2014) (Ungewiss 2015).
An event was defined in a qualitative manner as described in chapters 4.2.2.1–4.2.2.3 for the physiological parameters included. For false responses to catch trials, which was the gold standard parameter, an event occurrence was defined empirically as a number at least three false responses to catch trials with a period of less than one minute without a false response in between.
The agreement index was calculated as the ratio between event overlap and total event occurrence periods.

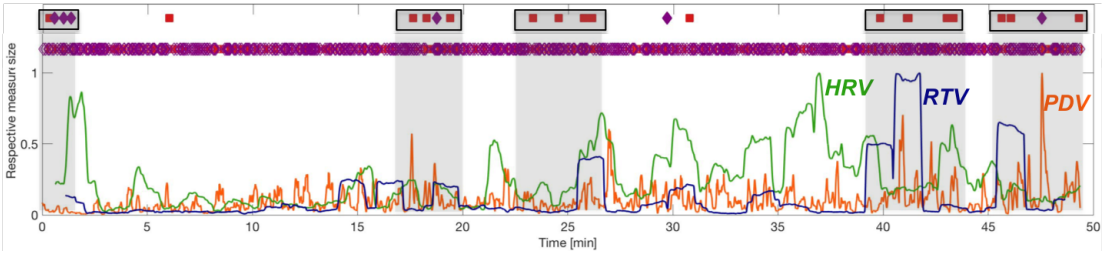

Figure 4.2: Description of event occurrence with regard to catch trials. Time periods with at least three false responses to catch trials with no more than 1 min. period without false response in between (empirically defined as an event occurrence) are highlighted in gray. PDV: pupil diameter variability HRV: heart rate variability, RTV: reaction time variability, red squares: false negative catch trials, filled red squares: false responses to false negative catch trials, purple diamonds: false positive catch trials, filled purple diamonds: false responses to false positive catch trials

Variabilities were calculated using sliding window algorithms. Such algorithms were originally used for data flow control in computer networks (Tanenbaum 2003) and are now widely used for the purpose of data analysis.
With the sliding window algorithm, data are analyzed gradually. A window of a certain length of frames is defined. This window slides over the data in the order of their recording. Since the same number of frames is processed at the same time, and the window slides one frame per calculation step, a time-based parameter is evaluated gradually for a certain period.

4.2.2.1 Pupil diameter variability

The pupil diameter variability (PDV) was computed as the variance of the pupil diameter over a time period of 60 seconds, using a sliding window algorithm.
Event occurrence was empirically defined as the occurrence of normed PDV values larger than 0.5. A time period was regarded as a coherent event if no more than 1 minute period without normed PDV values larger than 0.5 appeared.

4.2.2.2 Heart rate variability

The heart rate variability (HRV) was computed as the variance of the heart rate over a time period of 60 seconds, using a sliding window algorithm.

Event occurrence was empirically defined as the occurrence of normed HRV values larger than 0.5. A time period was regarded as a coherent event if no more than 1 minute period without normed HRV values larger than 0.5 appeared.

4.2.2.3 Response time variability

The response time variability (RTV) was computed as the variance of the response time over a time period of 60 seconds, using a sliding window algorithm.
Event occurrence was empirically defined as the occurrence of normed RTV values larger than 0.5. A time period was regarded as a coherent event if no more than 1 minute period without normed RTV values larger than 0.5 appeared.

4.2.2.4 Frequency of seeing (FOS) curves

Frequency of seeing (FOS) curves describe the relationship between the probability of seeing a stimulus and a stimulus property which can be contrast or size in perimetry. They can be seen as cumulative Gaussian functions depicting local threshold variability (Woodworth and Schlossberg 1954).
The characteristics of FOS curves have implications not only for perimetric thresholds but also for their variability. In FOS curves, a steep slope reflects low variability and therefore reliability, whereas a more shallow slope reflects higher threshold variability and therefore reliability (Chauhan et al. 1993).
Thus, in contrast to fluctuations of the FOS curves, that are described by false positive and false negative responses to catch trials, the slopes can also be used as a supplementary measure for the reliability of a subjects' performance and thus as a supplementary validity criterion. For *pilot study 1*, FOS curves were only displayed graphically.

4.3 Study design and methodology of *pilot study 2*

As the collection of the pupillary data was carried out in the same way as in *pilot study 1* (see chapter 4.2), a repetition of the information is not given here. Only the recording and evaluation of the EEG data is explained.

4.3.1 Experimental setup and subject sample for *pilot study 2*

The method of constant stimuli (MoCS) was applied to assess the differential luminance sensitivity with the OCTOPUS 900 perimeter (Haag-Streit AG, Koeniz, Switzerland). OPI (Open Perimetry Interface) (Turpin et al. 2012) was used to put together the test algorithms: Stimulus luminance was varied in 13 logarithmic steps (3 dB each) between 0.04 and 160 cd/m^2 at a background luminance of 10 cd/m^2. Goldmann size III (25,7') stimuli were presented 20 times each in three locations (-6.1°,-3.5°), (0°,7°), (6.1°,-3.5°), and a reference stimulus location was added at (0°,0°) with a weight of 0.1 (compared to a weight of 1.0 for all other stimuli locations) as additional fixation incentive. Stimuli presented at this reference location were excluded from data evaluation. The examination included 1,612 stimuli altogether. An increased portion of false positive and false negative catch trials was implemented (25% each). Pupil data were extracted from the built-in camera of the OCTOPUS 900 perimeter, which operated at a frequency of 20 fps.

In addition, a 32-channel EEG device with a sample rate of 30 Hz was used in combination with an actiCAP and an actiCAP Control Box with electrodes (Brain Products GmbH, Gilching, Germany) and 2 USBamp amplifiers (g.tec medical engineering GmbH, Schiedlberg, Austria). For data collection, the BCI2000 viewer as an open source software (Schalk et al. 2004) was used. Electodes were positioned as shown in Fig. 4.3. Electrode positions were F3, Fz, F4, T7, C3, Cz, C4, T8, CP3, CPz, CP4, P5, P3, P1, Pz, P2, P4, P6, PO7, PO3, POz, PO4, PO8, POO1, POO2, PO9, O1, O2, PO10, Oz (abbreviations as follows: F: frontal, T: temporal, P: parietal, O: occipital, C: central, z: midline sagittal plane; in addition: EOG1, EOG2). The reference electrode REF was placed at the left mastoid, the ground electrode GND was placed at the right mastoid.

Five test subjects were included in the *pilot study 2*.
Subjects were in general included if minimum distant visual acuity (without or with correction) was at least 0.8 (single letter optotypes [numbers], VISUCAT, argus individuell optic GmbH, Ottobrunn, Germany). The maxima of the acceptable ametropia were set to $\pm$8.00 dpt spheric and 2.50 dpt astigmatic ametropia. Ophthalmologic and general status had to be normal according to the exclusion criteria listed in chapter 4.4.2.2 in Tab. 4.1.

An additional proof-of-concept experiment was performed in the rooms of the EEG laboratory of the University Hospital in Tübingen, Department of Neurology and Epileptology with one subject (male, age 59 years).

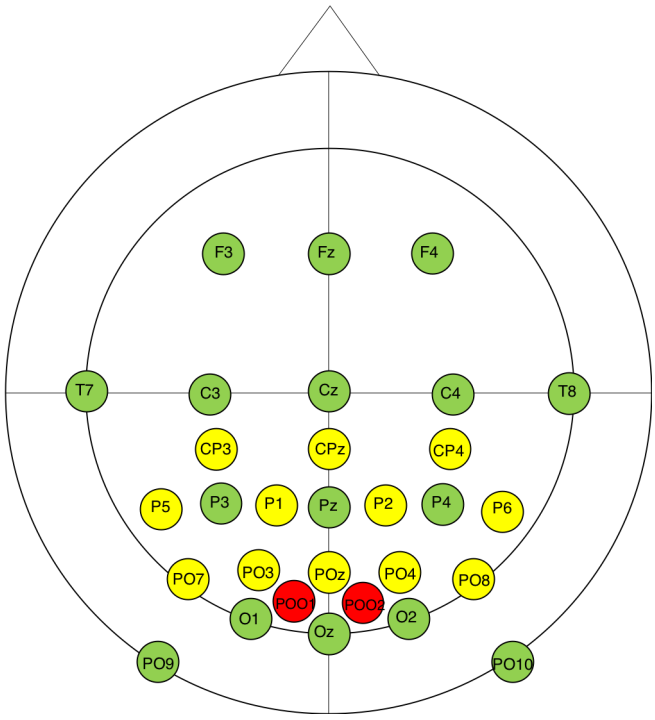

Figure 4.3: Positions of the EEG electrodes for *pilot study 2*. Abbreviations as follows: F: frontal, T: temporal, P: parietal, O: occipital, C: central, z: midline sagittal plane, colors refer to the coloring of the EEG cap (actiCAP, Brain Products GmbH, Gilching, Germany)

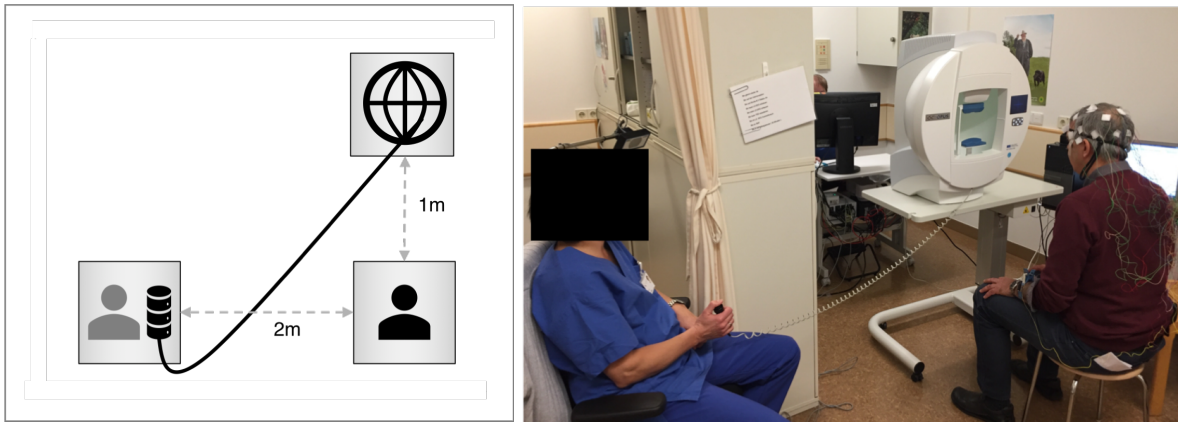

Figure 4.4: Experimental setup of the proof-of-concept study at the EEG laboratory of the University Hospital in Tübingen, Department of Neurology and Epileptology. The subject is placed at a distance of 1 m from the perimeter, an assistant operates the response button at a distance of 2 m from the subject

During this examination, only the number of false responses to catch trials and the EEG derivations were collected. Any collection of pupillary data was impossible because the subject had to keep up a distance of least 2 m from the perimeter due to electromagnetic interference between the perimeter and the EEG system. The test subject was also unable to operate the response button himself, as this also led to electromagnetic interference. The subject therefore gave the voice feedback ”yes” as soon as he saw a stimulus. An assistant immediately entered the response using the response button. The setup for this proof-of-concept experiment is shown in Fig. 4.4

4.3.2 Data evaluation for *pilot study 2*

The data for the *pilot study 2* (apart from the EEG data) were evaluated in the same way as the data for the *pilot study 1* (see chapter 4.2). Another separate description is therefore omitted.

EEG data analysis was performed for each of 30 channels, respectively (of the two remaining channels, one was used to synchronize the EEG system with the perimeter and the other for an accompanying EOG that was not evaluated for means of this specific study). Data analysis contained the evaluation of the relative alpha wave (which means the ratio between alpha-frequency waves and all waves found) and of an energy parameter. This energy parameter was defined as the alpha power spectral density of the signal.

Additionally, EEG data (especially with regard to their alpha power) were evaluated together with pupillary data with regard to their ability to predict false responses to catch trials. For this purpose, machine learning algorithms developed in a Bachelor's thesis by Dambros in 2017 (Vergani Dambros 2017) were applied (see chapter 3.4.3).

4.4 Study design and methodology of the *main study*

As the *pilot study 2* showed, the EEG recording in its present status was not a suitable option for measuring vigilance during perimetry. The remaining parameters were considered for the main study. In addition to the already known parameters (pupil diameter variability, heart rate variability, and response time variability), additional evaluation methods (wavelet

analysis for the pupil diameter variability and a frequency-dependent analysis for the heart rate variability) were used in order to make sure, that no possible parameter has been accidentally overlooked.
As it was possible to reliably extract the palpebral fissure height and therefore also eyelid closures using a machine learning algorithm (see chapter 3.4.4.2), these parameters were also included in the main study.

The experimental setup as well as any relevant information for the main study is documented in the study synopsis for this work (see App. A).

4.4.1 Sample size estimation

The main study was the first part of this work to perform a quantitative way of data analysis. Sample size estimation was carried out on the assumption that correlations for the recorded physiological parameters and the error rate with regard to catch trials produce significant results even for one subject due to the fact that there are 54,000 measurement values per subject per parameter within one session. The actual sample size estimation was therefore designed in a way that even correlation examinations that affect the entire sample and only contain one value per subject (for example the total number of errors, the subject's age or the scores of the ESS questionnaire) should result in significant values. A Spearman correlation with an intended correlation coefficient of ρ = 0.5 and a power of 0.95 was assumed. Using a bivariate two-tailed model, the number of cases was at least n = 46 test subjects.
In order to be able to divide the subjects into three age groups of the same size, n = 48 subjects were actually included.

4.4.2 Experimental setup and subject sample for the *main study*

4.4.2.1 Experimental setup

The method of constant stimuli (MoCS) was applied to assess the differential luminance sensitivity with the OCTOPUS 900 perimeter (Haag-Streit AG, Koeniz, Switzerland). OPI (Open Perimetry Interface) (Turpin et al. 2012) was used to put together the test algorithms: Stimulus luminance was varied in 13 logarithmic steps (3 dB each) between 0.04

and 160 cd/m^2 with a background luminance of 10 cd/m^2. Goldmann size III (25,7') stimuli were presented 20 times each in three locations (-6.1°,-3.5°), (0°,7°), (6.1°,-3.5°), and a reference stimulus location was added at (0°,0°) with a weight of 0.1 (compared to a weight of 1.0 for all other stimuli locations) as additional fixation incentive. Stimuli presented at this reference location were excluded from data evaluation. The examination included 1,612 stimuli altogether. An increased portion of false positive and false negative catch trials was implemented (25% each). Pupil data, blink rate and the height of the palpebral fissure were extracted from the built-in camera of the OCTOPUS 900 perimeter, which operated at a frequency of 20 fps.
Heart rate was recorded with the Ecgmove4 heart rate monitor using a chest strap (movisens, Karlsruhe, Germany).
The ESS questionnaire was filled in by all participants and evaluated in accordance with the existing guidelines (see chapter 3.3.7 (Johns 1991) (Sauter et al. 2007) (Deutsche Gesellschaft für Schlafforschung und Schlafmedizin (DGSM) 2007)).
Response time (i.e. the time interval between stimulus presentation and the subjects' confirmation of its recognition by pressing the response button) was monitored.

4.4.2.2 Description of the subject sample

Fourty-eight test subjects, equally distributed among three age groups (21–40 years, 41–60 years, 61–80 years) were included in the main study. Twenty-four dominant eyes and 24 non-dominant eyes were examined in randomized order.
Subjects were included if minimum distant visual acuity (without or with correction) was at least 0.8 (single letter optotypes [numbers], VISUCAT, argus individuell optic GmbH, Ottobrunn, Germany). The maxima of the acceptable ametropia were set to $\pm$8.00 dpt spheric and 2.50 dpt astigmatic ametropia. Ophthalmologic and general status (obtained by an ophthalmological examination and general history survey prior to the study) had to be normal according to the exclusion criteria listed in Tab. 4.1.
Informed consent was obtained from all test subjects and the study was approved by the ethics committee of the institutional review board (Landesärztekammer Baden-Württemberg, Germany, see App. B). All subjects were insured during their presence as well as for their arrival and return travel.
The test appointments were, as far as possible, evenly distributed over the day in order to avoid any circadian rhythm-related bias of the data. A controlled, exact equal distribution of the appointments over the day was not possible for organizational reasons.

Table 4.1: Exclusion criteria for the pilot and main studies

general exclusion criteria		**ophthalmological exclusion criteria**
epilepsy (potential triggering through flicker stimuli) / psychiatric disorders		strabism (also temporarily = intermittent)
medication affecting the reaction time		stereo angle measured with Lang I test $\geq$600" in 40 cm distance with adequate near-correction, if necessary
		eye movement disorders
		nystagmus
		eye surgery less than 3 months ago
		medication affecting the pupil dilatation and/or constriction
		relative afferent pupillary defect (RAPD)
		serious eye injuries
		indications of optic nerve or visual pathway diseases
		retinal or macular diseases

All documents used are attached to this work in App. C.

The individual ESS scores were tested for accordance to the existence of an onset of sleepiness (defined by the first occurrence of at least two false responses to catch trials within a 1-minute time period) by McNemar's test. Therefore, it was only tested, if an onset was present during the whole test period and if ESS scores were pathological concordantly. ESS scores were ranked as pathological, if a score of 11.7 or above occurred. This specific score was determined as former studies (Johns 1991) carried out, that the mean of ESS scores for obstructive sleep apnea syndrome (OSAS) subjects amounted to 11.7.

Sleepiness onset was calculated for each individual and correlated to age, ESS score and total number of errors. Total number of errors was also correlated to ESS score and age, and ESS score was, in turn, correlated to age by Spearman correlations. Spearman correlations were used as a normal distribution of the parameters was partly (i.e. in age) not intended and therefore not present. Decisions about significance were always carried out with regard to Bonferroni-corrected p values for the results (see chapter 4.4.3).

The individual peculiarities of the test subjects (diseases, etc.) were recorded. They are shown together with the individual data in one document per subject in the appendix of the work (see App. F).

4.4.3 Data evaluation for the *main study*

Error distribution and distribution forms of the examined parameters were analyzed. Consequently the statistical methods applied were chosen. First a global analysis of the data (under the same criteria for all subjects), then an individual analysis (under individual criteria) of the data was carried out.

Decisions about significance were always carried out with regard to Bonferroni-corrected p values for the results.
That means, that a result was only rated as significant, if

$$p < \frac{\alpha}{n} \tag{4.1}$$

with p: p value, α: significance level of 0.05 (as usual), n: number of test procedures.

Specific p values that were to be achieved, are stated for each evaluation carried out directly attached to the specific results in chapter 5.3.

4.4.3.1 Parameters considered in the *main study*

Some of the parameters involved allow for more than only one evaluation method. All evaluation methods applied are listed below.

False responses to catch trials: False responses to false positive as well as to false negative catch trials were summarized for evaluation, since it was observed during the conduct of the study that not all subjects reacted to the onset of fatigue or sleepiness in the same way. Some began to press the response button evenly with the acoustic stimuli that were presented together with the false positive catch trials, while other subjects missed the false negative catch trials. It was assumed that incorrect responses to both

types of catch trials were associated with sleepiness.
Periods with an increased number of false responses to catch trials were defined as a number of at least two errors per minute, calculated over a sliding window. This criterion of at least two false responses to catch trials per minute corresponded to the 95. percentile of the error rates for all test subjects.

Eyelid closures (blinks): Blink rate (BR) was included as well as blink rate variablity (BRV). As subjects were told to blink regularly after having perceived a stimulus, blink rate was rated as a parameter afflicted with artifacts. It was assumed, that BRV could show an unconcentrated behaviour with regard to eyelid closure. BR was assessed in blinks per minute and BRV was calculated as variance of BR over a 60-seconds-time period using a sliding window.

Pupillary oscillations: Blinks were removed prior to the further processing of the pupillary data.
Pupil diameter (PD) and pupil diameter variability (PDV) were included in the evaluation. PD was assessed by videopupillography and PDV was calculated as variance of PD over a 60-seconds-time period using a sliding window. For PD, a linear interpolation was performed for time periods where eyelid closures took place.
In addition, peaks in PDV (PDVpeaks, defined as the occurrence of values above the 95. percentile of the data of all subjects together), relating to an immediate dilatation and/or contraction of the pupil, were assessed and a wavelet transformation of the pupil data (PDVd10) was conducted according to the method Henson used in his work (Henson and Emuh 2010).

Palpebral fissure: The height of the palpebral fissure was defined as the distance between upper and lower lid edge in the course of the present work – in contrast to the width of the palpebral fissure, which would be defined as the distance between inner and outer lid corners (see Fig. 4.5).

The height of the palpebral fissure (PF) as well as its variability (PFV) were included in the main study. PF was evaluated from the pupillary data after excluding the blinks by

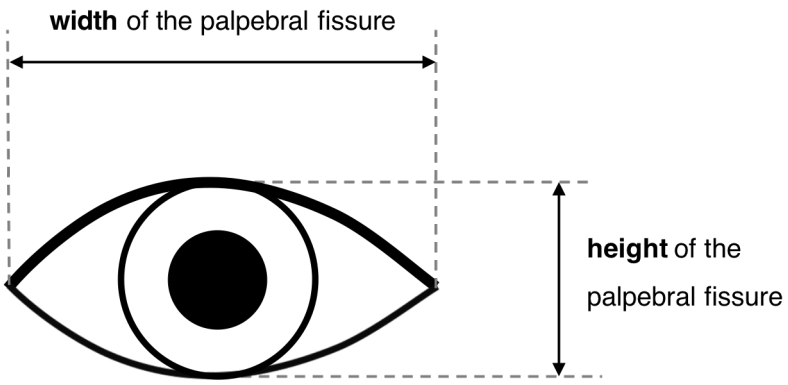

Figure 4.5: Definition of width and height of the palpebral fissure

application of a low pass filter via a 60-second-sliding window. Because of filtering due to blink exclusion, the first minute window of the examination was contaminated with calculation artifacts and therefore excluded from the further data evaluation procedure. PFV was calculated as the variance PF over a 60-seconds-time period using a sliding window.

Heart rate: Heart rate (HR) and heart rate variability (HRV) were included. HRV was calculated as variance of HR over a 60-seconds-time period using a sliding window.
In addition, a frequency-sensitive consideration of HRV took place, as HRV for *low* frequencies (HRVLF) and HRV for *high* frequencies (HRVHF) were calculated separately according to the frequency limits stated in 3.3.4.

Response time: Response time (RT) was included as well as response time variability (RTV). A linear interpolation was performed for response times as these were not available during time periods where below-threshold stimuli were presented.
RTV was calculated as variance of RT over a 60-seconds-time period using a sliding window.

4.4.3.2 Parameter overview

In order to get a coarse overview of the data, respective parameters were first evaluated using arbitrary and coarse granular assignment of the respective values to discrete intervals (minute 1, minute 2, etc.). As discrete time intervals were chosen, an evaluation

method was applied for each parameter that allowed also for discrete values (e.g. the discrete number of blinks instead of the blink rate over a specific time period). Only if this was not possible, mean values per minute were calculated. As short peaks that occurred were considered as important for the evaluation, these should be taken into account. Therefore, peak-sensitive mean values were chosen instead of median values only with regard to this specific case, although the data did not show a normal distribution.

False responses to catch trials: False responses to catch trials were counted per discrete minute interval as described above.

Corresponding parameters: The corresponding parameters listed in chapter 4.4.3.1 were analyzed.
For the blink rate (BR), discrete blinks were counted.
For the pupil diameter (PD), discrete peaks of the pupil diameter variability (PDVpeaks) were counted.
For the height of the palpebral fissure (PF), mean values of the PF were calculated, as it was assumed that PF decreased with increasing error rate.
For the heart rate (HR), mean values of the HR were calculated in order to check for a possible decrease of the HR with increasing error rate.
For the reaction time (RT), mean values of the RTV were calculated. This was done as from the evaluation of *pilot study 1*, it was assumed that RTV increased with increasing error rate whereas no reference for RT was available.

4.4.3.3 Parameter distributions and resulting statistical principles

Irrespective of the data analysis method described in chapter 4.4.3.2, sensitive cut-off values for each parameter had to be defined post hoc in order to differentiate normal from statistically noticeable or pathological values. As a second step, a global and individual analysis of the data could be conducted. It might be that the latter evaluation methods then showed results that could not be seen from the overview method.
For this more precise global and individual data analysis, however, the frequency distribution of the data were first required in order to be able to determine the appropriate statistical procedures.

All parameters were displayed graphically with regard to their frequency distribution (see chapter 5.3.4). Due to the fact that the majority of the parameters did not show normal distribution, parameter-free methods were selected for the statistical evaluation. This also seemed meaningful for the resulting rank correlations as it made no difference whether absolute or relative, normalized values (as described above) were used for the evaluation.

4.4.3.4 Global data analysis

Parameter selection for detailed analysis: All parameters listed in chapter 4.4.3.1 were examined for the global analysis. For this purpose, sensitivity and specificity for the entire collective were determined for each evaluation method depending on different cut-off values and visualized via ROC (receiver operating characteristics) curves. These were implemented in order to check whether a specific evaluation method seemed suitable at all if the cut-off values were selected correctly. AUROC (area under the ROC curve) values were used to select the most promising evaluation method per parameter.

As the parameter selection was completed, cut-off values had to be determined. The most relevant method to do this seemed to be the Youden index, also known as *Youden's J*, which was calculated as follows:

$$J = sensitivity + specificity - 1 \tag{4.2}$$

Cut-off values were selected for the maximum of Youden's J.

An alternative method for cut-off value selection would be the determination of sensitivity at a specificity aimed at, which has been done in the past specifically with regard to ophthalmological studies (Zangwill et al. 2001). For the purpose of this study, a specificity of 0.8 was chosen.

After cut-off values for sensitivity and specificity were defined, the corresponding percentile values for each of the selected evaluation methods per parameter were calculated.

Definition of the agreement index (AI): For the selected parameters, an agreement index was calculated for the agreement between the occurrence of false responses to catch

trials as a gold standard and noticeable values for the respective physiological parameter. The ratio between event overlap and total event occurrence periods was calculated.

An event was defined for each respective parameter/evaluation method as an occurring value above (for blink rate variability (BRV), the variability of the palpebral fissure height (PFV), the low frequency band of the heart rate variability (HRVLF), and response time variability (RTV)) or below (for pupil diameter (PD)) the specific percentile value corresponding to the cut-off values for sensitivity and specificity evaluated with Youden's J as well as for a specificity of 0.8 in a quantitative manner. An example of the analysis process is given in Fig. 4.6.

Agreement plots were created that show if an event occurred for the respective related parameters and if agreement to time periods with an increased error rate was existent. An example for the creation of an agreement plot is displayed in Fig. 4.7.

In addition, a "meta-correlation" of the total number of errors for each subject and the agreement indices was performed using Spearman's rank correlation method.

4.4.3.5 Individual data analysis

Parameter selection for detailed analysis: The global analysis method described above defines the same cut-off values for all subjects. This works well only as long as all subjects react to fatigue or sleepiness in the same or in a similar way. However, it is conceivable that some subjects give in to the onset of sleepiness quickly, while others fight it. In this case, physiological parameters would develop very differently with the onset of fatigue or sleepiness.

For this reason, an *individual* analysis was also carried out as a part of this study. For this purpose, the number of false responses to catch trials was calculated "pseudo-continuously" and correlated as an error rate to the various evaluation methods for the included physiological parameters, as listed in chapter 4.4.3.1. Since this was done individually for each parameter for each test subject, the potentially individually different reaction to the onset of fatigue or sleepiness was taken into account.
The evaluation methods with the highest median of correlation coefficients per parameter were selected for the final analysis.

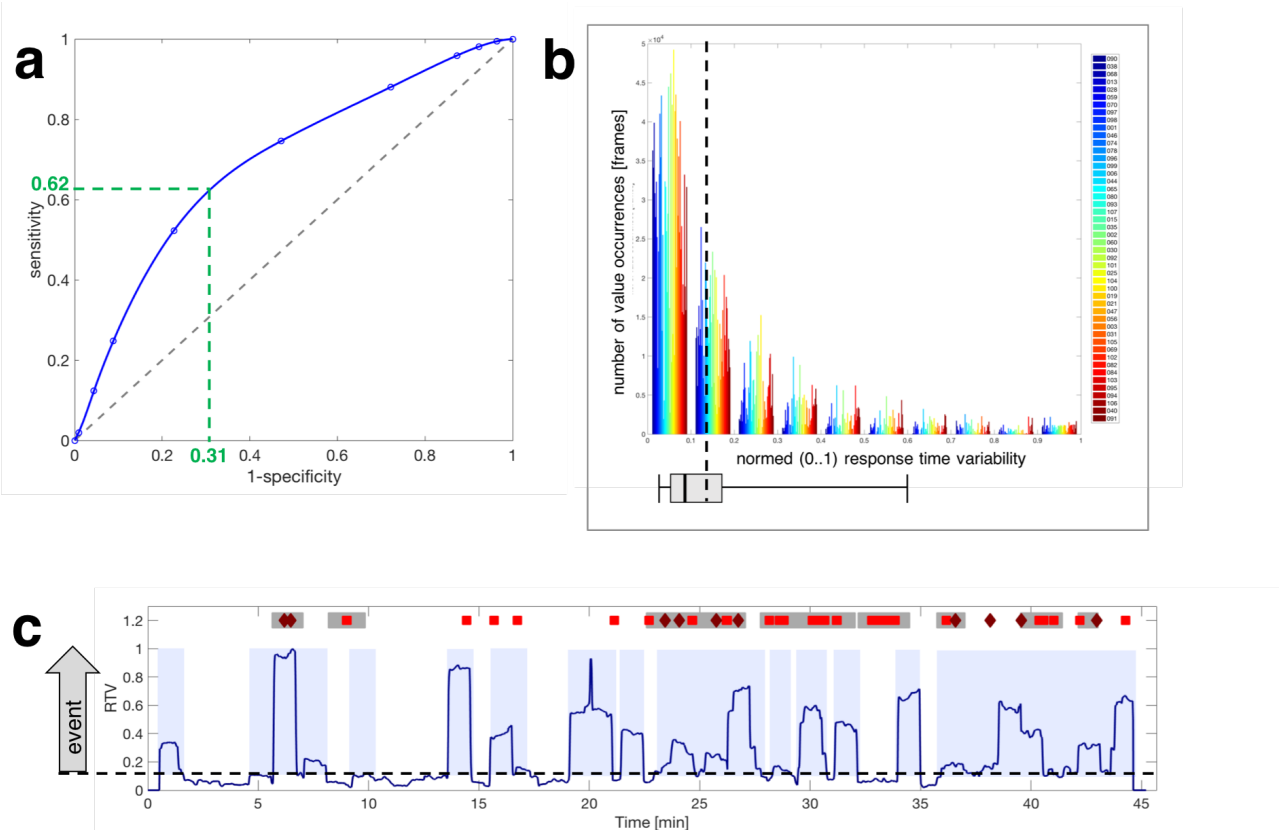

Figure 4.6: Example for global data analysis for the response time variability (RTV) for subject ID 106 and an evaluation with Youden's J. **a** A ROC curve was computed and cut-off values for sensitivity and specificity were defined (with sens. = 0.62 and spec. = 0.69 in this case, see green dashed lines). **b** Percentiles for cut-off values for sens. and spec. were calculated (in this case, the 66. perc. corresponded to the above mentioned values for sens. and spec.). By a parameter distribution for RTV for the whole subject sample (subjects are sorted by the total no. of false responses to catch trials), the specific cut-off value corresponding to the 66. perc. was defined (in this case, the value was 0.15), marked by the black dashed line. The box plot shows the distribution for the whole subject sample, whereas the median is marked by the bold black line, the box marks the 25. and 75. perc., and the whiskers stand for the 5. and 95. perc. In order to be able to give an overview, the illustration here is very small. Images in original size are shown in App. I. **c** Therefore, for the individual, time periods with values occurring above the value of 0.15 (marked by the black dashed line) were defined as an event for RTV (see light blue highlights). In contrast, events for false responses to catch trials are highlighted in dark gray. An event overlap is defined as the occurrence of both an event for RTV and for false responses to catch trials at the same time. For a more detailed explanation of an agreement plot, see Fig. 4.7

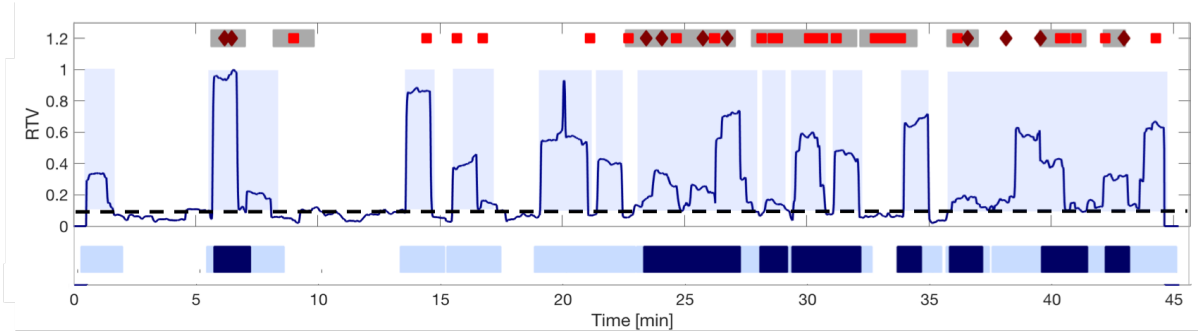

Figure 4.7: Exemplary creation of an agreement plot for the agreement of an increased error rate and the response time variability (RTV) for subject ID 106. **Upper part** Time periods with an increased error rate are highlighted in gray. **Middle part** By a parameter distribution for RTV for the whole subject sample, the specific cut-off value corresponding to the 66. perc. was defined (in this case, the value was 0.15), marked by the black dashed line. Time periods with an increased response time variability (e.g. event occurrence for response time variability) are marked in light blue. **Lower part** Transfer of periods with event occurrence for response time variability to the blue bar. If at the same time, the error rate was increased, the blue bar turns to a dark blue color. CAVE: In some places the blue bar in the lower part seems to be continuous, whereas the blue-marked areas in the upper part are interrupted. The interrupted areas are correct and accurate. The continuous effect occurs due to the circumstance, that the bars can only be displayed with a relatively low accuracy (protruding markers), for this reason short periods with short breaks in between in the agreement plot look like a continuous period of event occurrence. However, the agreement indices are always calculated with the correct, accurate values

Individual correlation coefficients: Individual correlation coefficients were calculated using Spearman's rank correlation method, as justified in chapter 4.4.3.3.

In addition, a "meta-correlation" of the total number of errors for each subject and the respective correlation coefficients was performed for each parameter included using Spearman's rank correlation method as well.

4.4.3.6 Frequency of seeing (FOS) curves

Frequency of seeing (FOS) curves were recorded for each test subject for each tested location as described in chapter 4.2.2.4.
FOS functions were calculated as follows:

$$FOS = SSL \cdot L[dB] \tag{4.3}$$

with FOS: frequency of seeing, SSL: slope steepness, L[dB]: luminance level in dB

In addition, for the main study, the steepness of the steepest slope (SSL) of the FOS curve within a monotonous drop (in order to exclude small fluctuations) was calculated for each subject. If the steepness of the slope was different for different test locations, the median of the slope steepness was taken.

A Spearman correlation between the steepness of the slope (SSL) and the total number of errors per subject was carried out.

False positive and false negative responses to catch trials refer to the fluctuation of the responses. The slope steepness – in contrast – served as a supplementary measure for the reliability of a subjects' performance (retest reliability for the respective luminance levels of the presented stimuli) and thus as a supplementary quality criterion. The interrelation is shown in Fig. 4.8.

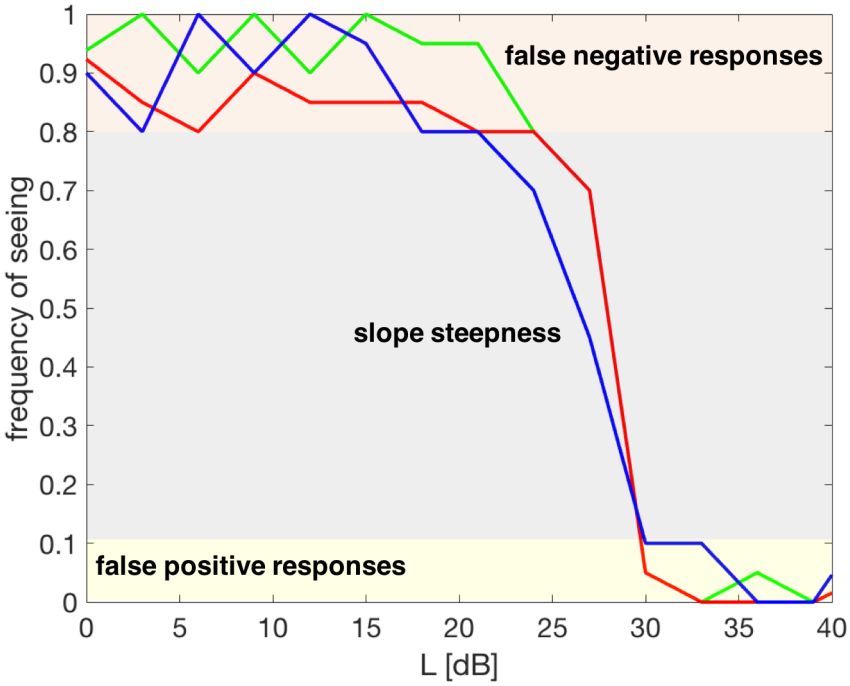

Figure 4.8: Exemplary visualization (for subject 106) of the different quality parameters a frequency of seeing (FOS) curve can provide. Fluctuations referring to false positive responses to catch trials are highlighted in yellow, fluctuations referring to false negative responses to catch trials are highlighted in orange, slope steepness referring to the reliability of a subjects' performance is highlighted in gray. Locations tested: blue (0°,7°), green (-6.1°,-3.5°), red (6.1°,-3.5°), L: luminance

5 Results

5.1 Results of *pilot study 1*

As the results of the first pilot study were already presented at the IPS Meeting 2016 in Udine (Ungewiss et al. 2016), they will only be displayed very briefly here. Poster and associated abstract can be found in App. E of this work.

Sufficient data were obtained from five subjects (3 male, 2 female; age range 25–58 years) that were ophthalmologically normal (exclusion criteria are listed in chapter 4.4.2.2 in Tab. 4.1).
Agreement indices (according to chapter 4.2.2) and time periods with increased number of false responses to catch trials are shown in Tab. 5.1.
The pupil diameter variability showed the highest agreement indices in three out of five subjects, whereas response time variability showed lower but still moderate and heart rate variability showed low or no agreement. It was assumed that the low agreement indices for the heart rate variability could be related to the fact that the measuring equipment was not sufficiently precise. For this reason, professional equipment for determining the heart rate was procured for the main study.

Table 5.1: Agreement indices and time periods with increased number of false responses to catch trials for *pilot study 1*

	Subject 1	**Subject 2**	**Subject 3**	**Subject 4**	**Subject 5**
Period with increased no. of false responses to catch trials	17.6 min	2.9 min.	2.0 min.	27.7 min.	0 min.
Pupil diameter variability	0.35	0.33	0.10	0.70	0
Heart rate variability	0	0	0	0.03	0
Response time variability	0.32	0.41	0	0.08	0

5.2 Results of *pilot study 2*

Pilot study 2 was added to evaluate the relevance of EEG data. Pupil diameter was evaluated again for plausibility testing as this was the parameter showing the highest agreement to false responses to catch trials in *pilot study 1*.

Sufficient data were obtained from five subjects (4 male, 1 female; age range 24–59 years) that were ophthalmologically normal (exclusion criteria are listed in chapter 4.4.2.2 in Tab. 4.1).

5.2.1 Results for pupillographic data and response time

Results for pupillographic data were evaluated in the same way as in *pilot study 1*. Agreement indices (according to chapter 4.2.2) and time periods with increased number of false responses to catch trials are shown in Tab. 5.2.

5.2.2 Results for EEG data

EEG data were only evaluated in a qualitative way. For each test subject, relative alpha waves and alpha power represented by an energy parameter based on power spectral density (PSD) were displayed for each channel separately, together with responses to catch trials and pupillary oscillations, as alpha frequencies were seen as relevant in the context of sleepiness detection. For time periods with an increased number of false responses to catch trials, EEG data were checked for remarkable characteristics. As none of these were found, results of the *pilot study 2* are only shown in App. G.

Table 5.2: Agreement indices and time periods with increased number of false responses to catch trials for *pilot study 2*

	Subject 6	**Subject 7**	**Subject 8**	**Subject 9**	**Subject 10**
Period with increased no. of false responses to catch trials	4.4 min	0 min.	2.0 min.	18.2 min.	0 min.
Pupil diameter variability	0	0	0.18	0.24	0

For the additional proof-of-concept examination of one test subject at the EEG laboratory of the University Hospital in Tübingen, Department of Neurology and Epileptology, results of responses to catch trials are shown below in Fig. 5.1.

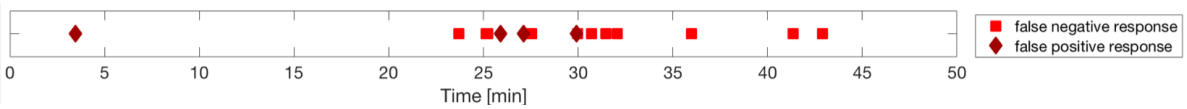

Figure 5.1: False responses to catch trials for the proof-of-concept examination of one test subject at the EEG laboratory of the University Hospital in Tübingen, Department of Neurology and Epileptology

It was neither possible to obtain the raw data, nor to extract a graphical representation from the system of the EEG laboratory of the University Hospital in Tübingen, Department of Neurology and Epileptology.
An analysis of the EEG data recorded there was carried out by Prof. Dr. Yvonne Weber, the senior chief physician of the EEG laboratory. This showed that only in minutes 2 and 3, first signs of sleepiness according to clinically relevant methods could be observed. Even at this stage, however, no change in the occipital basic rhythm was apparent, but horizontal eye movements were detected by an EOG (electrooculogram) electrode, which can indicate such a stage (Email correspondence between Prof. Dr. Yvonne Weber and the author is attached in App. H for the verification of this statement).

As can be seen from Fig. 5.1, false responses to catch trials occurred mainly beginning from minute 20 (only one false positive catch trial, that could not be rated as pathological, appeared in minute 3). Therefore, EEG alpha *waves* did not seem to be a relevant option for vigilance monitoring during perimetry for the reasons of both valide results and electromagnetic interference between the perimeter and the EEG system.

An evaluation of EEG alpha *power* and pupillary data with regard to their ability to predict false responses to catch trials was carried out with the help of algorithms developed by Dambros in his Bachelor's thesis (Vergani Dambros 2017) as described in chapter 4.3.2. The following results were found (see Tab. 5.3).
It can be seen from Tab. 5.3, that the overall results (with the exception of subject 9 for SVR and subjects 7 and 8 for LASSO) show rather weak correlations. It should also be noted that high correlation coefficients sometimes show an inter-individual difference in the direction of the relationship (see subjects 7 and 8 for LASSO).
For this reason, the algorithms tested cannot be regarded as reliable for the present study.

Table 5.3: Correlation coefficients of EEG and pupillary data analyzed with SVR and LASSO algorithms developed by Dambros (Vergani Dambros 2017)

	Subject 6	**Subject 7**	**Subject 8**	**Subject 9**	**Subject 10**
ρ (SVR)	0.17	0.02	-0.11	0.55	0.26
ρ (LASSO)	-0.01	0.49	-0.66	0.00	0.12

Therefore, EEG alpha *power* did not seem to be a relevant option for vigilance monitoring during perimetry in the course of this study as well.

5.3 Results of the *main study*

In contrast to the results of the pilot studies, data analysis for the main study was carried out in a quantitative way.

5.3.1 Description of the subject sample

Subsequently, the subject sample is described by its distribution among age and gender as well as for the individual ESS scores achieved. A correlation analysis of the information about the subject sample is performed.

5.3.1.1 Basic information

Every test subject was labelled by an ID number ranging from 001 to 107. Not every possible number was given to a test subject included in the main study of this dissertation, because subjects who had completed another study earlier, were addressed. A study ID was given to them already at the first point of contact, regardless if they agreed to take part in the present study or not. In addition, ID numbers were assigned to possible examination time slots in advance. Not every examination time slot was used due to the availability of the test subjects. The ID numbers were distributed as follows:

- 54 subjects of who had completed another study earlier were addressed.
  23 of them agreed to take part in the present study.

- 28 more subjects were recruited directly for the purpose of this study, all of whom agreed to take part in the present study.

- 25 examination time slots were assigned to ID numbers in advance, but could not be used.

Therefore, 107 subject IDs were assigned altogether. Fifty-one test subjects agreed to take part in the present study.

All 51 subjects who agreed to take part in the present study underwent a preliminary ophthalmological examination. Two of them had to be excluded due to in- and exclusion criteria (see Tab. 4.1). Reasons for exclusion were strabism in one case, and the indication of an optic nerve disease in another case. One subject cancelled participation in the study after the preliminary ophthalmological examination.

Sufficient data were obtained from 48 test subjects (in one case [subject 044] data recording stopped after some time for unexplained reasons, data were analyzed anyway). The subjects (18 male, 30 female, age range 22–78 years, median age 47 years) were distributed equally among the three age groups (21–40, 41–60, 61–80 years) as shown in Fig. 5.2.

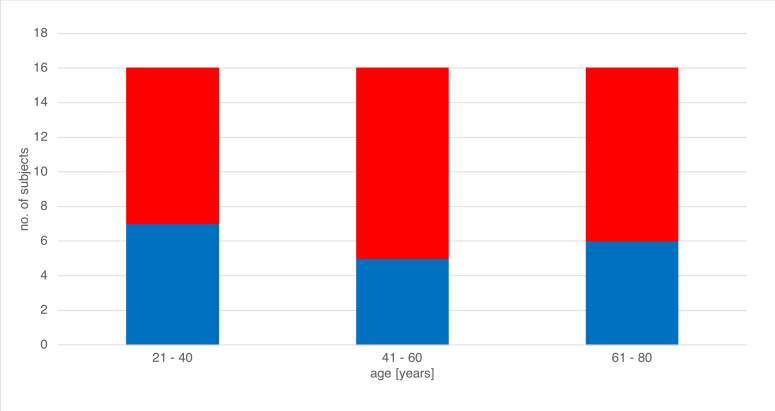

Figure 5.2: Age and gender distribution of subjects involved in the study (red: female, blue: male)

5.3.1.2 Epworth Sleepiness Scale (ESS)

The results for die Epworth Sleepiness Scale (ESS) scores for all test subjects, separated by age, are shown in Fig. 5.3.

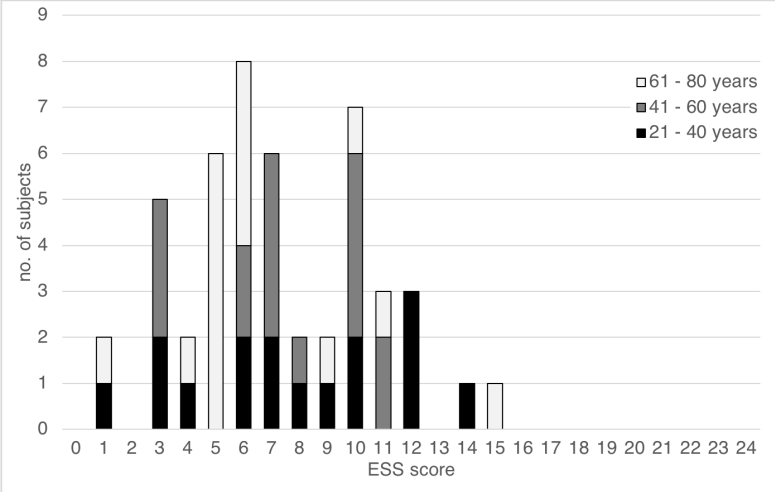

Figure 5.3: Distribution of the Epworth Sleepiness scale (ESS) scores by age. Black: age group 21–40 years, dark gray: age group 41–60 years, light gray: age group 61–80 years

5.3.1.3 Onset of sleepiness

The onset of sleepiness was defined as the point in time, when an increased number of false responses to catch trials occurred for the first time. An increased number of false responses to catch trials was defined as an error rate of at least 2 errors/min., corresponding to the 95. percentile for the error rates of all test subjects. Fig. 5.4 shows the onsets for all subjects involved. Only 26 our of 48 subjects showed any onset at all with a median of 5.9 minutes.

The results of an evaluation of the accordance of the ESS values and an occurrence of onset of sleepiness are shown in Tab. 5.4. With χ^2 = 16, df = 1, a resulting p value of $p = 6.33 \cdot 10^{-5}$ showed that there was a statistically significant difference between the ESS values and an occurrence of onset of sleepiness. Thus, no accordance of the ESS values and onset of sleepiness was present.

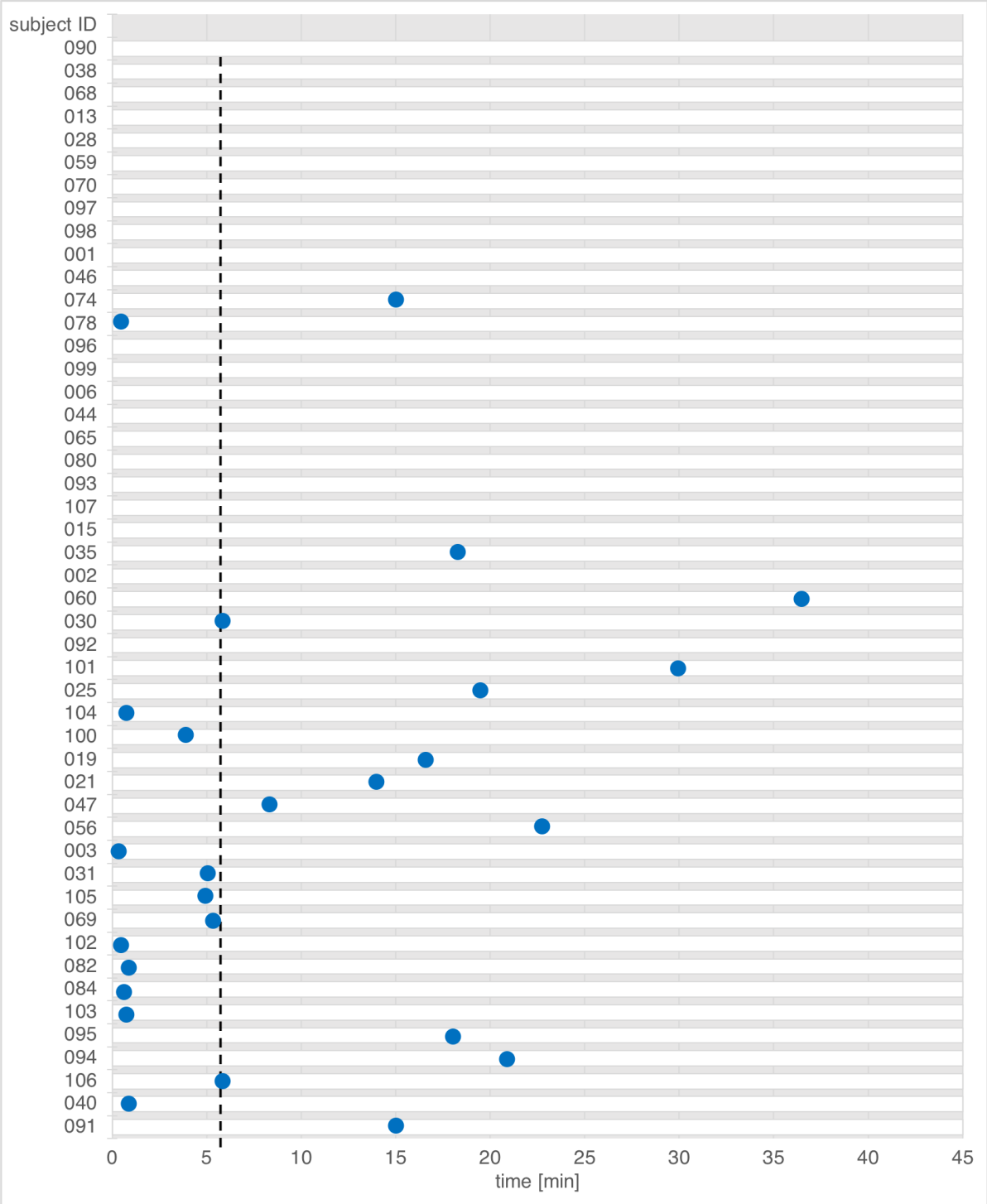

Figure 5.4: Onset of sleepiness for all subjects. IDs are shown on the left and sorted by the total no. of errors for each subject (according to Fig. 5.6). Blue dots: onset of fatigue (only for the 26 subjects showing an onset), black dashed line: median (only for the 26 subjects showing an onset)

Table 5.4: McNemar's test of accordance of onset of sleepiness and pathological ESS scores

	onset present	**onset not present**	**sum**
ESS pathological	3	2	5
ESS not pathological	23	20	43
sum	26	22	48

Table 5.5: Results of global correlation analysis (Spearman's rank correlation) for the parameters age, ESS, total no. of errors, and onset of sleepiness. Correlations to the onset of sleepiness were only carried out for a subgroup of 26 test subjects who showed an onset of sleepiness. Six correlation analyses were carried out, which led to a significance requirement of $p<0.008$

	Spearman's ρ	**p**
age x onset (subgroup)	-0.33	0.09
ESS x onset (subgroup)	0.36	0.07
age x total no. of errors	0.10	0.49
ESS x total no. of errors	0.05	0.73
onset (subgroup) x total no. of errors	-0.24	0.23
age x ESS	-0.23	0.11

5.3.1.4 Global correlation analysis

Globally assessed parameters were correlated to each other. Six correlation analyses were carried out, which lead to a significance requirement of $p < 0.05/6 = 0.008$. The correlation coefficients are listed in Tab. 5.5.

No significant correlation between ESS score, age, total number of errors, and onset of sleepiness occurred. This showed that neither ESS scores collected prior to a perimetric examination nor age could be taken as an indicator for the occurrence of a time period with an increased error rate or an increased total number of errors. In addition, total number of errors and onset of sleepiness did not correlate significantly. Therefore, some subjects seemed to be able to distribute single errors over a relatively wide time period, while others produced many errors in a short time period, referring to a limited period of sleepiness. The first case was often not rated as onset of sleepiness while the latter one was, as in the first case an error rate of at least 2 errors/min. often occurred while in the latter case that did not take place.

5.3.2 Principles of parameter evaluation

5.3.2.1 Parameters considered in the study

All parameters involved in the study were already listed in chapter 4.4.3.

5.3.2.2 Graphical representation of relative, normalized measures

First, all parameters (normalized, relative values) were displayed graphically as shown exemplarily for subject 106 in Fig. 5.5.
These graphics were conducted for all test subjects and can be found in documents created for each individual subject in App. F. Such a document could be used to show individual results of each test subject. In addition qualitative estimations about the relation of different physiological parameters to false responses to catch trials could be carried out. However, it was not possible to execute a quantitative analysis of data in that way.
For that reason, a cumulative approach was pursued subsequently.

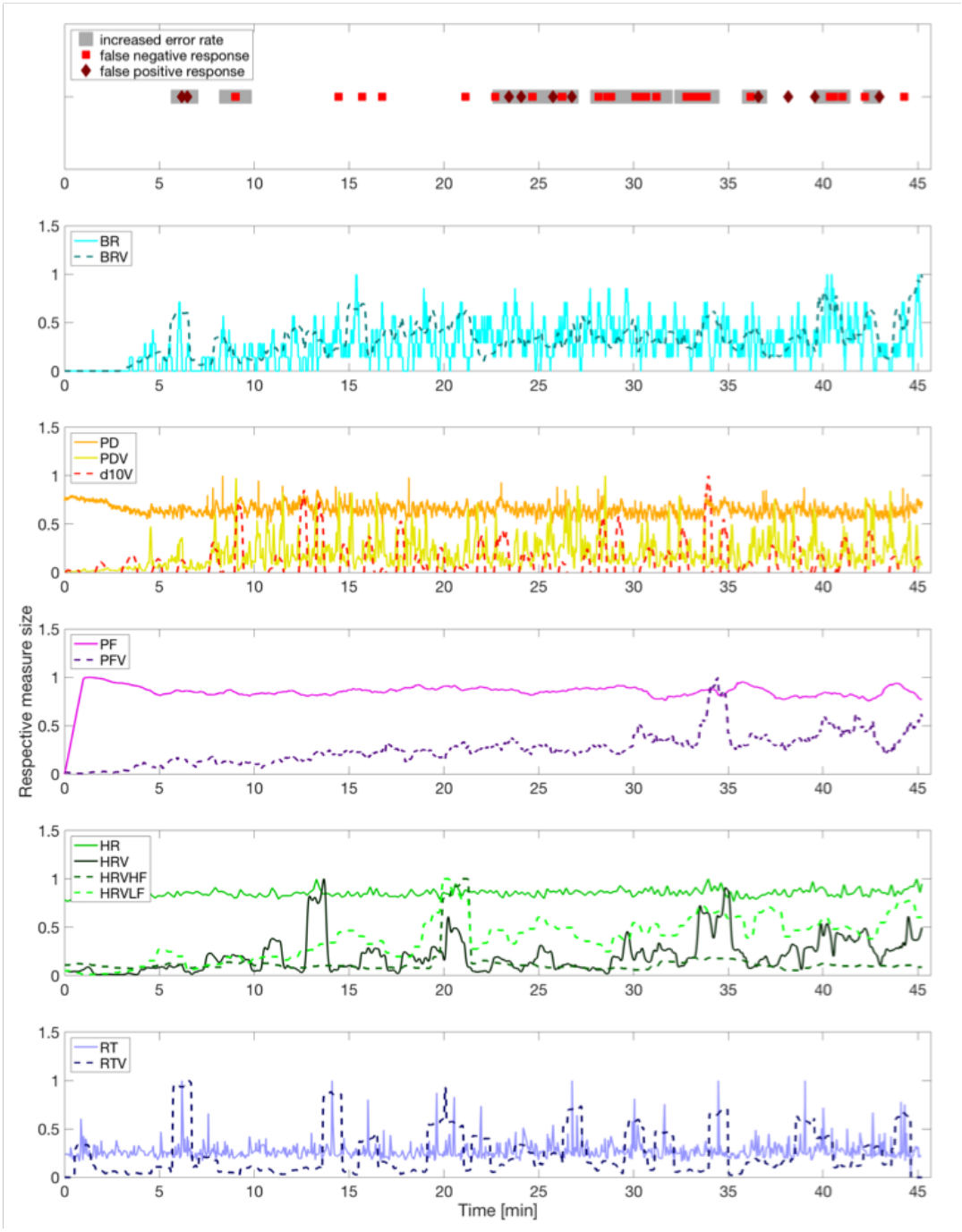

Figure 5.5: Parameters for subject 106 (normalized, relative values). BR: blink rate, BRV: blink rate variability, PD: pupil diameter, PDV: pupil diameter variability, d10V: variability of wavelet (d10) analyzed pupil diameter, PF: palpebral fissure height, PFV: variability of the palpebral fissure height, HR: heart rate, HRV: heart rate variability, HRVHF: heart rate variability (high frequency band), HRVLF: heart rate variability (low frequency band), RT: response time, RTV: response time variability

5.3.3 Parameter overview

An overview for different parameters, as described in chapter 4.4.3.2, is shown.
For each parameter, subjects were arranged by their total number of errors starting from a low number at the top to a high number at the bottom.
All overview figures are depicted in Fig. 5.6 – Fig. 5.11.

5.3.3.1 False responses to catch trials

Fig. 5.6 shows time periods with an increased number of false responses to catch trials for all test subjects. Time periods without false responses to catch trials are marked in white, whereas red-marked periods show that there an increased number (above the 95. percentile) of false responses to catch trials occurred. Color depth increases with an increasing number of false responses per minute. Altogether, an unexpectedly low number of time periods with an increased number of false responses to catch trials occurred among the vast majority of all test subjects. If false responses to catch trials were present in a subject, these occurred mostly during the second half of the examination.

5.3.3.2 Eyelid closures/blinks

Fig. 5.7 shows time periods with an increased number of blinks (above the 95. percentile, according to the requirements for false responses to catch trials) for all test subjects. Time periods without an increased number of blinks are marked in white, whereas teal-marked periods show that there an increased number of blinks occurred. Color depth increases with an increasing number of blinks.
The graphic shows that an increased number of blinks occurred mostly during the second half of the examination, as false responses to catch trials did (see Fig. 5.6). A subject-related assignment of increased numbers of blinks to an increased number of false responses to catch trials was not possible.

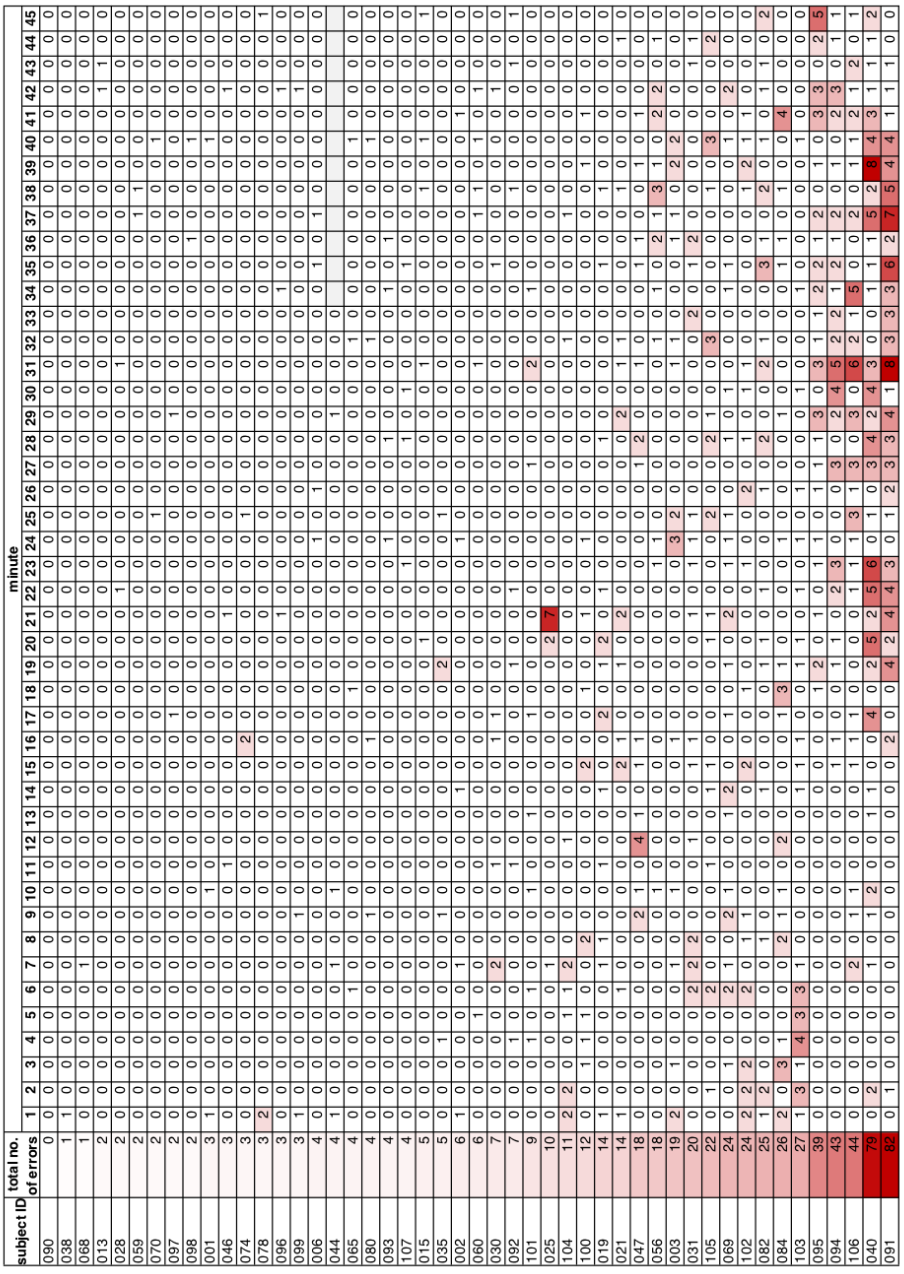

Figure 5.6: Time periods with increased number of *false responses to catch trials* for all test subjects. Subjects are arranged by their total no. of errors starting from a low number of errors at the top to a high number of errors at the bottom. Time periods without false responses to catch trials are marked in white, red-marked periods show that there an increased number (above the 95. percentile) of false responses to catch trials occurred. Color depth increases with an increasing number of false responses per minute

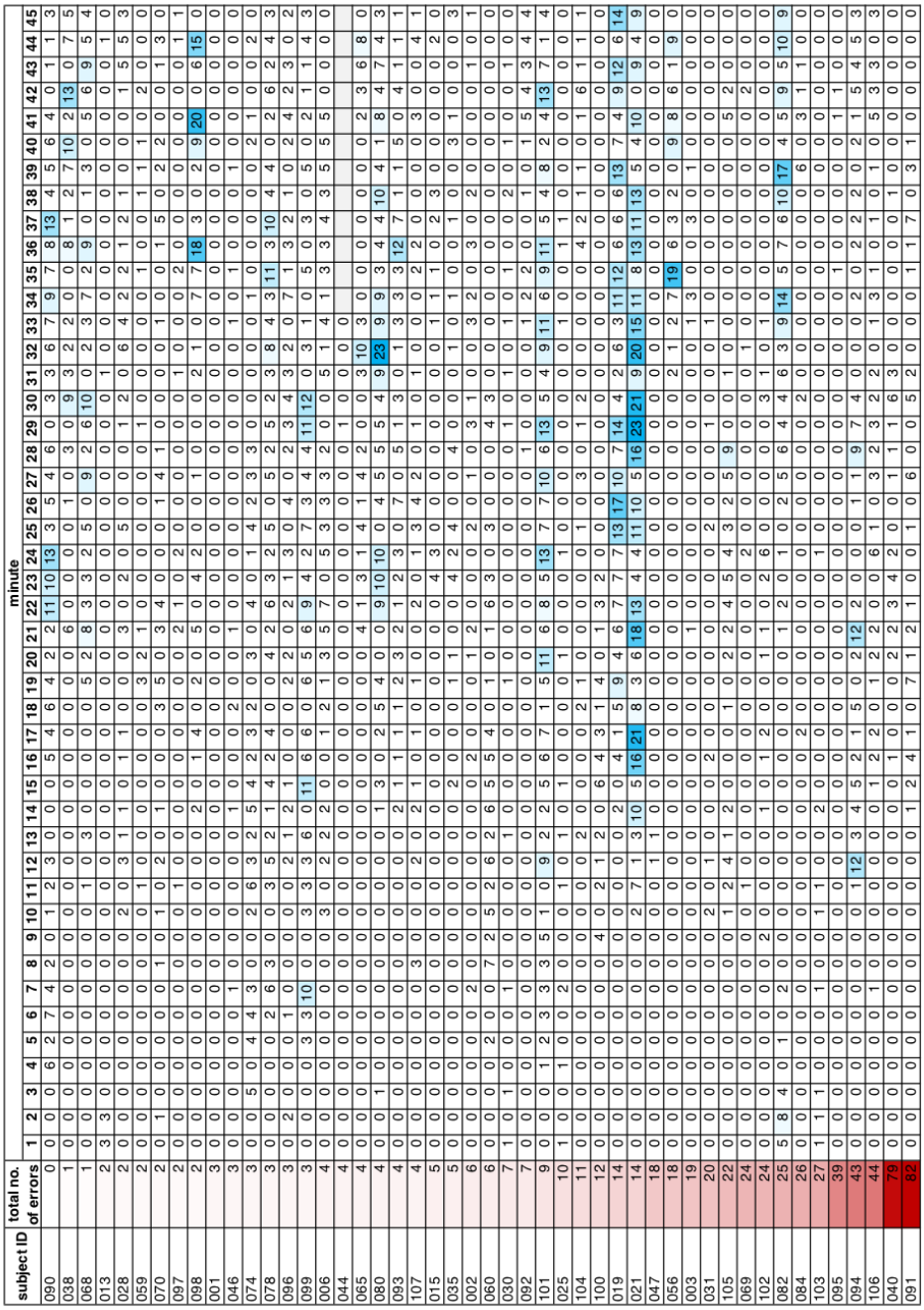

Figure 5.7: Time periods with increased number of *blinks* for all test subjects. For sorting criteria, see Fig. 5.6. Time periods without an increased number of blinks are marked in white, teal-marked periods show that there an increased number (above the 95. percentile) of blinks occurred. Color depth increases with an increasing number of blinks per minute

5.3.3.3 Pupil diameter variability

Fig. 5.8 shows time periods with an increased number of peaks in pupil diameter variability (above the 95. percentile, according to the requirements for false responses to catch trials) for all test subjects. Time periods without an increased number of peaks in pupil diameter variability are marked in white, whereas orange-marked periods show that there an increased number of peaks in pupil diameter variability occurred. Color depth increases with an increasing number of peaks in pupil diameter variability.
The graphic shows that neither a subject- nor a time-related assignment of an increased pupil diameter variability to an increased number of false responses to catch trials was possible.

5.3.3.4 Palpebral fissure height

Fig. 5.9 shows time periods with a decreased mean value (below the 5. percentile, according to the requirements for false responses to catch trials) of the palpebral fissure height for all test subjects. Time periods without a decreased mean value of the palpebral fissure height are marked in white, whereas purple-marked periods show that there a decreased mean value of the palpebral fissure height occurred. Color depth increases with a decreasing palpebral fissure height.
The graphic shows that a subject- and/or time-related assignment of a decreased palpebral fissure height to an increased number of false responses to catch trials was possible for individual subjects such as 040, 091 and 094. However, incorrect assignments occurred, for instance for subjects 013 and 060 – for these subjects, continuous periods with decreased mean values of the palpebral fissure were noticeable. For subject 060 in particular, it could be assumed that this was based on the individual standardization of the measured values. Subject 060 showed, compared to its maximum palpebral fissure height, relatively small palpebral fissure heights over the entire examination. This could be due to very high maximum values (wide openings of the eyes at times) or the fact that when relaxed, the palpebral fissure height decreaseed more than in all other test subjects, even if there were no other signs of sleepiness.

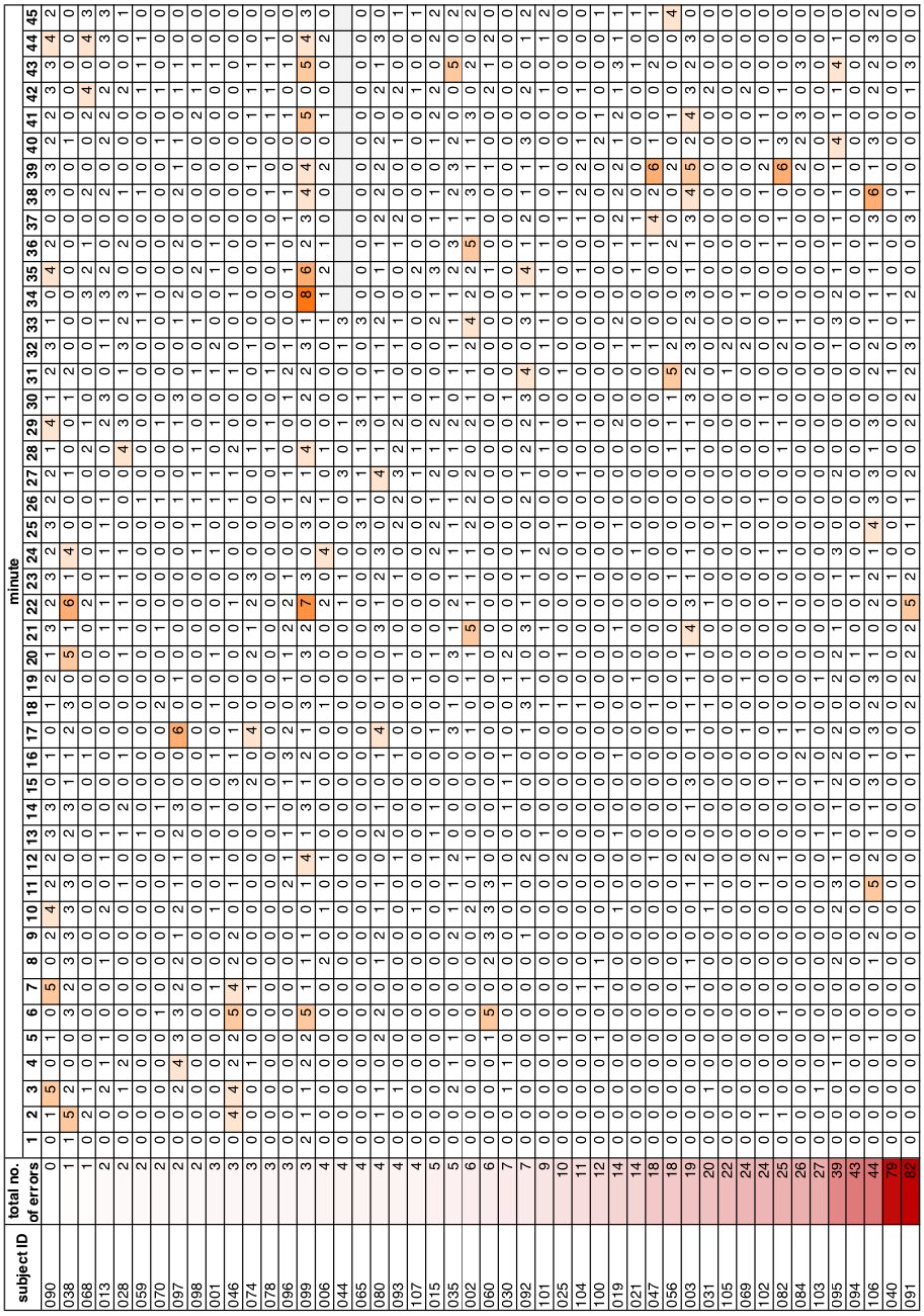

Figure 5.8: Time periods with increased number of *peaks in pupil diameter variability* for all test subjects. For sorting criteria, see Fig. 5.6. Time periods without an increased number of peaks in pupil diameter variability are marked in white, orange-marked periods show that there an increased number (above the 95. percentile) of peaks in pupil diameter variability occurred. Color depth increases with an increasing number of peaks in pupil diameter variability per minute

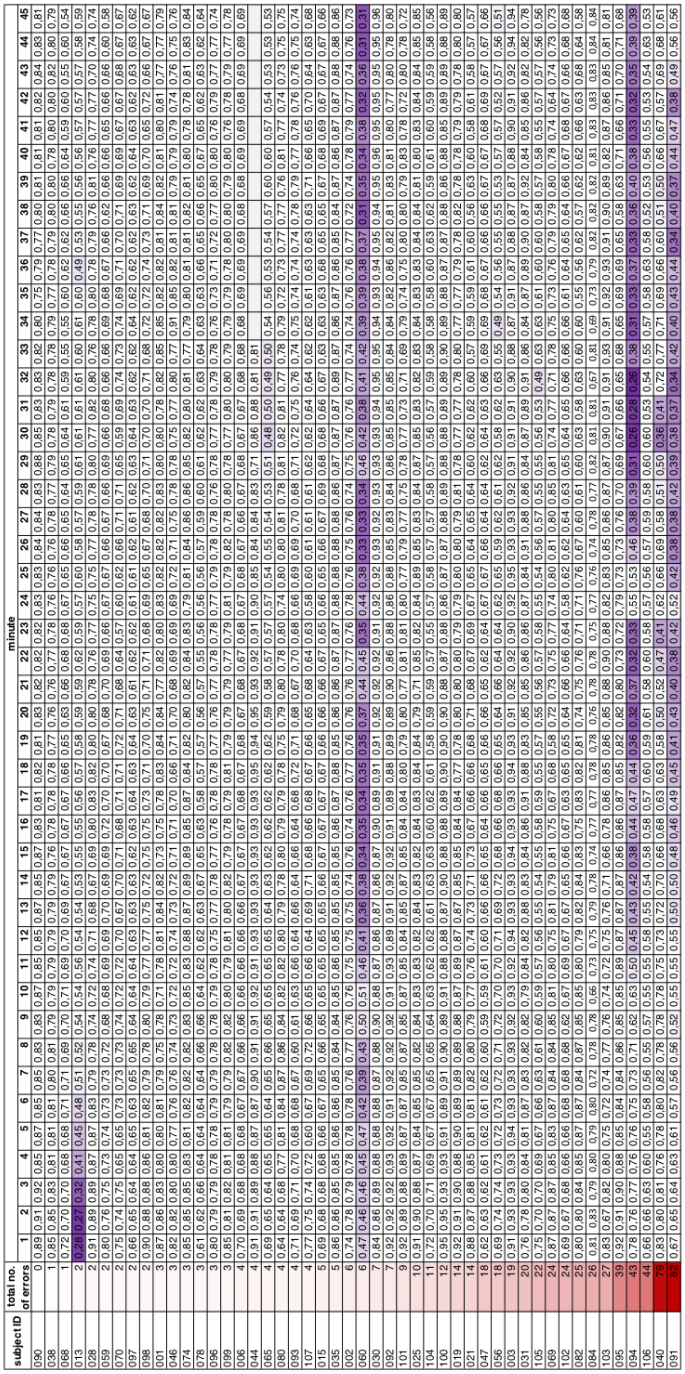

Figure 5.9: Time periods with decreased mean values for the *palpebral fissure height* for all test subjects. For sorting criteria, see Fig. 5.6. Time periods without decreased mean values for the palpebral fissure height are marked in white, purple-marked periods show that decreased mean values (below the 5. percentile) for the palpebral fissure height occurred. Color depth increases with decreasing mean values for the palpebral fissure height per minute

5.3.3.5 Heart rate

Fig. 5.10 shows time periods with a decreased mean value (below the 5. percentile, according to the requirements for false responses to catch trials) of heart rate for all test subjects. Time periods without a decreased mean value of heart rate are marked in white, whereas green-marked periods show that there a decreased mean value of heart rate occurred. Color depth increases with a decreasing heart rate.
The graphic shows that neither a subject- nor a time-related assignment of a decreased heart rate to an increased number of false responses to catch trials was possible. For subjects 025 and 107, continuous periods with decreased mean values of the heart rate were noticeable. This might be due to the individual standardization of the measured values. If heart rate was very high during a very short period within the examination, all other values were compared to that relatively low. For subject 025, this occurred due to a very loud audio signal in the laboratory building, that could be heard in minute 20 of the examination. Subject 107 was reported to almost fall asleep and was then startled by the examiner who spoke to him in minute 36 of the examination.

5.3.3.6 Response time variability

Fig. 5.11 shows time periods with an increased mean value (above the 95. percentile, according to the requirements for false responses to catch trials) of response time variability for all test subjects. Time periods without an increased mean value of response time variability are marked in white, whereas blue-marked periods show that there an increased mean value of response time variability occurred. Color depth increases with an increasing response time variability.
The graphic shows that neither a subject- nor a time-related assignment of an increased response time variability to an increased number of false responses to catch trials was possible.

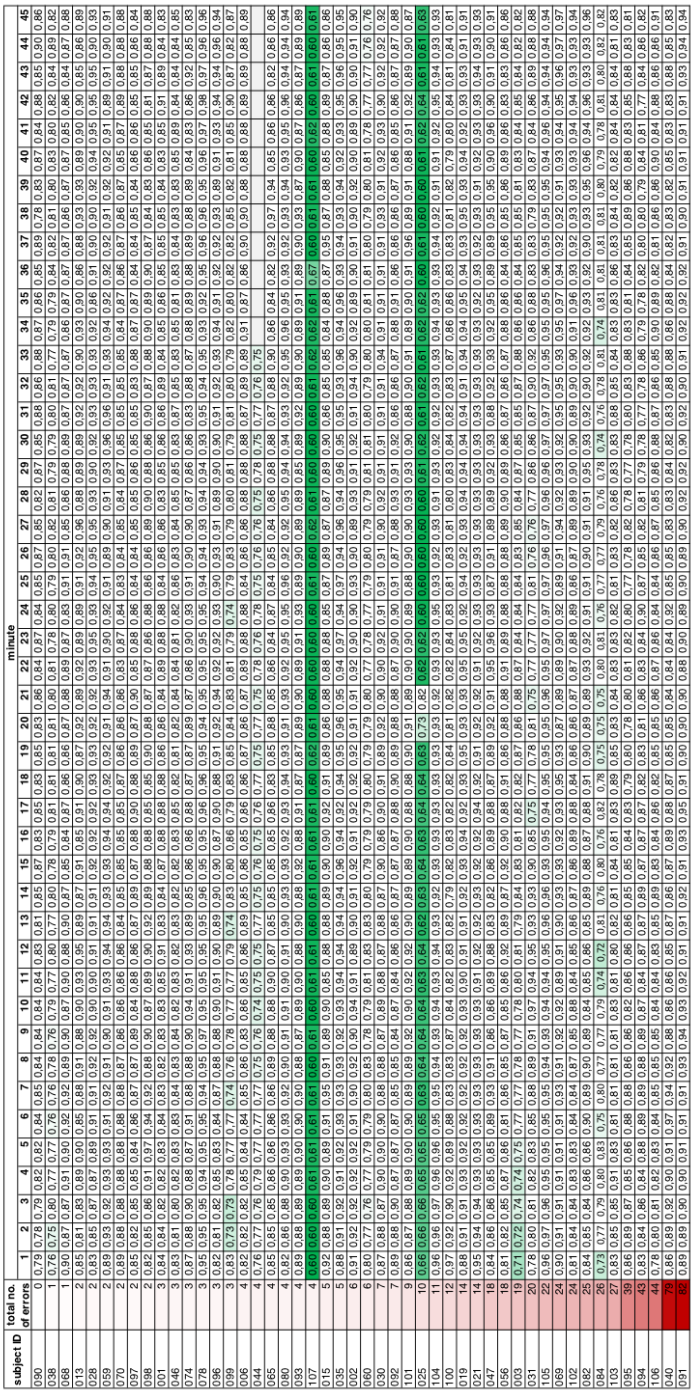

Figure 5.10: Time periods with decreased mean values for the *heart rate* for all test subjects. For sorting criteria, see Fig. 5.6. Time periods without decreased mean values for the heart rate are marked in white, green-marked periods show that decreased mean values (below the 5. percentile) for the heart rate occurred. Color depth increases with decreasing mean values for the heart rate per minute

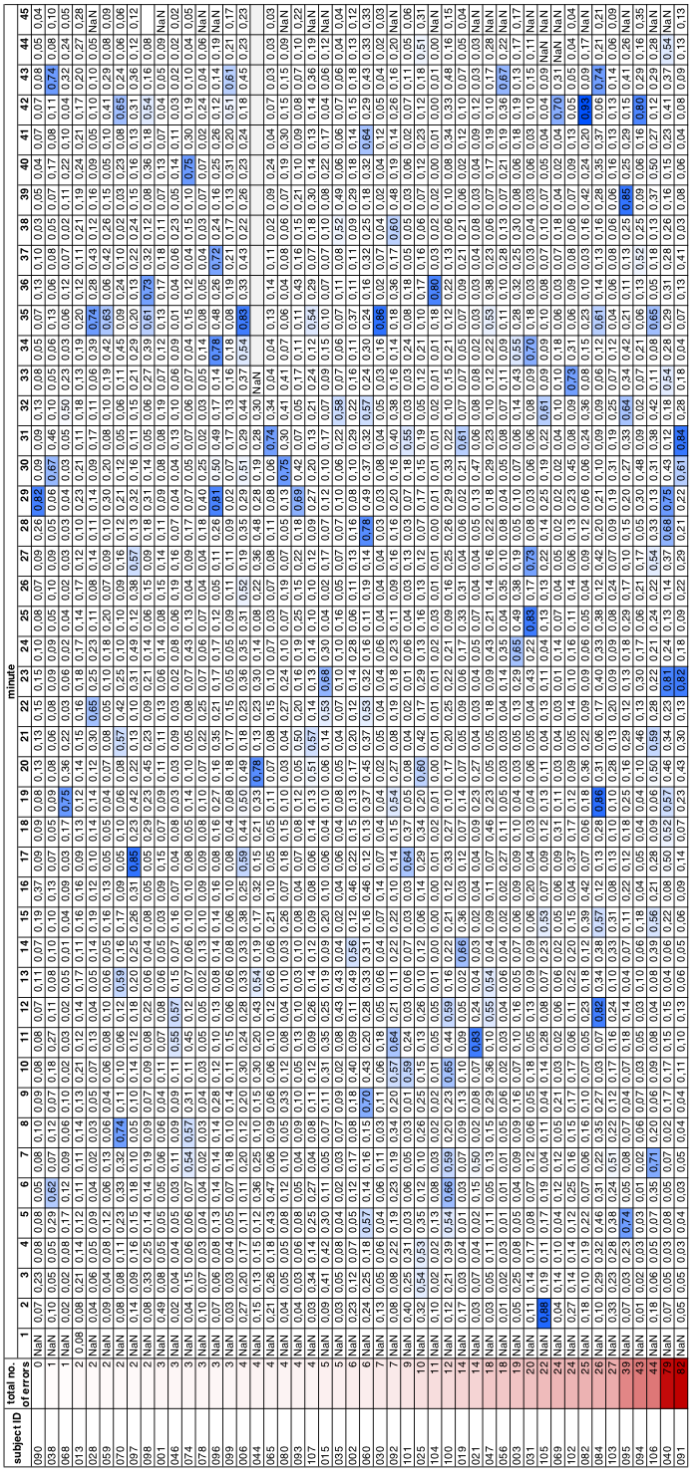

Figure 5.11: Time periods with increased mean values for the *response time variability* for all test subjects. For sorting criteria, see Fig. 5.6. Time periods without increased mean values for the response time variability are marked in white, blue-marked periods show that increased mean values (above the 95. percentile) for the response time variability occurred. Color depth increases with increasing mean values for the response time variability per minute

5.3.3.7 Summary of parameter overview

A comparison of all overview charts displayed above shows, that there were accordances of an *increased number of false responses to catch trials* and the *palpebral fissure height* visible for individual subjects. Time-related accordances were visible for an *increased number of false responses to catch trials* and an *increased pupil diameter variability*. However, a real qualitative accordance in a subject- and time-related manner for all subjects and for the whole examination duration did not occur for any of the related parameters.

It must be stated, that an exclusion of individual test subjects or a consideration of certain events (e.g. an audio signal and the consequences of the startling for this reason) did not take place at this point. This was deliberately intended as such occurrences could also appear during any regular visual field examination in a clinical context.

For that reason, a more detailed data analysis was carried out and is shown in the following sections.

5.3.4 Parameter distributions

Prior to a detailed analysis of the study data, parameters were tested for their distribution forms in order to decide, what statistical test methods were appropriate.

For *false responses to catch trials* as a gold standard, the total number of errors per subject was tested for normal distribution.
Fig. 5.12 shows a histogram of the total number of errors for all subjects. Data were tested for normal distribution using Shapiro-Wilk's test. According to that, the total number of false responses to catch trials was not normally distributed (W = 0.69599, p value $p = 1.13 \cdot 10^{-8}$).

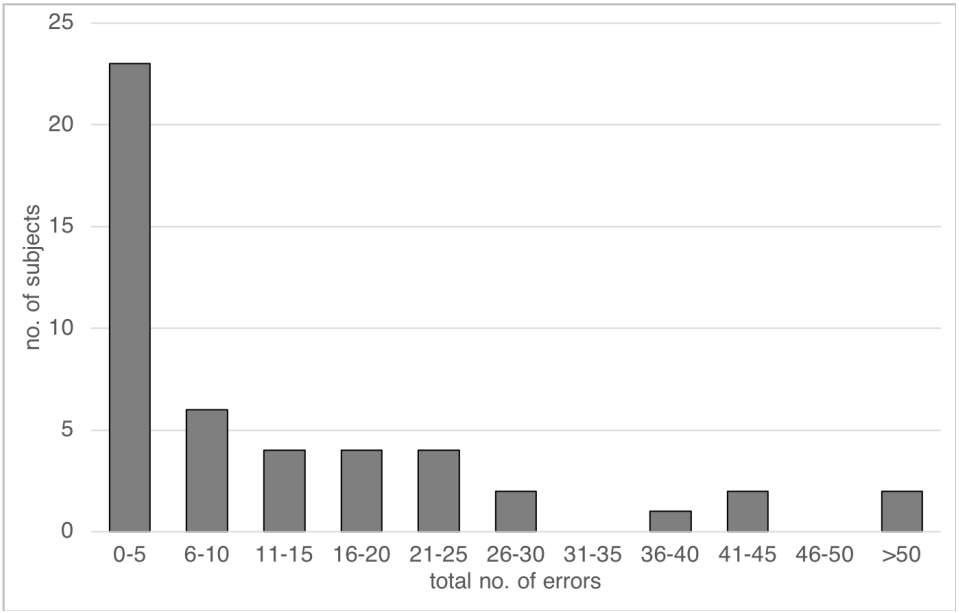

Figure 5.12: Histogram for the total no. of errors for all test subjects

Fig. 5.13 shows the distribution of the *error rate* (calculated over a 60 seconds sliding window) over time, divided into false positive and false negative as well as combined error rate. It can be seen, that false positive responses appeared mainly in the beginning of the measurement, while false negative errors increased with examination time. However, this was only an overall approach, while individual behavior with regard to false positive and false negative errors could not be derived from that.

As false responses to catch trials were seen as the gold standard with regard to this examination and the total number of errors for all subjects was not distributed normally, it was decided to go for non-parametric testing for the whole data analysis. Distribution plots for all related parameters were created. Fig. 5.14 shows an exemplary plot for the pupil diameter variability (PDV). This plot shows the distribution of values for each individual subject condensed in one graphic (for sorting criteria, see Fig. 5.6, subjects are marked by individual colors, as can be seen from the legend on the right side of the figure). A boxplot showing the distribution of values for the whole subject sample was added (box: 25. and 75. percentile with 50. percentile marked as black line in the box; whiskers: 5. and 95. percentile).

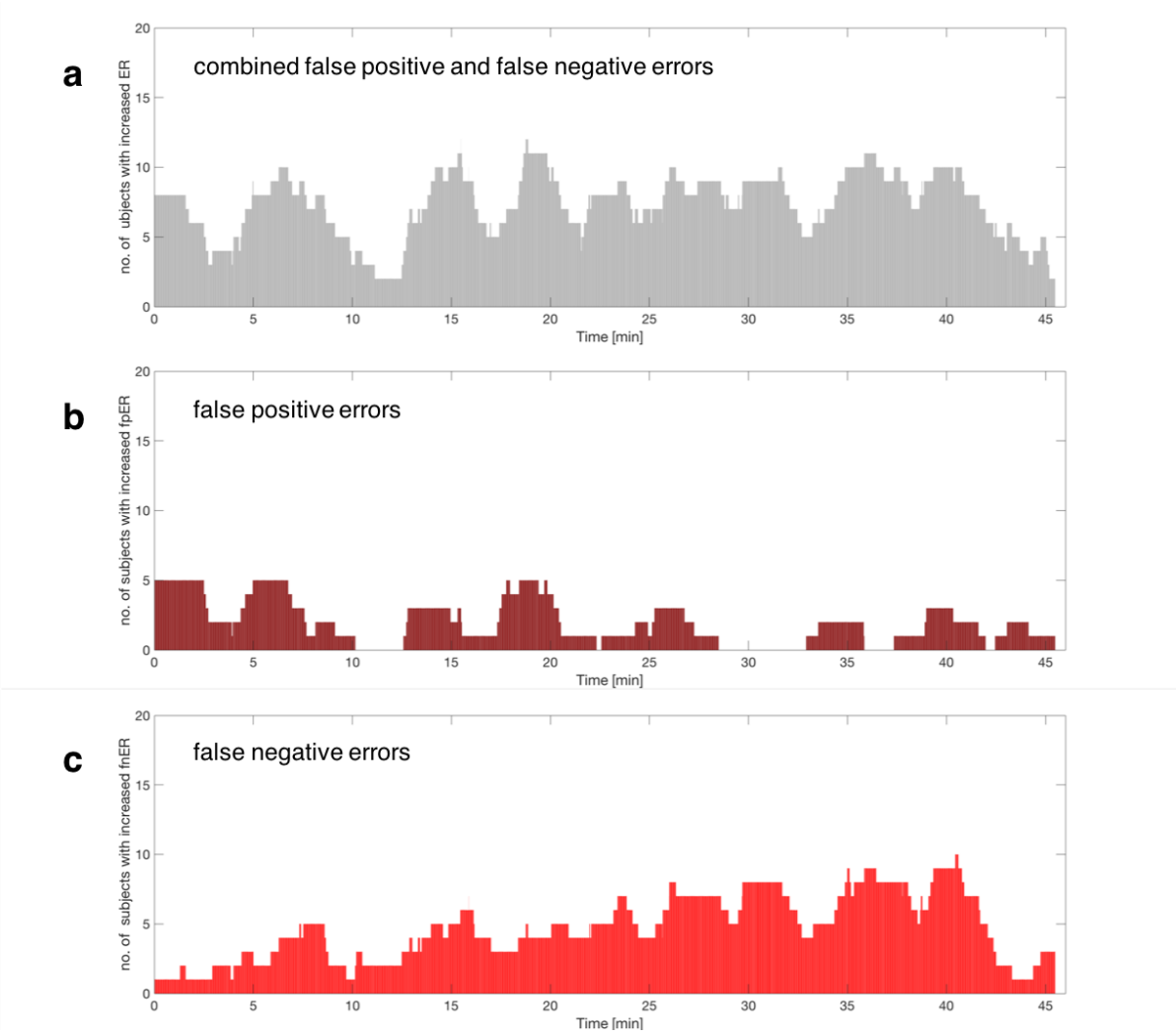

Figure 5.13: Error rate for false positive and false negative errors over time for all subjects. **a** false positive and false negative errors combined (gray), **b** false positive errors (dark red), **c** false negative errors (light red)

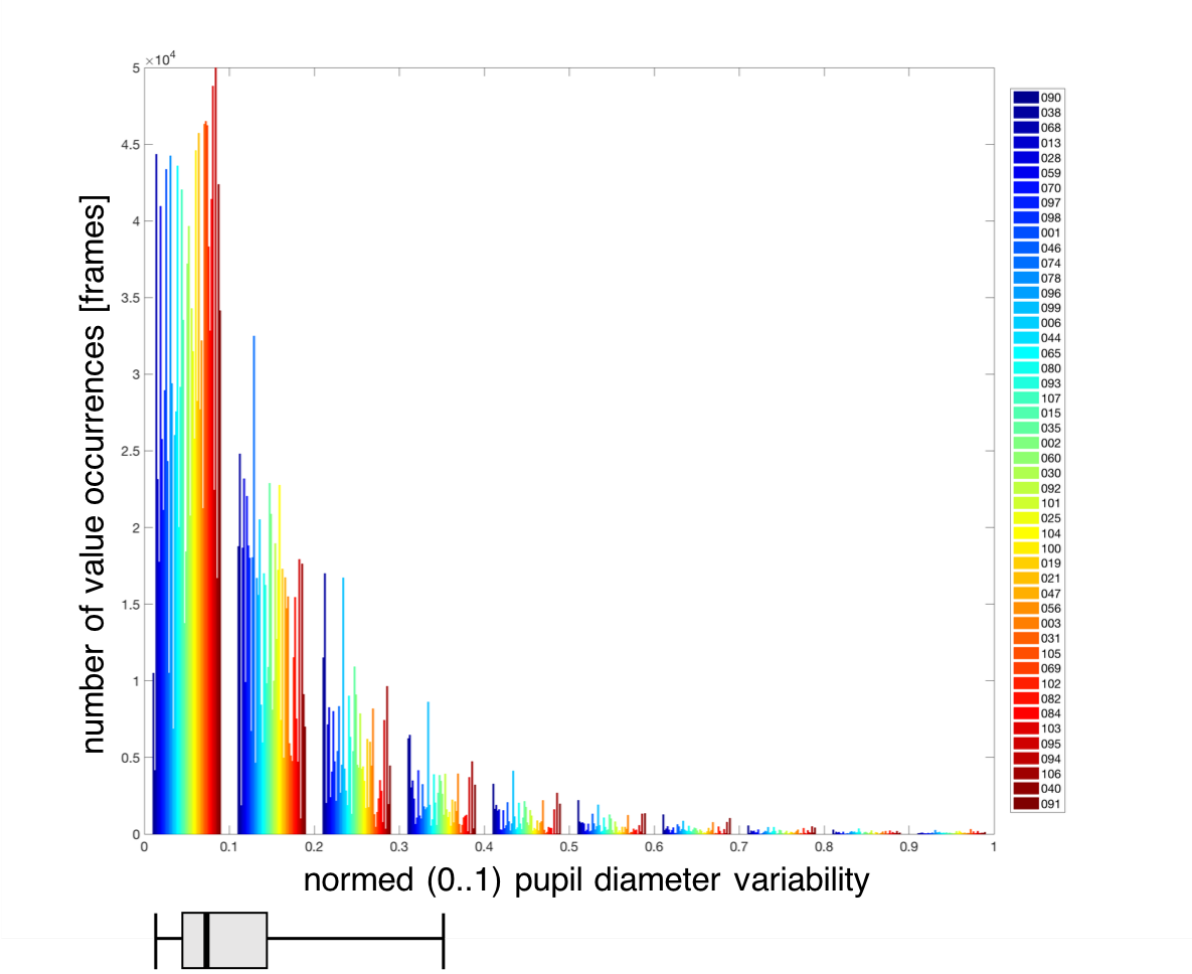

Figure 5.14: Exemplary distribution plot for the normed (0..1) pupil diameter variability. The distribution of values for each individual subject is shown (for sorting criteria, see Fig. 5.6, subjects are marked by individual colors, as can be seen from the legend on the right side of the figure). A boxplot showing the distribution of values for the whole subject sample was added (box: 25. and 75. percentile with 50. percentile marked as black line in the box; whiskers: 5. and 95. percentile)

As can be seen from the distribution plot in a qualitative manner, these parameters were not distributed normally either. Plots for any of the other parameters included can be found in App. I.

5.3.5 Global data analysis

5.3.5.1 Parameter selection for the global analysis

For a detailed, yet global analyisis of the data set, the most promising evaluation method for each parameter according to 4.4.3.1 had to be identified.
Therefore ROC curves were calculated for all evaluation methods mentioned. Area under the ROC curve (AUROC) was calculated, as displayed in Fig. 5.15. For each parameter, the evaluation method with the largest AUROC value was selected for global data analysis. Afterwards, cut-off values were calculated for both, Youden's J and a pre-defined specificity of 0.8.

With regard to AUROC values, blink rate variability (BRV, AUROC = 0.5424), pupil diameter (PD, AUROC = 0.5857), variability of the palpebral fissure height (PFV, AUROC = 0.7242), heart rate variability for low frequencies (HRVLF, AUROC = 0.5972), and response time variability (RTV, AUROC = 0.6934) were selected for further global data analysis.

Tab. 5.6 shows sensitivitiy and specificity values for Youden's J and a pre-defined specificity of 0.8 as well as the cut-off percentiles for the selected evaluation methods.
Variability of the palpebral fissure height (PFV) and response time variability (RTV) showed the highest values for sensitivity and specificity for Youden's J as well as the highest values for sensitivity at a specificity of 0.8. As these evaluation methods also showed the largest area under the ROC curve values, this observation met the expectations. For all evaluations methods, sensitivity values were relatively low at a pre-defined specificity of 0.8 compared to Youden's J sensitivities, as for Youden's J, specificity values were below 0.8 for all evaluation methods.

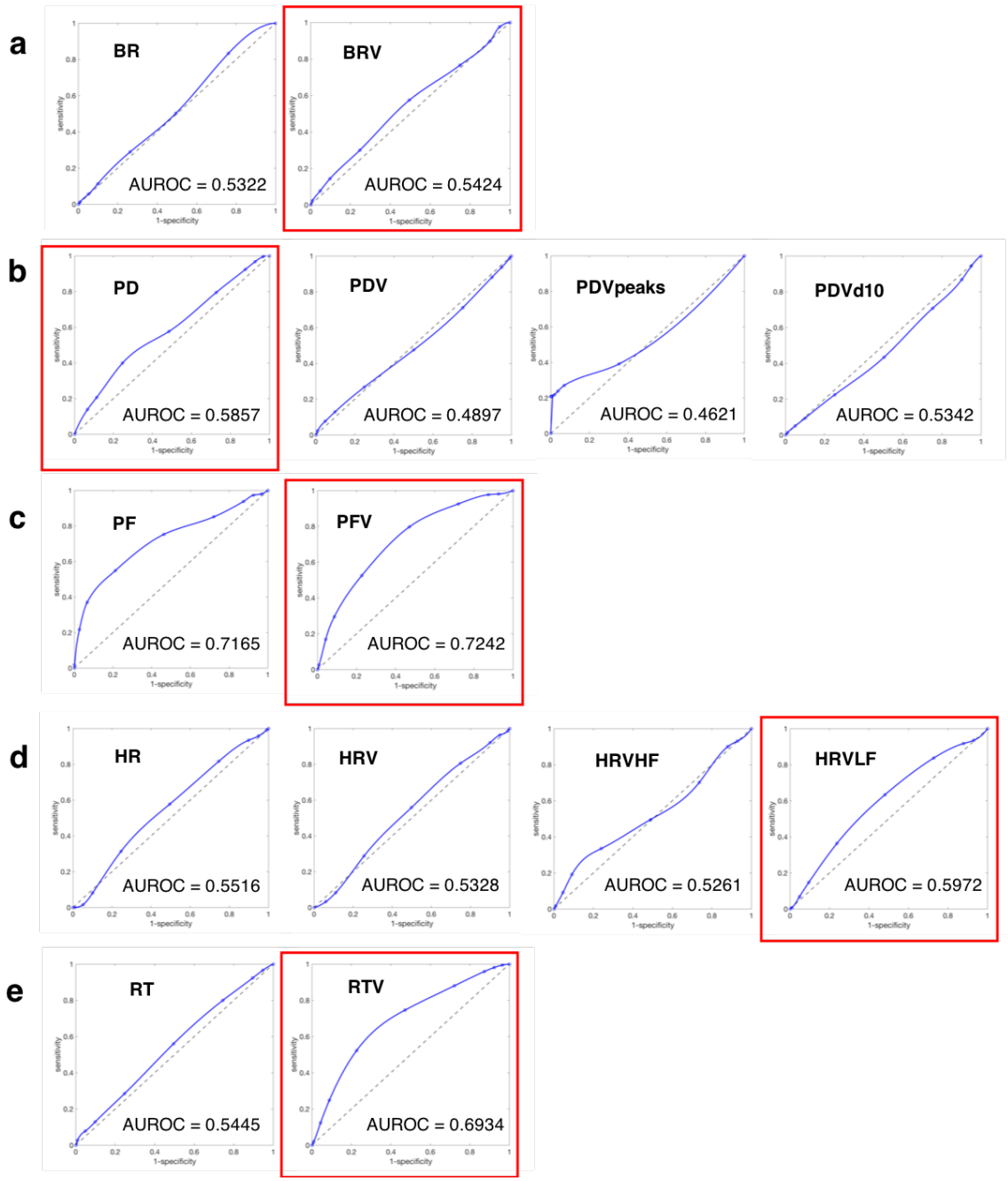

Figure 5.15: ROC curves and corresponding values for the area under the ROC curves (AUROC): **a** blink rate (BR), blink rate variability (BRV), **b** pupil diameter (PD), pupil diameter variability (PDV), wavelet transform of pupil diameter variability (PDVd10), peaks in pupil diameter variability (PDVpeaks), **c** palpebral fissure height (PF), variability of the palpebral fissure height (PFV), **d** heart rate (HR), heart rate variability (HRV), heart rate variability for high frequencies (HRVHF),heart rate variability for low frequencies (HRVLF), **e** response time (RT), response time variability (RTV). For each parameter, the evaluation method with the largest AUROC value was selected. Selected methods are marked by the red rectangles

Table 5.6: Sensitivitiy and specificity values for Youden's J and a pre-defined specificity of 0.8 as well as cut-off percentiles (highlighted in gray) for the selected evaluation methods

parameter	**sens. (Youden's J)**	**spec. (Youden's J)**	**sens. at spec. 0.8**		**cut-off perc. (Youden)**	**cut-off perc. (sens. at spec. 0.8)**
blink rate variability (BRV)	0.58	0.50	0.25		50	80
pupil diameter (PD)	0.45	0.71	0.34		30	19
variability of the palpebral fissure height (PFV)	0.73	0.6	0.49		57	78
heart rate variability for low frequencies (HRVLF)	0.57	0.58	0.31		56	79
response time variability (RTV)	0.63	0.69	0.48		66	78

5.3.5.2 Agreement index (AI)

Agreement indices were calculated for both methods Youden's J and a pre-defined specificity of 0.8. Tab. 5.7 shows the results. The data were sorted by the total number of errors starting from a low number of errors at the top to a high number of errors at the bottom. As agreement indices were evaluated on the basis of time periods, the periods with an increased number of false responses to catch trials were displayed as well. Median values were calculated only for the subgroup of subjects that showed any time period with an increased number of false responses to catch trials at all. In Tab. 5.7, color depth for errors increases with increasing error-related values. Color depth for the agreement indices for each parameter and evaluation method increases with increasing agreement indices.

As shown in Tab. 5.7, the highest agreement indices (with regard to both median and maximum values) were obtained for the variability of the palpebral fissure height (PFV) with an agreement index of up to 0.52 and a median value of 0.09 and for response time variability (RTV) with an agreement index of up to 0.47 and a median value of 0.14 according to Youden's J.

In general, the agreement index values seemed to be comparably low, when median values were regarded. This was due to the comparatively low number of false responses to catch trials that occurred. For subjects with a higher number of errors, agreement indices increased.

It has to be stated, that the designation of cut-off values seemed to be more meaningful using Youden's J than using a pre-defined specificity of 0.8 due to the fact that the agreement index is so to say an "individualized sensitivity" value. As Youden's J data resulted in higher sensitivity (yet lower specificity) values than data for a pre-defined specificity of 0.8 altogether, agreement indices were expectedly higher for Youden's J-calculated values. For this reason, agreement plots (see chapter 5.3.5.3) were only created for the agreement indices obtained from the data set related to Youden's J.

In addition, a "meta-correlation" of the total number of errors per subject and the agreement index (obtained from the data set related to Youden's J) was performed using Spearman's rank correlation method. Five "meta-correlations" were carried out. Thus, a significance requirement of $p<0.01$ was determined. Tab. 5.8 shows the results.

Table 5.7: Results for the agreement indices for all selected parameter evaluation methods. The data were sorted by the total no. of errors starting from a low number of errors at the top to a high number of errors at the bottom. AI: agreement index, ER: error rate (marked in red color), BRV: blink rate variability (marked in teal color), PD: pupil diameter (marked in orange color), PFV: variability of palpebral fissure height (marked in purple color), HRVLF: heart rate variability for the low frequency band (marked in green color), RTV: response time variability (marked in blue color). Color depth increases with increasing error-related values and agreement indices

subject ID	total no. of errors	period with increased ER [min]	AI BRV (sens at spec. 0.8)	AI BRV (Youden's J)	AI PD (sens at spec. 0.8)	AI PD (Youden's J)	AI PFV (sens at spec. 0.8)	AI PFV (Youden's J)	AI HRVLF (sens at spec. 0.8)	AI HRVLF (Youden's J)	AI RTV (sens at spec. 0.8) 0,8	AI RTV (Youden's J)
090	0	0	0	0	0	0	0	0	0	0	0	0
038	1	0	0	0	0	0	0	0	0	0	0	0
068	1	0	0	0	0	0	0	0	0	0	0	0
013	2	0	0	0	0	0	0	0	0	0	0	0
028	2	0	0	0	0	0	0	0	0	0	0	0
059	2	0	0	0	0	0	0	0	0	0	0	0
070	2	0	0	0	0	0	0	0	0	0	0	0
097	2	0	0	0	0	0	0	0	0	0	0	0
098	2	0	0	0	0	0	0	0	0	0	0	0
001	3	0	0	0	0	0	0	0	0	0	0	0
046	3	0	0	0	0	0	0	0	0	0	0	0
074	3	0,98	0,07	0,03	0,00	0,00	0,06	0,04	0,09	0,04	0,00	0,00
078	3	0,24	0,00	0,01	0,00	0,00	0,00	0,00	0,00	0,00	0,06	0,03
096	3	0	0	0	0	0	0	0	0	0	0	0
099	3	0	0	0	0	0	0	0	0	0	0	0
006	4	0	0	0	0	0	0	0	0	0	0	0
044	4	0	0	0	0	0	0	0	0	0	0	0
065	4	0	0	0	0	0	0	0	0	0	0	0
080	4	0	0	0	0	0	0	0	0	0	0	0
093	4	0	0	0	0	0	0	0	0	0	0	0
107	4	0	0	0	0	0	0	0	0	0	0	0
015	5	0	0	0	0	0	0	0	0	0	0	0
035	5	0,74	0,00	0,03	0,00	0,00	0,00	0,05	0,00	0,00	0,00	0,00
002	6	0	0	0	0	0	0	0	0	0	0	0
060	6	0,22	0,00	0,00	0,00	0,00	0,00	0,01	0,00	0,00	0,01	0,01
030	7	0,94	0,03	0,02	0,00	0,01	0,00	0,05	0,00	0,04	0,00	0,07
092	7	0	0	0	0	0	0	0	0	0	0	0
101	9	1,19	0,07	0,03	0,00	0,00	0,05	0,04	0,03	0,03	0,15	0,13
025	10	1,64	0,00	0,07	0,01	0,01	0,25	0,09	0,13	0,06	0,10	0,06
104	11	1,29	0,02	0,01	0,00	0,00	0,09	0,04	0,00	0,00	0,00	0,18
100	12	1,27	0,07	0,03	0,00	0,00	0,00	0,02	0,00	0,06	0,02	0,02
019	14	0,68	0,03	0,02	0,00	0,00	0,00	0,02	0,00	0,01	0,00	0,01
021	14	2,36	0,06	0,06	0,05	0,05	0,07	0,07	0,00	0,00	0,03	0,02
047	18	3,19	0,40	0,27	0,00	0,00	0,05	0,08	0,07	0,06	0,20	0,14
056	18	3,62	0,09	0,11	0,19	0,17	0,12	0,11	0,16	0,09	0,14	0,19
003	19	4,09	0,14	0,17	0,01	0,03	0,06	0,17	0,09	0,15	0,17	0,12
031	20	4,66	0,02	0,02	0,00	0,00	0,08	0,09	0,01	0,04	0,07	0,08
105	22	5,13	0,05	0,10	0,12	0,12	0,13	0,12	0,14	0,13	0,25	0,25
069	24	4,17	0,20	0,12	0,01	0,06	0,09	0,09	0,06	0,06	0,18	0,32
102	24	5,45	0,00	0,03	0,12	0,12	0,02	0,07	0,01	0,14	0,20	0,24
082	25	5,04	0,04	0,14	0,09	0,11	0,10	0,12	0,11	0,12	0,13	0,11
084	26	5,49	0,08	0,11	0,01	0,01	0,10	0,12	0,00	0,00	0,24	0,20
103	27	4,94	0,18	0,14	0,00	0,00	0,25	0,17	0,04	0,05	0,30	0,25
095	39	10,27	0,10	0,25	0,16	0,23	0,30	0,33	0,41	0,33	0,25	0,30
094	43	11,06	0,19	0,31	0,01	0,02	0,25	0,27	0,28	0,44	0,32	0,32
106	44	11,09	0,17	0,31	0,14	0,24	0,16	0,24	0,23	0,28	0,21	0,24
040	79	17,03	0,23	0,42	0,10	0,15	0,45	0,41	0,10	0,20	0,43	0,47
091	82	21,00	0,13	0,49	0,43	0,44	0,36	0,52	0,35	0,60	0,36	0,43
median			**0,07**	**0,08**	**0,01**	**0,01**	**0,08**	**0,09**	**0,05**	**0,06**	**0,15**	**0,14**

Table 5.8: Correlation coefficients and p values for Spearman's rank correlation of the total no. of errors per subject and the agreement index (obtained from the data set related to Youden's J). AI: agreement index, BRV: blink rate variability, PD: pupil diameter, PFV: variability of the palpebral fissure height, HRVLF: heart rate variability for low frequencies, RTV: response time variability. Five correlation analyses were carried out, which led to a significance requirement of $p<0.01$

	total no. of errors x AI BRV	**total no. of errors x AI PD**	**total no. of errors x AI PFV**	**total no. of errors x AI HRVLF**	**total no. of errors x AI RTV**
Spearman's ρ	0.94	0.81	0.96	0.85	0.91
p value	$4.80 \cdot 10^{-23}$	$2.21 \cdot 10^{-12}$	$2.58 \cdot 10^{-28}$	$1.17 \cdot 10^{-14}$	$1.06 \cdot 10^{-19}$

As can be seen from Tab. 5.8, agreement indices correlated strongly with the total number of errors per subject. The higher the number of errors occurred, the higher the correlation. Accordingly, the idea of an agreement index seemed to be sufficient for test subjects that showed clear signs of sleepiness. In contrast to that, for subjects that were vigilant, and did not produce many errors, the agreement index obviously could not work as well.

5.3.5.3 Agreement plots

Agreement periods were displayed in agreement plots separately for each subject. An exemplary agreement plot for subject 106 is shown in Fig. 5.16.
The agreement plot shows events for both error rate as a gold standard and related parameters. Event occurrence was defined as explained in chapter 4.4.3.4. These graphics were conducted for all test subjects and can be found in schemes created for each individual subject in App. F.
This type of representation did not allow for any further conclusions in the sense of the data evaluation, but was only intended to illustrate the agreement index described above for each individual subject.

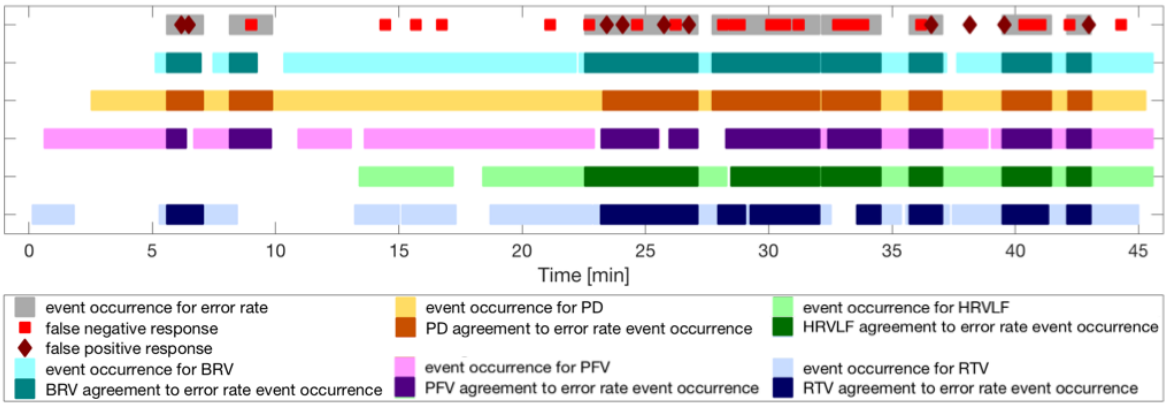

Figure 5.16: Agreement plot for subject 106. Events are shown over time and are highlighted in the colors that are depicted in the legend. Agreement for all related parameters to the error rate are is highlighted in the same color as events but in a darker shade (see legend)

5.3.6 Individual data analysis

5.3.6.1 Parameter selection for the individual analysis

For a detailed, individual analysis of the data set, the most promising evaluation method for each parameter according to chapter 4.4.3.1 had to be identified.
Therefore, median values of all correlation coefficients obtained were calculated. The evaluation method with the largest median correlation coefficient per parameter was selected for further correlation analysis.
A table showing all correlation coefficients along with their p values for all evaluation methods is attached in App. J. As correlations were carried out individually for 48 subjects and for 14 parameters, respectively, the requirement for significance was set to $p < 7.44 \cdot 10^{-5}$.

For further individual correlation analysis, blink rate variability (BRV), peaks in pupil diameter variability (PDVpeaks), height of the palpebral fissure (PF), heart rate variability for low frequencies (HRVLF), and response time variability (RTV) were selected.

5.3.6.2 Individual correlation coefficients

A table showing the correlation coefficients for the selected evaluation methods for all parameters is shown below (see Tab. 5.9). This table does only show the specific correlation coefficients. p values were excluded for clarity reasons. Because of the large number of

data points per subject, almost all of the p values obtained were significant – especially with regard to the evaluation methods selected for further analysis. All p values can be found in the above-mentioned App. J. Data was sorted by the total number of errors as described above.

As stated, not all p values were significant. Therefore, p values that did not show significance were marked in gray in App. J. As non-significant values did only occur for few, individual subjects per parameter, an ”overall significance” was assumed for all parameters tested.

Highest correlation coefficients (with regard to both median and maximum values) were obtained for the response time variability (RTV) with a correlation coefficient of up to 0.61 and a median value of 0.27 and for the height of the palpebral fissure (PF) with a correlation coefficient of up to -0.82 and a median value of -0.05 .

An exemplary, artificial enrichment of the prevalence was simulated for the height of the palpebral fissure by only considering the five subjects with the highest total number of errors. The median Spearman correlation coefficient for this subgroup increased to -0.60, indicating a strong correlation.

In addition, a ”meta-correlation” of the total number of errors per subject and the correlation coefficients obtained within the individual analysis was performed using Spearman’s rank correlation method. Five correlation analyses were carried out, which led to a significance requirement of $p<0.01$. Tab. 5.10 shows the results.

As can be seen from Tab. 5.10, correlation coefficients, in turn, correlated moderately with the total number of errors per subject. The higher the number of errors occurred, the higher the correlation. This shows, that the idea of Spearman correlation coefficients seemed to be sufficient for test subjects that showed clear signs of sleepiness. In contrast to that, for subjects who were vigilant, and did not produce many errors, correlation coefficients did not work as well.

Table 5.9: Results for the correlation coefficients for all selected parameter evaluation methods. The data are sorted by the total no. of errors (marked in red color) starting from a low number of errors at the top to a high number of errors at the bottom. Color depth increases with increasing correlation coefficients or total no. of errors, respectively. BRV: blink rate variability (marked in teal color), PDVpeaks: peaks in pupil diameter variability (marked in orange color), PF: palpebral fissure height (marked in purple color), HRVLF: heart rate variability for the low frequency band (marked in green color), RTV: response time variability (marked in blue color)

subject ID	total no. of errors	rho(BRV x ER)	rho(PDV peaks x ER)	rho(PF x ER)	rho(HRVLF x ER)	rho(RTV x ER)
090	0	NaN	NaN	NaN	NaN	NaN
038	1	-0,11	0,01	NaN	0,06	0,06
068	1	0,01	-0,11	0,24	0,05	0,12
013	2	0,13	0,03	0,04	0,14	0,28
028	2	0,01	0,18	0,03	-0,15	0,26
059	2	0,14	0,14	-0,26	0,26	0,30
070	2	0,04	0,25	-0,21	-0,03	0,10
097	2	-0,03	0,24	-0,01	0,06	0,32
098	2	0,18	-0,01	-0,07	0,11	0,22
001	3	-0,05	-0,09	-0,04	-0,17	0,27
046	3	0,15	-0,01	-0,15	-0,01	0,16
074	3	0,32	-0,08	0,01	0,14	0,19
078	3	-0,02	0,10	-0,04	0,12	0,07
096	3	-0,01	0,06	-0,01	0,04	0,27
099	3	-0,13	-0,09	0,02	-0,09	0,16
006	4	0,20	0,26	0,18	0,06	0,40
044	4	-0,09	0,00	-0,17	-0,14	0,15
065	4	0,05	-0,14	0,03	0,12	0,18
080	4	-0,14	0,12	0,13	-0,04	0,21
093	4	0,17	0,15	0,00	0,29	0,30
107	4	0,16	0,26	-0,30	0,22	0,16
015	5	0,11	0,01	0,07	-0,07	0,14
035	5	-0,02	-0,05	-0,16	-0,22	0,29
002	6	-0,13	-0,09	0,18	-0,03	0,29
060	6	-0,09	0,12	-0,09	0,10	0,19
030	7	0,00	0,06	-0,11	0,05	0,48
092	7	-0,10	-0,13	-0,04	0,06	0,40
101	9	-0,04	0,00	0,04	-0,22	0,54
025	10	0,19	0,10	-0,09	0,12	0,13
104	11	-0,25	0,02	0,43	-0,13	0,56
100	12	-0,07	0,24	0,13	0,05	0,07
019	14	0,18	-0,26	0,11	-0,27	0,39
021	14	0,01	-0,02	-0,08	-0,10	0,09
047	18	0,25	0,06	-0,15	0,01	0,40
056	18	0,15	0,26	-0,50	0,20	0,44
003	19	0,10	-0,07	-0,17	-0,05	0,04
031	20	0,02	-0,16	-0,02	0,06	0,28
105	22	0,07	0,33	-0,29	0,34	0,34
069	24	-0,16	0,03	0,07	-0,09	0,16
102	24	0,02	0,28	-0,02	0,07	0,34
082	25	0,15	-0,01	-0,34	0,11	0,20
084	26	0,11	0,01	-0,05	NaN	0,31
103	27	0,31	0,19	-0,32	0,14	0,61
095	39	0,45	0,05	-0,60	0,59	0,48
094	43	0,33	0,15	-0,71	0,61	0,43
106	44	0,26	0,21	-0,11	0,37	0,27
040	79	0,35	0,21	-0,59	0,17	0,50
091	82	0,50	0,61	-0,82	0,67	0,46
median values		0,05	0,05	-0,05	0,06	0,27

Table 5.10: Correlation coefficients and p values for Spearman's rank correlation of the total no. of errors per subject and the correlation coefficients obtained from the individual data analysis. BRV: blink rate variability, PDVpeaks: peaks in pupil diameter variability, PF: palpebral fissure height, HRVLF: heart rate variability for low frequencies, RTV: response time variability, ER: error rate. Five correlation analyses were carried out, which led to a significance requirement of $p<0.01$

	total no. of errors x ρ (BRVxER)	**total no. of errors x ρ (PDVpeaks xER)**	**total no. of errors x ρ (PFxER)**	**total no. of errors x ρ (HRVLFx ER)**	**total no. of errors x ρ (RTVxER)**
Spearman's ρ	0.61	0.45	-0.69	0.58	0.45
p value	$3.89 \cdot 10^{-06}$	$1.26 \cdot 10^{-3}$	$5.43 \cdot 10^{-08}$	$1.55 \cdot 10^{-05}$	$1.33 \cdot 10^{-3}$

5.3.6.3 Frequency of seeing (FOS) curves

Frequency of seeing (FOS) curves were conducted for all test subjects for each tested location, respectively and can be found in schemes created for each individual subject in App. F.

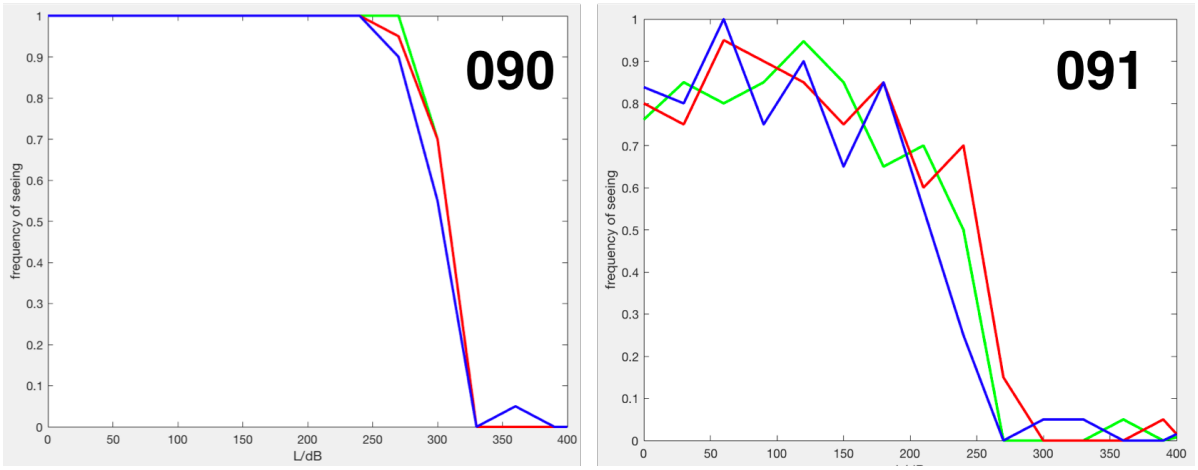

Figure 5.17: FOS curves for subjects 090 (left side, total no. of false responses to catch trials: 0) and 091 (right side, total no. of false responses to catch trials: 82) for different locations tested: blue (0°,7°), green (-6.1°,-3.5°), red (6.1°,-3.5°)

Fig. 5.17 shows two exemplary FOS curves for subjects 090 (total number of false responses to catch trials: 0) and 091 (total number of false responses to catch trials: 82). The first-mentioned FOS curve shows few fluctuations whereas the latter one shows many and prolonged fluctuations. Therefore, it could be assumed, that response quality with regard to reliability was more stable for subject 090 than for subject 091, which could be

seen as an individual indicator for a higher validity of subject 090's results.

The steepness of the slope (SSL) was calculated for each subject. The results for all subjects (median values of the different locations) are shown in Tab. 5.11.

Table 5.11: Steepness of the slope (SSL) of the frequency of seeing (FOS) curve for each subject. The data are sorted by the total no. of errors starting from a low number of errors at the top to a high number of errors at the bottom.

subject ID	total no. of errors	SSL		subject ID	total no. of errors	SSL		subject ID	total no. of errors	SSL
090	0	-0.23		044	4	-0.20		021	14	-0.15
038	1	-0.20		065	4	-0.13		047	18	-0.17
068	1	-0.20		080	4	-0.25		056	18	-0.20
013	2	-0.25		093	4	-0.23		003	19	-0.12
028	2	-0.22		107	4	-0.23		031	20	-0.10
059	2	-0.23		015	5	-0.23		105	22	-0.13
070	2	-0.25		035	5	-0.18		069	24	-0.18
097	2	-0.20		002	6	-0.22		102	24	-0.28
098	2	-0.16		060	6	-0.18		082	25	-0.20
001	3	-0.30		030	7	-0.20		084	26	-0.18
046	3	-0.22		092	7	-0.18		103	27	-0.14
074	3	-0.27		101	9	-0.18		095	39	-0.20
078	3	-0.25		025	10	-0.25		094	43	-0.17
096	3	-0.22		104	11	-0.17		106	44	-0.22
099	3	-0.27		100	12	-0.14		040	79	-0.17
006	4	-0.28		019	14	-0.20		091	82	-0.17

As luminance levels were varied in steps of 3 dB, an ideal steepness of the slope would be -0.33 (referring to a decrease in the frequency of seeing of 100% [equivalent to 1] for one luminance step [equivalent to 3 dB]).

Fig. 5.18 shows a scatter plot for the steepness of the slope in dependence of the total number of errors for all test subjects. It seemed that slope steepness flattened with an increasing number of errors, although fluctuations occurred.
A Spearman correlation analysis was carried out for steepness of the slope (SSL) and total number of errors per subject. A moderate correlation coefficient of ρ = 0.48 ($p = 5.53 \cdot 10^{-4}$) appeared.
Therefore, the slope of the frequency of seeing curves could actually be taken as a supplementary measure for the reliability of a subjects' performance within the scope of the present study.

Figure 5.18: Scatter plot for the steepness of the slope (SSL) in dependence of the total no. of errors for all test subjects. Each blue dot represents one test subject. Red dashed line: linear trend line (SSL = 0.0008 n - 0.2139; n: total no. of errors)

5.3.6.4 Summary of the results

In order to sum up the results obtained within the main study briefly, it can be stated, that the most useful parameter for both global and individual analysis seemed to be the response time variability (RTV) with an agreement index of up to 0.47 for the global analysis and correlation coefficients of up to 0.61 for the individual analysis.
The variability of the palpebral fissure height (PFV) seemed also meaningful for global analysis with agreement indices of up to 0.52, whereas the height of the palpebral fissure (PF) seemed meaningful for individual analysis with correlation coefficients of up to -0.82.

Most promising evaluation methods differed between global and individual analysis. This may be due to the fact, that not every subject behaved in the same manner, if sleepiness occurred. Some parameters seemed to be more susceptible to such inter-individual differences than other ones. A further discussion of this can be found in chapter 6.

Altogether, it is remarkable, that only a comparatively low number of false responses to catch trials occurred for the majority of subjects. At this point, it must be noted that only healthy normal subjects were examined in the present study. In patients with advanced visual field loss, significantly higher error rates would be expected (Birt et al. 1997).
Obviously, sufficient results for the detection of sleepiness could only be achieved if sleepiness was present according to the gold standard criterion of false responses to catch trials. Against this background, the above-mentioned results can be seen as very promising, as relatively high agreement indices and correlation coefficients could be obtained for test subjects with a comparatively large total number of errors or a long time period of an increased number of false responses to catch trials, respectively.

6 Discussion

The limitations of this research are discussed. The results found in this study are critically compared to existing studies. Possible benefits of this work are mentioned. Finally, conclusions are drawn and an outlook is given to show what findings may be applicable to clinical considerations and subsequent studies.

6.1 Limitations of study design and methodology

This work is limited for several reasons:

The assumptions underlying this study should first be evaluated for a standardized case. In (ophthalmic) diseases, certain physiological reactions may be restricted or occur in a different form than in healthy subjects. For instance, false response rates and the extent and/or depth of visual field defects are known to correlate (Birt et al. 1997), and neuro-ophthalmological diseases such as a stroke lead to a decrease in concentration (Hom and Reitan 1990).
To exclude a bias in the data, only *healthy subjects* were included in this study.
In addition, the study took place under optimal conditions with regard to supervision of the test subjects: An examiner was present during the whole examination and monitored the subjects. In case of advanced signs of sleepiness, the examiner also motivated the test subjects to stay alert.
Although an examination took over 45 minutes, there were significantly fewer sleepiness periods than initially assumed – that may have occurred due to optimal supervision of the test subjects, as stated above. Almost half of the subjects showed no time period with an increased number of false responses to catch trials.
Of course, this circumstance affected the analysis of the data. If subjects show no signs of fatigue or sleepiness, no obvious connection between sleepiness and other physiological parameters can be found. In the present study, this was demonstrated by the fact that both agreement indices and correlation coefficients for subjects with a high number of incorrect responses to catch trials and in this context a lower vigilance level yielded significantly

better values than for subjects with consistently good vigilance and a lower error rate.
In a future study, it could be meaningful to carry out a type of measurement in which an individual baseline is recorded and each subject is then assessed on the basis of this baseline. Thus each subject, possibly even those with temporary pathologies, could serve as its own control.

The infrared camera built into the OCTOPUS 900 perimeter (Haag-Streit AG, Koeniz, Switzerland) only allows for an image resolution of 320x240 px. With more recent devices, such as the imo perimeter (CREWT Medical Systems Inc., Tokyo, Japan), a resolution of up to 1280x960 px is possible (Matsumoto et al. 2016). It is conceivable that a more precise resolution of the camera could lead to an enhanced image quality and thus better detection of the pupil diameter and the height of the palpebral fissure, which could affect some of the measured parameters.

The temporal resolution of the pupillographic recordings was also limited. The maximum temporal resolution that could be achieved with the existing equipment was 20 fps. Due to bottlenecks in the RAM memory of the available hardware, the recording software was designed in a way that individual frames were aborted as soon as the hardware was no longer able to adequately process the amount of data. This led to a temporary decrease of the frame rate, which was corrected in the post-processing of the data by a resample and smooth procedure. It cannot be ruled out that this process could have had an impact on the high- and lowpass filters applied for the evaluation of the height of the palpebral fissure and the heart rate variabilities for high and low frequencies (as described in chapters 3.3.4 and 4.4.3.1). An even more precise evaluation would have been possible without the need for such a process.
In particular, the wavelet transformation process may possibly have worked only to a limited extent under these conditions. Pupillary oscillations that took place at high frequency may not have been fully investigated with the present experimental setup. However, it should be noted that from the known literature, pupil oscillations with rather low-frequency (up to a maximum of 5 Hz) have to be assumed (Lowenstein et al. 1963) (Korczyn 1987).

It is known that the circadian rhythm and thus the time of day have an influence on vigilance (Kraemer et al. 2000). Under normal conditions, performance and vigilance are subject to a time of day fluctuation. A low performance is usual between 3:00 and 4:00 a.m. and in the afternoon between 1:00 p.m. and 3:00 p.m. A maximum vigilance is found

in the early morning between 7:00 a.m. and 11:00 a.m. and between 4:00 p.m. and 8:00 p.m. (Lehmann and Michaelis 1943) (Davies and Parasuraman 1982), as cited in (Weeß et al. 1998).
For this reason, attempts were made to distribute the patient examinations evenly over different times at least during the day. For organizational reasons (examination appointments had to be adjusted to the availability of the test subjects), however, no equal distribution could be achieved. More subjects tended to be measured in the morning or early afternoon than in the evening. In particular, possible confounders such as age and gender could not be considered to be equally distributed throughout the day.

It is known that age has an impact on pupil size (pupil diameter decreases by about 0.4 mm per decade), as well as on the height of the palpebral fissure (Iliff and Pacheco 2001) (Joos et al. 2003). It would be desirable to be able to eliminate such effects and thus potential confounders from the results. However, this was not possible within the scope of the experimental setup of this study, since both the pupil size and the height of the palpebral fissure were measured through a (near) lens set in the perimeter. This affected the absolute size, since plus lenses (which are usually required especially by older emmetropes for perimetric examination) enlarged and minus lenses (which have to be used by stronger myopes) reduced the resulting image. In addition to the thickness and power of the lenses, the distances between the eye and the recording video camera from the lens were decisive for the image enlargement or reduction. On the one hand, these could change due to movements of the test subject, which could not be completely ruled out even with the use of a chin and forehead rest over a period of 45 minutes. On the other hand, the anatomic variation between the subjects made it necessary to adapt the lens position accordingly. The distance to the camera adjusted in this way could not be measured easily since the main plane of the camera lens was neither known nor visible.

6.2 Discussion of the results

6.2.1 Discussion of results for *pilot study 1*

The results for *pilot study 1* were only partially reliable, as this was a proof-of-concept study including five subjects who were not stratified in any way. Not all subjects showed relevant sleepiness periods at all. For this reason, the agreement indices determined were

only meaningful for some of the test subjects.

In advance, it was expected that the heart rate variability (HRV) was related to the vigilance of the test subjects. Several studies suggested this, as already described in chapter 3.3.4.
However, a relation between HRV and false responses to catch trials was not shown in *pilot study 1*. At first it was suspected that the inadequate quality of the heart rate recording was due to the recording technology (H7 heart rate monitor, Polar Elektro GmbH, Buettelborn, Germany) which is suitable for athletes. For this reason, a more sophisticated version of a heart rate sensor designed for scientific purposes was procured for the main study (Ecgmove4 heart rate monitor, movisens, Karlsruhe, Germany). For a discussion of the results of heart rate related parameters in the main study, see chapter 6.2.3.

For PDV and RTV, subjects with longer periods of sleepiness showed, as expected, connections between vigilance and the respective parameter, as was to be expected. A more in-depth discussion of all parameter-related results can be found in chapter 6.2.3.

6.2.2 Discussion of results for *pilot study 2*

EEG measurement was not sufficient within this pilot study. One factor for that may be that electrode caps were used instead of cup or needle electrodes. Even though, it was found out, that quality of EEG measurement does not decline by the use of electrode caps (Shields et al. 2016), and data quality with regard to the signal to noise ratio (SNR) was still acceptable for a 32-channel EEG device (Scarff et al. 2004), the fit of EEG caps may not have been ideal, causing the caps to move around (Lloyd et al. 2015).

Dambros (2017) carried out a relation between EEG data and vigilance, even in experiments that required visual attention. He found, that EEG data (alpha power) was – among other eye-related parameters recorded via eye tracking – able to predict errors in a campimetric examination (Vergani Dambros 2017). However, as already stated in chapter 5.2.2, these algorithms were applied to the data of the present study, and did not lead to any sufficient outcome.
Possible reasons are, that Dambros evaluated his algorithms only by a small sample size (n = 9, 4 female and 5 male, age range 20–32 years), that was thus very homogenuous at least with respect to age.

EEG signals were used within different studies recently in order to predict fatigue or sleepiness. Power spectral density (PSD), which has also been used in the present work, is one of the most frequently used tools. This transforms the EEG signal from time to frequency domain to show its distribution as a function of frequency. In neuroscientific regards, this curve is usually divided in 4 intervals of delta, theta, alpha and beta waves (Teplan et al. 2002). However, there is no accordance with regard to frequency boundaries for the named intervals until today.
Åkerstedt (1991) discovered a relation between alpha power density and sleepiness during a night shift. The results also indicated that EEG spectra did induce effects outside the alpha intervals. However, measurement took place in time periods, when subjects fell asleep and for that, had their eyes closed. It was reported, that specifically during actual sleep phases, alpha activity increased (Åkerstedt et al. 1991).
The same effect was found during the evaluation of an exhausting driving task (Gharagozlou et al. 2015) (Kong et al. 2015).

In addition, clinical applicability was tested as a proof-of-concept study arm in one subject, as described in chapter 5.2.2. As this did not show any promising result, EEG evaluation was aborted from this study at that point. In addition to the non-promising results, inclusion of EEG in this study would have caused electro-magnetical interference between the perimeter and the EEG device. Although, the perimeter does fulfill the IEC norm 60601-1-2 EMC, interference with other electrical devices is possible as this is not forbidden by means of this norm.
In principle, it would be possible to eliminate such interference from a signal, especially if interference referred to power line signals (Leske and Dalal 2019). However, this was not done in connection with the non-promising results of the proof-of-concept study at the EEG laboratory of the University Hospital in Tübingen, Department of Neurology and Epileptology. In any case, this would have been complex and would probably not have been possible in the context of this work alone, as not only power line signals would have to be eliminated, but different interfering signals (at least produced by the perimeter itself and the response button, respectively).

In contrast, several recent studies have tried to prove that there is an effect of vigilance on EEG measures – specifically during monotonous tasks such as driving, when test subjects had to keep their eyes open.

Alpha power can possibly reflect mind-wandering when perceptual demands are reduced, e.g., during a driving situation (Lin et al. 2016). This assumption is supported by the observation that an increase in alpha power with time on task cannot be observed, when task demands are high (Fairclough and Venables 2006). The reason for this observation is that participants remain involved in a given task when it is challenging.
Another study by Schmidt et al. reported a relationship between EEG measured alpha power and sleepiness during an on-road driving task of about four hours time. It has to be noticed that sleepiness was not measured during this examination but interrogated by questionnaires during the driving task (Schmidt et al. 2007).

For an implementation of EEG into driving tasks, EEG measurement would have to be simplified. Bajwa et al. tried to detect distraction while driving using EEG recording. In order to simplify the setup, they tried to reduce the number of electrodes used by isolating one electrode (FC5) from 14 initial electrode locations. They reported to experience a big challenge in EEG analysis and were not able to distiguish between the five distraction cases they used (read, text, call, and snapshot) using a single electrode with sufficient accuracy (Bajwa et al. 2019).

Another way to simplify EEG measurement would be the use of dry electrodes. Zander et al. reported that with the help of dry electrode caps, test subjects were able to apply and adjust a pre-customized cap with the help of a little mirror (like the rear view mirror of a car) in only a few minutes. However, signal quality was poor at times and a system to better support the evaluation of signal quality was not available at that time, but would have been beneficial (Zander et al. 2017).
Efforts have been made to simplify EEG measurement by using so-called ”cEEGrids”. These are flex-printed, multi-channel sensor arrays that are placed around the ear using an adhesive. cEEGrids are reported to be lightweight, comfortable to wear and unobtrusive (Debener et al. 2015) (Bleichner et al. 2015) (Bleichner et al. 2016). Debener et al. were able to confirm an already known effect, a difference in 8-13 Hz (alpha) activity between eyes open and eyes closed resting conditions, with cEEGrid recordings (Debener et al. 2015).

To the knowledge of the author, there is currently no study that would prove a simply EEG measurement using only one or a few dry electrodes to work sufficiently. Nevertheless, there are various (non-scientific) articles that report that such devices are being

developed, for instance with regard to an implementation in the head rest of a car in order to monitor driver's vigilance and attention status (for instance, see (Burgess 2017) or (Dormehl 2017)).
As soon as there is evidence that such systems work, an implementation also in perimetry would seem to be meaningful.

6.2.3 Discussion of results for the *main study*

First, general considerations regarding analysis methods and statistical approaches are discussed. A detailed discussion for the parameters applied is added.

6.2.3.1 General considerations

There are various procedures for monitoring vigilance.
The most common tests for vigilance monitoring currently seem to be the Psychomotor Vigilance Task (PVT) (Dinges and Powell 1985) and the Pupillographic Sleepiness Test (PST) (Wilhelm et al. 1998). The latter one was already described in chapter 3.4.1.1.
In contrast to perimetry, which is be executed under (low) photopic conditions, the PST does only work under scotopic conditions (Wilhelm et al. 1998). PST values cannot be validated against any gold standard apart from actually falling asleep. In addition, it is not possible to evaluate vigilance while fulfilling any other task such as perimetry or driving. The PST can only be applied prior to or following another test procedure. Therefore, time-correlated predictions about vigilance during any other task are not possible.

The PVT test, on the other hand, is a sustained-attention, reaction-timed task that evaluates the speed with which subjects respond to a visual stimulus. The PVT was first published by Dinges and Powell in 1985 (Dinges and Powell 1985).
The PVT is carried out as a task where a subject has to press a response button as soon as a light stimulus appears in front of a dark background. The light stimulus turns on randomly every few seconds during a total examination duration of 5–10 minutes. Response time and number of lapses are assessed.
The current study worked quite similar to that. In addition to the PVT, different types of stimuli were presented and it could be tested whether a subject overlooked stimuli (as in the PVT) or whether a subject, for example due to a lack of concentration, also pressed

the response button if no stimulus was visible at all. In addition, the present vigilance perimetry had the advantage that stimuli were continuously offered, which could allow for a more precise distinction between sleepy and vigilant subjects.

However, it is nearly impossible to find any test procedure which allows for vigilance monitoring *during* a psychophysical or (traffic) ophthalmological procedure. The only way to realize that seems to be the observation of physiological parameters related to vigilance, which has also been done in the context of the present study. Results of the respective parameters are discussed below (see chapters 6.2.3.2–6.2.3.8).

If one or more parameters are found that lead to reliable results for the complete sample of subjects, there is generally the difficulty that one cannot assign them to inter-individual differences.
To illustrate such inter-individual differences, an observation made during the course of the investigations should only be mentioned as an example. Accordingly, most of the subjects examined reported that they were very exhausted after completing the present task, which was monotonous for a relatively long period of time. However, it was noticed that certain subjects obviously had no problems with the monotony. At the end of the examination, for example, these subjects stated that they had experienced a ”flow” feeling or even found the examination to be stimulating.
As the number of subjects increased, a suspicion arose that these people might have a common hobby of playing computer games. Whenever asked by the examiner, the subjects confirmed this.
It must be stated that this information was not collected in a standardized manner. Not all subjects were interviewed because the described observation only occurred during the course of the examinations and only by chance.
In addition, presence of an obstructive sleep apnea syndrome (OSAS) was not an exclusion criterion for this study. However, this information was also not collected in a standardized manner, particularly with regard to its severity. It is conceivable that subjects with more pronounced OSAS tend to fall asleep very quickly and therefore would perceive the examination as excessively stressful.

With regard to the statistical evaluation procedures applied within this study, various considerations have to be made:
The total number of false responses to catch trials was the only parameter tested for nor-

mal distribution due to the fact that it was rated as the gold standard. In addition, it was the only parameter which could be – except for the ESS score – carried out as a single value per subject for the whole examination. The distribution of the values evaluated for the other parameters varied strongly inter-individually. Therefore, mean or median calculation did not seem to be a sufficient approach. For this reason, it was decided that the frequency distributions were only evaluated by the related histograms, so that inter-individual differences remained visible.

In principle, sliding window data was used for periods with or without an increased number of errors, since otherwise the errors must have been allocated arbitrarily at a ”specific minute”. However, this was avoided when displaying the data in the parameter overview (see chapter 5.3.3) and when displaying the error frequencies over time (see chapter 5.3.4). Hence, the errors were randomly assigned to a specific time period (minute). This was done because it was the only possibility to obtain a reasonable overview of the data that was intuitively understandable and therefore meaningful. In that way, the total number of errors could be obtained as the sum of the number of errors in the individual bars of the histogram.
As stated, especially overview data (see chapter 5.3.3) were randomly assigned to a specific time period (minute). This lead to an inaccuracy in the time point annotation of the false responses to catch trials of up to ± 1 minute, which had to be accepted for the above-mentioned reasons. For statistical analysis, the data were always evaluated via the above-mentioned sliding window procedure. The overviews were only used for the graphic representation and visualization of the data.

In ophthalmology there is an unwritten law that for clinical studies the measurements from only one eye (only right, only left or one randomly selected eye) are included in the evaluation. The reason for this is the correlation (dependence) between right and left eye.
However, it is possible to include both eyes of a subject in a study. This may only happen if it is taken into account that the organ is in pairs and that there is a correlation between measurements for both eyes. Herber et al. found that if they were evaluating measurement data of both eyes without consideration of their correlation, using classic statistical tests, an overestimation of the statistical significance resulted. That could be avoided by using a linear mixed model (Herber et al. 2020).
In the present study, one eye was included per subject, selected in a randomized manner with regard to the leading eye.

Requirements for the significance of the statistical tests applied were set using a Bonferroni correction. Hence, specific p values were determined separately for the different analysis types: the global correlation analysis of the basic characteristics of the subject sample carried out in chapter 5.3.1.4, the global data analysis via agreement indices (see chapter 5.3.5.2), the individual data analysis (see chapter 5.3.6), the frequency of seeing (FOS) curve analysis (see chapter 5.3.6.3) and both meta-correlation analyses (see chapters 5.3.5.2 and 5.3.6.2).
Bonferroni correction was therefore carried out for analyses that referred to the same raw data, respectively.
An ”overall Bonferroni correction” taking into account solely the number of statistical tests carried out altogether, would have led to a inexpertly collective analysis of different data sets with regard to data quality (for instance, individual correlation coefficients were carried out for each ob 48 subjects separately in a time-resolved manner with 54,000 data points per subject, whereas global correlation analysis took place for one data point per subject for each parameter evaluated, respectively).

With regard to *global* data analysis (see chapter 5.3.5), it has to be stated that as already described, the cut-off values were determined empirically via the distribution of the data collected in the context of this study. Since the author is not aware of any generally applicable cut-off values for such purposes, this seemed to be the only way.
In order to determine a cut-off value for the false responses to catch trials, the available data was analysed in 1-minute time intervals. For consistency reasons, a sliding window with a length of 60 seconds was also applied for all other parameters.
This was necessary, on the one hand, to ensure a sufficient number of errors per unit of time (a specification of the errors per shorter unit of time did not seem to be sensitive enough). On the other hand, the temporal resolution of the examination method would have been lost if a division into longer units of time took place (see also the comments on the rate of interspersed catch trials in chapter 6.2.3.2).

Evaluation methods for the different parameters in the study were selected by ROC curve analysis. Values for the area under the ROC curve (AUROC) were comparatively low in this study, even for those evaluation methods that have been selected, which means that sensitivity and specificity values are also comparatively low for the selected cut-off values. This can be explained by the fact that relatively few false responses to catch trials were

made by the test subjects and that the physiological parameters evaluated cannot be regarded as exactly specific as well.
Cut-off values were finally determined by applying Youden's J. Another option that has also been pursued, was the determination of the cut-off value by setting a fixed specification as published in (Zangwill et al. 2001). For the present study, a specificity value of 0.8 was fixed, although Zangwill et al. suggested values of 0.85 or above. As sensitivity values were inappropriately low for specificity values of 0.85 and above, specificity was lowered to a value of 0.8, which also seemed to be adequate in the context of this study due to the low number of false responses to catch trials.

With regard to *individual* data analysis (see chapter 5.3.6), it has to be considered what values of correlation coefficients could have been expected. The measurements were not quite uniform in terms of their sample rate, since frames were irregularly aborted at times, as explained in chapter 6.1. At the appropriate points, resampling and smoothing had to be carried out, which could lead to a slight shift of the ranks assigned for the Spearman correlation.
The recorded physiological parameters were compared to the "pseudo-steady" error rate for each individual frame. Therefore, the slightest shift (e.g. due to resampling) might have been of importance. For this reason alone, correlation coefficients close to 1 were hardly possible.
Against this background, the correlation coefficients of up to (-)0.82 achieved in this study for subjects with a high number of false responses to catch trials should be rated as extremely meaningful.

The calculation of multiple correlations was completely dispensed within this study. In general, multiple correlations should be viewed with caution as the tested parameters can mutually interfere. Correlation coefficients can appear to be excessively high, which is caused by the correlation of the dependent variables with each other (and especially not to the gold standard) (Bortz 2013). This would have been expected especially for the parameters examined in this work, which were all associated with vigilance.
It seems desirable to examine the combination of the two most promising parameters (palpebral fissure height and response time variability) to monitor vigilance. However, it would have to be established beyond any doubt that there is no inherent connection between these two parameters. As stated above, this is fundamentally questionable, which is why a multiple correlation analysis would not be rated as suitable for such an evaluation.

”Meta-correlations” were performed for the total number of errors per subject and the agreement indices as well as Spearman correlation coefficients from the individual data analysis, respectively. The method of a ”meta-correlation”, specifically to re-correlate correlation coefficients, is not a common statistical evaluation method. Yet it has been used in the present work – not for the purpose of statistical data testing itself, but only for illustrating the relation of the results for the agreement indices and individual correlation analysis and total number of errors occurred per subject. Thus, both methods do work if sleepiness occurs in subjects – especially the agreement index shows a strong dependence in this regard.

For the main study, the steepness of the steepest slope (SSL) of the frequency of seeing (FOS) curves within a monotonous drop (in order to exclude small fluctuations) was calculated for each subject. If the steepness of the slope varied for different test locations, the median of the slope steepness was taken.
It would also have been possible to fit a logistic function to the FOS curves before calculating the steepness of the slope in order to obtain smoother results. However, this has been avoided to be able to distinguish between fluctuation and slope steepness.

6.2.3.2 False responses to catch trials

In conventional perimetry, a catch trial rate of about 3–5% each false positive and false negative catch trials is implemented (Schiefer et al. 2006). The presented work implements a catch trial rate of 25%, each for false positive and false negative catch trials.
Assuming a catch trial rate of 4%, a stimulus duration of 200 ms and an inter-stimulus interval of 1500 ms, it results that a catch trial (either false positive or false negative) is shown approximately every 21 seconds. The catch trial rates implemented in the present study result in a catch trial (either false positive or false negative) approximately every three seconds.
Assuming that not all responses to catch trials are automatically and immediately false as soon as sleepiness begins, a conventional catch trial rate of 4% (or even less) would not allow for sufficient time-resolved detection of sleepiness.

Larger studies on glaucoma or ocular hypertension that have been carried out in the recent past, monitored vigilance and response quality with the help of catch trials as well.

Some examples are displayed as follows:
The Advanced Glaucoma Intervention Study (AGIS) enrolled 5000 patients suffering from open-angle glaucoma. Perimetry was conducted with a Humphrey Visual Field Analyzer (HFA) set for the central 24-2 threshold test with full-threshold strategy, and the foveal threshold test turned on. A usual catch trial rate of 3% each false positive and false negative catch trials was implemented (**?**).
The Collaborative Initial Glaucoma Treatment Study (CIGTS) was initiated to investigate whether medication or filtrating surgery was more beneficial to patients with primary open angle glaucoma (POAG). 607 patients at 14 participating centers were enrolled. Visual fields were recorded using the HFA 24-2 full-threshold strategy with a usual catch trial rate of 3% each false positive and false negative catch trials (Wahl 2005).
The Ocular Hypertension Treatment Study (OHTS) investigated the safety and efficacy of topical hypotensive medication in delaying or preventing the onset of primary open-angle glaucoma (POAG) in participants with ocular hypertension. 11,584 visual fields of 1,636 participants at 22 participating clinical centers were involved. Quality of visual fields was rated as sufficient if two out of three tests met reliability criteria of less than 33% false positives, less than 33% false negatives, (and also less than 33% fixation losses) using a HFA 30-2 full-threshold strategy with a usual catch trial rate of 3% each false positive and false negative catch trials (Johnson et al. 2002) (Kass et al. 2002) (Keltner et al. 2003).
There are various other studies that used visual fields as a primary outcome criterion. As can be seen from the description of studies above, quality monitoring usually only played a subordinate role, as a catch trial rate of only 3–5% was implemented. Therefore, quality control could not have been carried out with sufficient time resolution, as stated above.

A parameter that is often used for quality monitoring during perimetry is fixation control. Therefore, stimuli are either placed in the location of the blind spot and must not be detected (method after Heijl-Krakau (Heijl and Krakau 1975)) or in the center of the visual field and have to be seen.
The Heijl-Krakau method is associated with several problems: It must be assumed that the initial determination of the blind spot works optimal. Movement or changes in size of this reference due to bulbus rotation, higher ametropia or papillary changes can significantly affect the validity of this method. This also applies in the case of extended scotoma in the neighborhood to or under the inclusion of the blind spot.
Presentation of slightly supra-threshold central stimuli for fixation control, on the other hand, can also be criticized: If fixation is shifted only for a few degrees, stimuli for fixation

control are not visible anymore. In addition, the fixation of central stimuli is difficult or even impossible for patients who suffer from central scotoma or paracentral, extensive scotoma (e.g. arcuate scotoma in glaucoma patients). Central luminance sensitivity can also be seen as a quite variable parameter that is initially often comparatively high, but decreases during the course of an examination due to lack of concentration and vigilance (Schiefer et al. 2006).
Therefore, quality monitoring via fixation control is seen as critical and controversial at times.

This study implemented a catch trial rate of 25%, each false positive and false negative catch trials, which were not regarded separately with respect to vigilance. This decision was made because it could be observed during the experiments that not all subjects reacted equally when they started to get tired. Some began to overlook stimuli, while others began to press the response button regularly, guided by the acoustic cues that the perimeter created parallel to the stimulus presentation – regardless of whether a stimulus could be seen or not.
In connection with the generally low number of false responses to catch trials in this study, a joint consideration of the false positive and false negative catch trials seemed appropriate.

A global correlation of total number of errors and the onset, i.e. the point in time when an increased number of false responses to catch trials was available for the first time, did not show a statistically significant relationship. This is not intuitive to understand.
However, it turned out that some subjects made many mistakes in a short time (corresponding to a short but strong sleepiness period), while other subjects made fewer mistakes over a longer period (corresponding to a general fatigue status or lack of concentration).
This raises the question of whether certain errors are more important than others in the present evaluation. In fact, one error per minute is even ”tolerated” without an increased number of false responses to catch trials being assumed. This is obviously an arbitrary decision. In connection with the frequencies mentioned above, in which catch trials occurred (every three seconds), this definition seemed reasonable. Finally, it must also be taken into account that individual errors can also result from nervousness with fully preserved vigilance.

6.2.3.3 Eyelid closures (blinks)

As stated in chapter 3.3.1, blink rate increases with an increase in fatigue or sleepiness (De Padova et al. 2009).
As subjects are told to blink regularly (after having perceived a stimulus) during perimetry, blink rates carried out during perimetric examinations must be seen as highly artificial.
Therefore eyelid closures were involved in this study, but the fact that these parameter does not show any high relation to vigilance during perimetry, does not seem to be surprising.

Nevertheless, it is a concerning issue, to which proportion the ocular surface has to be covered by the upper eyelid. The phenomenon of incomplete eyelid closure during blinks is well-known and reported (McMonnies 2007).
The US Federal Highway Administration (FHWA) and the National Highway Traffic Safety Administration (NHTSA) proposes to detect sleepiness and/or drowsiness during driving by the PERCLOS. The PERCLOS is the percentage of eyelid closure per unit of time. P80 is considered the most effective standard to define eyelid closure (meaning that the eyelid is determined to be closed when palpebral fissure height is reduced to 20% or below the normal height) (Dinges and Grace 1998) as cited in (Nie et al. 2017).

As some individuals tend to not close their eyelid completely while blinking and the individual percentage of closure is not known, the approach applied during the present work did not take into account the remaining palpebral fissure but the visibility of the pupil. If the pupil was detected, no blink was assumed. If no pupil was detected in a specific frame, but it had been detected in the previous frame, a blink was assumed.

6.2.3.4 Pupillary oscillations

According to Lowenstein, all of the pupil-related phenomena stated in chapter 3.3.2 are known to exist under *scotopic conditions* only. In contrast, under *photopic conditions*, there is additional increased activity from the parasympathetic nervous system, which reacts to light levels and accommodation (Lowenstein et al. 1963).

Nevertheless, efforts were made to prove that the pupillary oscillations that occur under scotopic conditions are also present under photopic conditions. Nishiyama et al. observed

miosis and pupillary fatigue waves in subjects that had to perform an uneventful simulated driving task. They found out that pupillary fatigue waves occurred in 80% of subjects during the 10-minute recording session and that during periods when pupillary fatigue waves were present, there was an increase in the number of targets missed and a decrease in the saccade velocity, which can be seen as evidence of reduced vigilance (Nishiyama et al. 2007).

Henson and Emuh found fatigue waves in patients performing a campimetric examination under low photopic conditions (background luminance: 10 cd/m^2) (Henson and Emuh 2010).
In contrast to Henson and Emuh (2010), the present work did not identify pupillary oscillations, especially computed with the help of wavelet analysis, as a parameter with strong correspondence to fatigue or sleepiness. One reason for that may be limitations in temporal and spatial resolution of the video frames as already stated above (see chapter 6.1).
In addition, Henson and Emuh executed measurement under different conditions and for a different group of subjects (elder glaucoma patients or glaucoma suspects), as carried out in chapter 3.3.2.

On the other hand, Loewenfeld postulated in 1993, that pupillary oscillations correlated with the luminance level (Loewenfeld 1993) and overlaid fatigue waves. The first examination regarding this issue was carried out by Warga et al. in 2009, specifically designed to answer the question, if it was possible to filter pupil data collected in daylight to identify sleepiness during activities in the daytime (like e.g. driving). They found that light-induced pupillary oscillations in fact correlated positively with luminance levels, as postulated by Loewenfeld.
Warga et al. stated that the observed light-induced oscillations were hard to differentiate from sleepiness waves. In some cases, especially under stable alertness levels, they did not come along with a general decline of the pupil diameter. The latter observation was regarded to be a typical characteristic of sleepiness waves. Light-induced oscillations did not occur in all twelve young (23–28 years) healthy subjects they examined and the temporal and spatial characteristics were considerably different between the subjects. Oscillations under photopic conditions were not continuously present during the entire recording time and periods with and without oscillations alternated although alertness of the subjects was monitored and stable. Altogether, they noticed an increase in the amplitude and frequency of pupillary unrest with increasing luminance levels up to 400 cd/m^2. Below, light-induced

oscillations often were similar to the well-known sleepiness waves (Warga et al. 2009).

In general, light-induced oscillations tend to be more vigorous in young, excitable people than in older persons (Loewenfeld 1993).

In summary, it must be said that the relationship between the frequency and amplitude of the pupil oscillations and vigilance under photopic conditions has not yet been definitely clarified.

It has also to be mentioned, that Henson and Emuh derived so-called fatigue waves. It seems to be questionable, if this is feasible in relation to a method such as perimetry, which is thought to be more affected by sleepiness than fatigue. However, as both concepts are dependent, this may only be a wording issue.
In contrast to Henson and Emuh's experiment, the present study was carried out using the built-in camera of a conventional, commercially available perimeter rather than a campimetric device with attached eye tracking unit. Clinical applicability therefore is given for the first time by this approach.

With regard to the pupil and pupillary oscillations, it has also to be considered, that changes in pupil dilation accompany effortful cognitive processing (Kahneman 1973).
A dilatation of the pupil can be observed in subjects with increased cognitive workload, e.g. subjects instructed to solve a task associated with concentration, such as mental arithmetic. Pupil dilatation refers to the complexity of the given arithmetic task. Calculating the product of two large numbers results in greater pupil dilatation than for small numbers. Pupils return to their previous size within a few seconds of completing the mental work. Therefore, it can be stated that cognitive workload, which is related to attention, affects the pupil and, in turn, that pupil size over time can indicate cognitive workload (Beatty and Lucero-Wagoner 2000).
While performing a perimetric task, subjects could react to an onset of sleepiness in completely different ways. Some allow the lack of concentration due to sleepiness, while others fight it. The latter will likely experience a higher cognitive workload. These inter-subject differences could affect the pupil and its oscillations and be an opponent to the fatigue waves.

6.2.3.5 Palpebral fissure

Fox reported back in 1966, that literature on the subject of the palpebral fissure was scarce yet available. However, where it existed, no two authorities could agree on the size, shape and proportions of the palpebral fissure (Fox 1966).
Adler stated that the palpebral opening usually is 25 mm wide in adults (Moses 1981), Duke-Elder and Wybar reported it to be 30 mm wide (Duke-Elder and Wybar 1961). According to Kestenbaum, the palpebral fissure height is 9-10 mm in adults (Kestenbaum 1963), whereas Whitnass stated that it is 15 mm (Whitnall 1932).

Hanada et al. examined three different racial groups with regard to their palpebral fissures. They stated that the mean horizontal dimension of the palpebral fissure of Japanese was not statistically different from the mean of Indians, yet both were significantly greater than the mean fissures of Whites. Vertical dimension of the palpebral fissure, however, was not examined (Hanada et al. 2001).
Yuzuriha et al. stated, that the typical Mongoloid eye differs from the Occidental one in puffiness of the upper eyelid and in narrowness of the palpebral fissure. They surmised that an anatomical structure might exist in the preaponeurotic fat space, which determined the features of the Mongoloid eye (Yuzuriha et al. 2000).

Hill et al. found out that the whole lateral canthus becomes lax and drifts medially with age, resulting in a decline of the height of the palpebral fissure (Hill 1975).

In summary, palpebral fissure parameters vary vastly inter-individually due to race and age. It is not possible to determine normal values and/or absolute cut-off values for the height of the palpebral fissure, also in dependence of a subject's vigilance status. The palpebral fissure can only be evaluated in relation to an intra-individual baseline, as done within the present study.

According to chapter 3.3.3, the upper eyelid is lowered when sleepy, inattentive and exhausted (Records 1979). Results of this study confirmed this statement.

In addition, findings of this study suggest that the palpebral fissure height gets more variable with decreasing vigilance. This could be due to the fact, that some individuals tend to fight the occurrence of sleepiness and therefore open their eyes wide occasionally. This behavior was observed several times in different subjects by the examiner.

A decrease in the height of the palpebral fissure could possibly interfere with other parameters, for instance with pupil size. If the upper eyelid is lowered, the pupil may only be partially visible. This has been a problem during the *pilot studies* in the present work, and has then been corrected by an algorithm that was able to detect the pupil as a circular or elliptic section (see chapter 3.4.4.2).
A possible interference of the height of the palpebral fissure and the blink rate has been eliminated by filtering out any blink from the recorded data of the height of the palpebral fissure prior to further data procession.

As already stated in chapter 6.2.3.3, the percentage of eyelid closure (PERCLOS) can be used as a drowsiness detection technology. Dinges and Grace declared PERCLOS to be the most reliable and effective parameter to judge the level of alertness of a driver (Dinges and Grace 1998) as cited in (Nie et al. 2017).
However, it has to be said that PERCLOS has been used throughout various studies to detect fatigue and that the PERCLOS cut-off value as a threshold for determining fatigue ranges from 7.5% to 80% (Papadelis et al. 2007) (Di Stasi et al. 2010) (Abe et al. 2011) (Jo et al. 2014).
Reasons can be, for instance, differences in the recognition of fatigue grading standards among researchers, differences in the eye contour, which is detected by different image processing algorithms, or various methods of eye identification and edge segmentation (Nie et al. 2017).

PERCLOS is simple and robust, and it has long been a widely used feature. Yet it has been reported to be insufficient to estimate mild drowsiness, and estimation accuracy with PERCLOS alone is not high (Nagai et al. 2008).
Tsujikawal et al. therefore suggested that PERCLOS should only be used in combination with other methods such as gaze movements or blink rate. Another method would be to not only investigate the PERCLOS, but also the eyelid variability. It was found that eyelid variability (correlation coefficient = 0.55 at frame rate of 20 fps) led to a significantly better correlation to drowsiness than PERCLOS alone (correlation coefficient = 0.45 at frame rate of 20 fps), specifically for lower frame rates (below 30 fps) (Tsujikawal et al. 2018).
The latter approach was therefore also used within the present study. Instead of the palpebral fissure height (referring to PERCLOS) only, also the variability of the palpebral fissure height was investigated.

6.2.3.6 Heart rate (HR) and heart rate variability (HRV)

Heart rate variability (HRV) time-domain measurements are related to age and gender, as they decline with age. Bonnemeier et al. (2003) assessed 24 h recordings from 166 healthy subjects (85 male, 81 female, age range 20–70 years). It was found that the most dramatic HRV parameter decrease occurred between the second and third decades (Bonnemeier et al. 2003) as cited in (Shaffer and Ginsberg 2017).
In the present study, heart rate related parameters were not corrected for age or gender. Hence, test subjects were equally distributed among different age groups in order to keep any bias as small as possible.

With regard to heart rate related measures, several studies were carried out in the past, that have shown a relation between heart rate and vigilance level. As already stated in chapter 3.3.4, it is possible to divide the HRV into components of different frequency ranges by a Fast Fourier Transformation (FFT):
The low frequency (LF) band (0.04 to 0.15 Hz) was formerly known as the baroreceptor range because it mainly reflects baroreceptor activity during resting conditions. LF power may be produced primarily by the sympathetic nervous system (SNS). The sympathetic nervous system does not produce rhythms above 0.1 Hz, while the parasympathetic nervous system (PNS) can affect heart rhythms down to 0.05 Hz (Shaffer and Ginsberg 2017).
The high frequency (HF) band (0.15 to 0.40 Hz) on the other hand reflects parasympathetic activity. Lower HF power is often correlated with panic, anxiety or stress (Shaffer and Ginsberg 2017).
The ratio of LF to HF power (LF/HF ratio) was formerly based on 24 h recordings, during which both PNS and SNS activity contribute to LF power. PNS activity, on the other hand, primarily contributes to HF power. The concept of the LF/HF ratio is the idea of LF power being generated by the SNS while HF power is produced by the PNS. Shaffer (2017) warned that the LF/HF ratio was controversial because 24 h and 5 min values were generated by different procedures, and the results correlated poorly. The SNS contribution to LF power varies with testing conditions. Therefore, no reliable LF/HF ratio results for (ultra-)short term measurement are available (Shaffer and Ginsberg 2017).
The present study investigated a relation between vigilance and the heart rate variability for low frequencies (HRVLF). As it can be assumed that the SNS is related to vigilance,

it is possible that the correspondence between vigilance and *low* frequencies of the HRV occurred when test subjects started to fight the onset of sleepiness.

With regard to monotonous psychophysical examinations, already in 1963, Griew et al. found a connection between heart rate and vigilance performance. He examined 24 test subjects for their auditory attention. To do this, a response button had to be pressed during a 60-minute examination whenever a certain auditory signal could be heard. The results showed that the heart rate decreased with increasing number of errors (Griew et al. 1963).

In addition, it was shown by Chua et al. that heart rate variability (HRV) measures can be used to predict daytime performance levels (Chua et al. 2008). This is also meaningful for perimetric tasks. Chua et al. also investigated, whether changes in psychomotor vigilance during sleep deprivation can be estimated using HRV. They carried out that HRV was able to give information about a person's vigilance state and stated that HRV measures could potentially be used to predict when an individual is at increased risk of (visual) attentional failure. They suggested that HRV monitoring, either alone or in combination with other physiologic measures, could be incorporated into safety devices to warn drowsy operators when their performance was impaired (Chua et al. 2012). In contrast to the present study, they examined subjects who were sleep deprivated for 40 hours. Subjects had to undergo the Psychomotor Vigilance Task (PVT) every 2 hours for about 10 minutes within the 40 hour examination duration. Vigilance tasks were shorter, but results were correlated to actual sleep deprivation, which was not applied in the present study.

Henelius et al. found that HRV alone explained 33% of PVT variance during a study that evaluated the impact of sleep deprivation. Therefore, a sleep restriction group (n = 15) was restricted to 4 hours of sleep for 5 nights whereas a control group (n = 8) had 8 hours of sleep during all nights. All of them underwent the PVT. HRV was examined within a frequency band in the range [0.00, 0.40] Hz according to both, high and low frequency bands together (Henelius et al. 2014). In contrast to that, the present study showed best accordance to vigilance only for the HRVLF band (i.e. low frequencies of the heart rate variability).

6.2.3.7 Response time (RT) and response time variability (RTV)

As shown in chapter 3.3.5, response times are known to be linked to vigilance, as response times increase with a decrease in vigilance (Freeman 1933) (Broadbent 1971) (Welford 1980).
This was also found within the present study. Surprisingly, response time variability (RTV) was (cor)related even more to vigilance by the means of the present study. To the author's knowledge, response time variability has not been connected to vigilance before.
However, RTV has been linked to attention in a vast amount of studies and is well-known to be increased globally in patients suffering from attention deficit hyperactivity disorder (ADHD, see for instance (Zakzanis 2001) (Klotz et al. 2012)).
Most studies of response or reaction time variability implicitly assume that increased reaction time variability reflects occasional lapses in attention, and the dominant neurophysiological interpretation suggests that variability is linked to intrusions of task-negative brain network activity during task performance. (Tamm et al. 2012).
This could be related to the lack of concentration often occurring during perimetry.

6.2.3.8 Epworth Sleepiness Scale (ESS)

A questionnaire for evaluating sleepiness can generally be criticized for not being able to be assessed during the examination. It is only possible to record the subjects' usual tendency to fall asleep before the start of an examination or retrospectively for once.

Questionnaires are, as described in chapter 3.3.7, methods of self-assessment.
In general, self-assessment as a common approach for gathering data in epidemiologic and medical research, is known to require participants to respond to the questions asked without personal interference. Relative to other sources of information, specifically laboratory measurements, self-reported data are often argued to be unreliable and threatened by self-reporting bias (Althubaiti 2016).

In the present work, no correlation between total number of errors as well as onset of sleepiness and ESS scores were found. Even accordance to onset of sleepiness could not be found. This may depend on the choice of a cut-off criterion for whether a subject shows a normal or pathological ESS score. The value of 11.7 was taken as a cut-off criterion. No norm values were available, only mean values for different patient groups

were published by Johns (1991). This publication stated a mean value of 11.7 for patients suffering from obstructive sleep apnea syndrome (OSAS), which is known to be related to daytime sleepiness (Bixler et al. 1979) (Breslau et al. 1997) (Ohayon et al. 1997). As no further relevant information was available, this value was defined as a cut-off criterion.
In addition, it has to be stated that the diagnostic value of the ESS was classified as low by the author himself (Johns 1991). Significant correlations to the Multiple Sleep Latency Test (MSLT) reported by the author could not be confirmed in further studies (Benbadis et al. 1999). Yet the questionnaire has meanwhile found widespread use in clinical research and is internationally known (Johns 1991).
Additionally, no correlation of ESS scores and age were found. This result corresponds to what has been published by the author of this questionnaire (Johns 1991) and was therefore expected.

6.2.3.9 Frequency of seeing (FOS) curves

Frequency of seeing (FOS) curves were included in the evaluation as a supplementary measure for the reliability of subjects' performance (Woodworth and Schlossberg 1954) (Chauhan et al. 1993). As these are only available retrospectively for the entire investigation, it is unclear how the fluctuations develop over time and whether this varies from person to person. A time-resolved investigation of these fluctuations could not be covered in the context of this study.
For future studies, however, it would be interesting to determine the fluctuations of FOS curves during perimetric examinations depending on the number of questions already asked per location. This could also be used to define a cut-off, at which fluctuation rate, based on the number of questions asked, a perimetric examination could be terminated. For future applications, it would even be conceivable that such a FOS curve could replace or supplement the presentation of catch trials in perimetric sessions with live recording and evaluation of the perimetric data. Fluctuations in the high-threshold areas of the curve could be used for such an analysis.
The available data carried out within this study could be re-evaluated in this regard during a future study.

6.3 Conclusion

The purpose of this work was to to develop a methodology to monitor and validate vigilance during static automated perimetry. Vigilance (and also reduced vigilance, i.e. sleepiness) was operationalized by several parameters such as eyelid closures (blinks), pupil diameter, the height of the palpebral fissure, heart rate, and response time. These parameters were (cor)related to the number of false responses to catch trials given by a subject, which was seen as the gold standard for vigilance and therefore also for the validity of the perimetric results.

Response time variability and the height of the palpebral fissure were identified as the most promising and valid parameters to fulfill the requirements with regard to the purpose. Specifically with regard to less vigilant subjects that generated a comparably high number of false responses to catch trials, relatively high agreement indices and correlation coefficients could be obtained.

The main benefit of the this new method is, that compared to other vigilance tests such as the Pupillographic Sleepiness Test (PST) or the Psychomotor Vigilance Task (PVT), the findings of this study allow for vigilance monitoring *during* a psychophysical examination or other task such as driving in a highly time-resolved manner due to a considerably increased portion of catch trials.

The following chapter 6.4 gives a short overview, how further developments and studies could even improve vigilance monitoring by means of the results of the present study.

6.4 Outlook

6.4.1 Implementation in conventional perimetry

As already stated in chapter 5.3.6.4, only normal subjects without any visual field loss were included in the present study. Patients with advanced visual field loss could be included in a future study. In patients with advanced visual field loss, significantly higher error rates can generally be expected (Birt et al. 1997).
A future study could also clarify, if the results of this work were reproducible also with pa-

tients who suffer from different pathologies such as the obstructive sleep apnea syndrome (OSAS), hypersomnia, narcolepsy, or insomnia, which could lead to a higher rate of false responses to catch trials. It would be very interesting to investigate, whether similar phenomena occurred.
In addition, if patients with sleep disorders as listed above were examined, a higher prevalence of sleepiness would occur. Therefore, results could show higher accordance or correlation levels. This was exemplarily shown already in chapter 5.3.6.2 by the simulation of an artificial prevalence enrichment for the individual analysis of the palpebral fissure height. This immediately led to a strong correlation for the selected subgroup.
For all the reasons stated above, it would be meaningful to carry out a future study in cooperation with a clinic that has access to a large number of patients suffering from the respective pathologies.

A fixed implementation of the test procedure in a perimeter for live monitoring of vigilance during examinations could be executed. The palpebral fissure is easy to determine using the built-in camera for fixation control and can be seen as a valid parameter. Response time is usually recorded during the examination anyway. Since these were the two most promising parameters during the investigation, implementation would be comparatively easy. A follow-up study could clarify the feasibility.

6.4.2 Implementation in a portable, headmounted perimeter

For further studies, spatial resolution as well as frame rate would have to be improved. Frame rate would have to be at least 20 fps constantly without rejecting frames due to a lack of processing power.
It was already investigated, that the imo perimeter (CREWT Medical Systems Inc., Tokyo, Japan) would be feasible for such an implementation due to its resolution of up to 1280x960 px and the possibility of pupil recording.

With the implementation of the method for vigilance monitoring during perimetry found in the present study, vigilance-controlled perimetry could be integrated into a headmounted and thus portable and not stationary perimeter.

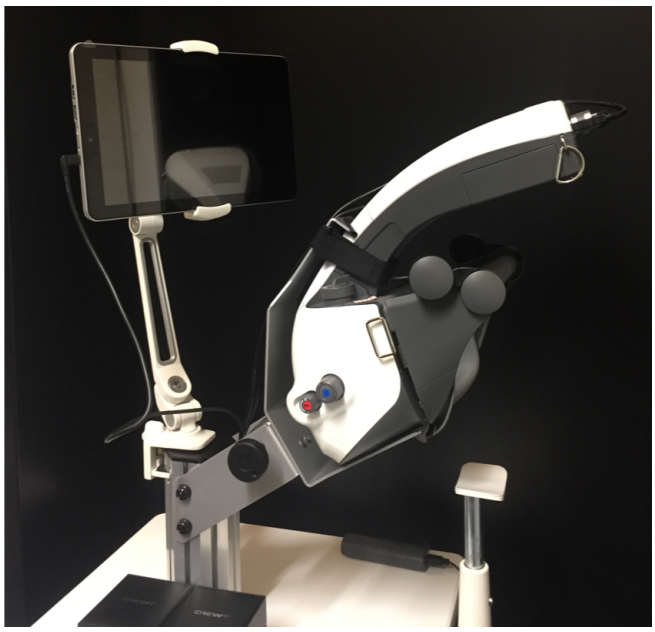

Figure 6.1: imo perimeter (CREWT Medical Systems Inc., Tokyo, Japan)

In occupational medicine, it is important to have a device that is as compact as possible and portable, but still offers a variety of standardized examination options. The imo perimeter (CREWT Medical Systems Inc., Tokyo, Japan) would basically be well suited for this. It could not only serve as a perimeter, but also as a portable vigilance test on its own and potentially as a multipurpose visual function test device. This may have a considerable impact on occupational medicine.

6.4.3 Implementation into vigilance monitoring during driving

Bergasa et al. tried to come up with a system to monitor drivers' vigilance in real-time. They developed a non-intrusive prototype based on a hardware system for a real-time acquisition of drivers' images using an active IR illuminator. Software algorithms for the real-time monitoring of six parameters that better characterize the fatigue level of a driver were implemented. These visual parameters were eye closure duration, blink frequency, nodding frequency, face position, and fixed gaze. The system worked robustly during day- and nighttime, but only for test subjects that did not wear glasses (Bergasa et al. 2006).

In the present study, the height of the palpebral fissure was found as a reliable parameter for vigilance monitoring. Therefore, real-time systems could be improved and made sufficient even for subjects wearing glasses.

Finally, it has to be stated that vigilance perimetry could serve as a test for vigilance itself in the future. This may especially be suitable for standardized driving tasks or with regard to testing for immediate effects of alcohol or drug abuse as well as for sleep disorders such as sleep apnea.

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A Study synopsis

The following pages show the study synopsis for the *main study* and overall timeline for the present study.

Title of the project Subtitle **Assessment of vigilance and quality during static automated perimetry (SAP)** A study using the method of constant stimuli (MoCS) and an enhanced presentation rate of catch trials		**Name Examiner:** Judith Ungewiß **Acronym:** ViPer **Date / Version:** 2019-10-27 / V9
1. Aims of this project		
1.1 Main purpose **→ Primary objective** What goals shall be achieved at the end of this project – which results shall be achieved?	1.1.1 To monitor vigilance and error rate and their (cor)relation in time during SAP by video-pupillography and an increased no. of catch trials as "ground truth" in order to specify a valid termination criterion.	
1.2 Null Hypothesis/es for primary objective	1.2.1 There is no agreement of (i) blinks and blink rate, (ii) pupil diameter, (iii) palpebral fissure height, (iv) heart rate, (v) response time as well as their variabilities *and* error rate due to agreement indices. 1.2.2 There is no correlation of (i) blinks and blink rate, (ii) pupil diameter, (iii) palpebral fissure height, (iv) heart rate, (v) response time as well as their variabilities *and* error rate.	
1.3 Other purpose(s) **→ Secondary objective(s)**	1.3.1 To assess accordance of an onset of sleepiness and pathologic Epworth Sleepiness Scale (ESS) scores 1.3.2 To assess global correlations of (i) age and onset of sleepiness, (ii) ESS and onset of sleepiness, (iii) age and total number of errors, (iv) ESS and total number of errors, (v) onset of sleepiness and total number of errors, (vi) age and ESS	
1.4 Null Hypothesis/es for secondary objective/s	1.4.1 There is no accordance of an onset of sleepiness and pathologic Epworth Sleepiness Scale (ESS) scores 1.4.2 There is no correlation of (i) age and onset of sleepiness, (ii) ESS and onset of sleepiness, (iii) age and total number of errors, (iv) ESS and total number of errors, (v) onset of sleepiness and total number of errors, (vi) age and ESS	
1.5 Specify relevant/critical effect size Please differentiate carefully from statistically significant result!	1.5.1 For the definition of agreement indices, error rate is rated as pathological, if error rate is at least 2 errors/min. 1.5.2 For analysis of 1.2.1, relevant cut-off values are investigated via ROC curves and AUROC values 1.5.3 Epworth Sleepiness Scale (ESS) scores were rated as pathologic, if a score of ESS > 11.7 was obtained	
2. Project organization		
2.1 Technical requirements	2.1.1 OCTOPUS 900 perimeter (Haag-Streit, Koeniz, Switzerland) 2.1.2 PC: DELL Optiplex 7010 (DELL, Round Rock, Texas, USA) 2.1.3 2x hard disc for data backup (My Book, Western Digital, Irvine, California, USA) 2.1.4 translucent, reusable, sanitizable eye patch (Haag-Streit, Koeniz, Switzerland) 2.1.5 heart rate monitor and chest strap (Ecgmove4, movisens, Karlsruhe/Germany) 2.1.6 VISUCAT (argusindividuell optic GmbH Putzbrunn/Germany) optotype-display with single optotypes (numbers) for initial measurement of visual acuity	
2.2 Tasks	**Name**	**Comments**
1. supervisor	Prof. Dr. H.A. Mallot	Tübingen University
2. supervisor	Prof. Dr. med. U. Schiefer	Aalen and Tübingen University
Examiner	Judith Ungewiß	
Study group	Competence Center "Vision Research"	Aalen University

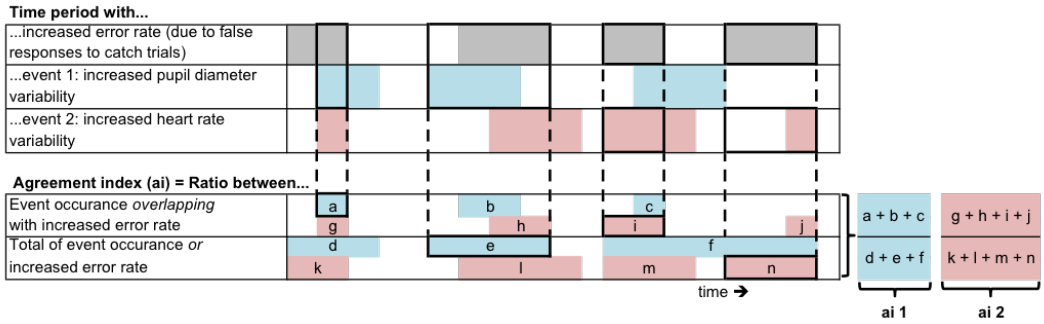
2.3 Quality management Contact, meetings, supervision	2.3.1 e-Mail contact between 1. supervisor and examiner, when needed 2.3.2 continuous personal contact between 2. supervisor and examiner 2.3.3 meetings, when needed
2.4 Time frame	February 2016 – January 2020
2.5 Scheduled launch of the project	May 01, 2016 (*pilot studies*), May 01, 2018 (*full-scale study*)
2.6 End of the project	January 31, 2020
3. Project related issues	
3.1 Study design	explorative study
3.2 Sample size	*pilot study part 1* and *pilot study part 2*: 5 patients *full-scale study*: 48 patients (due to G*Power; Correl: Bivariate model, : n > 46)
3.3 In- and Exclusion criteria? *further specification depending on project*	3.3.1 age ≥ 18 years, patients equally distributed among groups: 21 – 40 years, 41 – 60 years, 61 – 80 years 3.3.2 minimum distant visual acuity (without/with correction) 0.8 (VISUCAT, single letter optotypes [numbers]). 3.3.3 Ametropia: maximum myopia sph -8.00dpt, maximum hyperopia sph +8.00 dpt, maximum astigmatism cyl 2.50 dpt 3.3.4 normal ophthalmologic status (ophthalmological examination) 3.3.5 informed consent
3.4 Recruitment of patients	employees of Aalen University, citizens of Aalen
3.5 Randomization	randomization with respect to the leading eye
3.6 Data analysis / Statistics	3.6.1 Software: MatLab Release 2018a – academic use (The MathWorks, Natick, Massachusetts, USA) 3.6.2 "Agreement index", defined as i.e. the ratio between the time periods of event occurrence as specified in clauses 1.5.1 and 1.5.2 *overlapping with* the time periods with increased error rates AND the total time period with increased error rates or occurrence of events as specified in clause 1.5.1 and 1.5.2 3.6.3 Spearman correlation coefficients regarding clauses 1.2.2 and 1.4.2 3.6.4 McNemar's test regarding clause 1.4.1 3.6.4 Variabilities are calculated as variances within a sliding window over a 1 min.-period 3.6.5 Visualization of differential luminance sensitivity by FoS-Curves
3.7 Methodological sequence of the project (*full-scale study*)	3.7.1 Subject selection according to in-/exclusion-criteria 3.7.2 Determination of the leading eye by Rosenbach test 3.7.3 Assessment of sleepiness status by questionnaires (Epworth sleepiness scale) 3.7.4 Assessment of differential luminance sensitivity with the OCTOPUS 900 perimeter (Haag-Streit, Koeniz, Switzerland) using OPI at 3 locations (-6.1,-3.5), (0,7), (6.1,-3.5) 3.7.5 Using MoCS (Method of Constant Stimuli) and an increased number of catch trials (false pos./false neg. 25% each) 3.7.6 Variation of stimulus intensity in 13 steps betw. 0.04 cd/m^2 (39dB) and 160 cd/m^2 (3 dB) with background luminance of 10 cd/m^2
4. Resources and Costs	
4.1 What **Costs** arise? What **Resources** are needed? *Personnel/Staff, Material costs, Equipment, Space/Rooms*	4.1.1.OCTOPUS 900 perimeter (Haag-Streit, Koeniz, Switzerland) 4.1.2 PC: DELL Optiplex 7010 (DELL, Round Rock, Texas, USA) 4.1.3 2x hard disc for data backup (My Book, Western Digital, Irvine, California, USA) 4.1.4 heart rate monitor and chest strap (Ecgmove4, movisens, Karlsruhe/Germany) 4.1.5 Examination room with full-blinding curtains (AMPEL II – INNO-Z 1.11/1.12) 4.1.6 MatLab License Release 2018a – academic use (The MathWorks, Natick, Massachusetts, USA) 4.1.7 patient insurance 4.1.8 ethics commitee approval by institutional review board (Ethik-Kommission der Landesärztekammer)

4.2 Patient- or other insurance needed?	yes
4.3 Institutional review board / Ethics committee approval needed?	yes

Abbreviations

MoCS	method of constant stimuli	OPI	Open Perimetry Interface
FOS	frequency of seeing	SAP	static automated perimetry
ROC	receiver operating characteristics	AUROC	area under the ROC curve

Determination of the "Agreement index"



range: 0 ≤ agreement index ≤ 1

Timeline

Feb 2016 – Mar 2016	Subject search and definition
Apr 2016 – May 2016	Experimental setup for *pilot study 1: perimetry and heart rate monitoring*; Measurement period for *pilot study 1*
Jun 2016	Analysis of data for *pilot study 1*
Jul 2016 – Dec 2016	Determination of final methodology for parameters included in *pilot study 1*
Jan 2017 – Mar 2017	Experimental setup for parameters not included in *pilot study 1* → *pilot study 2: perimetry and EEG*
Apr 2017 – May 2017	Measurement period for *pilot study 2*
Jun 2017 – Aug 2017	Analysis of data for *pilot study 2*
Sep 2017 – Feb 2018	Determination of final methodology for parameters included in *pilot study 2* and for *full-scale study*
Mar 2018 – May 2018	Ethics committee approval
Jun 2018 – Dec 2018	Recruitment of patients for *full-scale study*; Measurement period for *full-scale study*
Jan 2019 – Jul 2019	Analysis of *full-scale study* data
Aug 2019 – Jan 2020	Preparation and final arrangement of dissertation

B Ethics committee approval

The following pages show the ethics committee approval of the institutional review board (Landesärztekammer Baden-Württemberg, Germany) for the present study.

LANDESÄRZTEKAMMER BADEN-WÜRTTEMBERG
KÖRPERSCHAFT DES ÖFFENTLICHEN RECHTS

ETHIK-KOMMISSION

Landesärztekammer Baden-Württemberg • Postfach 700361 • 70573 Stuttgart

09.05.2018

Ansprechpartnerin:
monika.kretschmer@laek-bw.de
Tel.: 0711 76989-19
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Hochschule Aalen
Kompetenzzentrum Vision Research
Herrn Prof. Dr. med. Ulrich Schiefer
Fakultät Optik und Mechatronik
Studiengang Augenoptik / Augenoptik - Hörakustik
Anton-Huber-Str. 23
73430 Aalen

Internes Aktenzeichen:	F-2018-028
Titel:	Messung von Vigilanz und Qualität während statischer automatisierter Perimetire (SAP) unter Zuhilfenahme der Methode der konstanten Stimuli (MoCS) und einer erhöhten Anzahl an Fangfragen
Antrag vom:	28.03.2018

Sehr geehrter Herr Prof. Schiefer,

besten Dank für Ihre E-Mail vom 04.05.2018 samt u. g. Unterlagen in Antwort auf unser Schreiben vom 30.04.2018.

Von Seiten der Ethik-Kommission bestehen nunmehr keine Bedenken.

Allgemeine Hinweise:

- Wir möchten Sie außerdem bitten, für eine raschere Bearbeitung bei zukünftigen Einreichungen jede einzelne Änderung im Text deutlich zu markieren (gestrichener Text wird durchgestrichen, ergänzter Text wird unterstrichen).
- Sämtliche Dokumente sind mit Versionsnummer und Versionsdatum zu versehen, um geänderte Dokumente voneinander unterscheiden zu können. Der Prüfplan ist zu unterschreiben (samt Datum, zu welchem unterschrieben wurde); Gleiches gilt für Amendments.
- Wir möchten darauf hinweisen, dass die Stellungnahme der Ethik-Kommission und die studienrelevante Korrespondenz an alle teilnehmenden Ärzte weiterzuleiten ist.
- Wir bitten um Mitteilung der teilnehmenden Ärzte im Zuständigkeitsbereich der Landesärztekammer Baden-Württemberg, sobald diese bekannt sind bzw. sofern im Verlauf weitere Ärzte hinzukommen.
- Bitte teilen Sie uns das Ende der Studie mit und senden Sie uns eine Synopsis des Abschlussberichts.
- Datenschutzrechtliche Aspekte von Forschungsvorhaben werden durch die Ethikkommission grundsätzlich nur kursorisch geprüft. Dieses Votum ersetzt mithin nicht die Konsultation des zuständigen Datenschutzbeauftragten.
- Unabhängig vom Beratungsergebnis macht die Ethik-Kommission darauf aufmerksam, dass die ethische und rechtliche Verantwortung für die Durchführung einer Studie beim Studienleiter und bei allen teilnehmenden Ärzten liegt.

LANDESÄRZTEKAMMER BADEN-WÜRTTEMBERG
KÖRPERSCHAFT DES ÖFFENTLICHEN RECHTS

ETHIK-KOMMISSION

- Die Ethik-Kommission der Landesärztekammer Baden-Württemberg setzt sich zusammen und arbeitet gemäß den nationalen gesetzlichen Bestimmungen und der ICH-GCP-Leitlinie. Den Beratungen der Ethik-Kommission der Landesärztekammer Baden-Württemberg liegt die Deklaration des Weltärztebundes von Helsinki zugrunde.

Mit freundlichen Grüßen

Dr. med. G. Hook
Stellvertretender Vorsitzender der Ethik-Kommission

Eingereichte Unterlagen:
Mit Schreiben vom 04.05.2018
- Studienplan Version 7 vom 04.05.2018
- Probandeninformation Version 2 vom 04.05.2018
- Einwilligungserklärung Version 2 vom 04.05.2018

Mit Schreiben vom 28.03.2018
- Antragsformular vom 28.03.2018
- Probandenversicherung vom 28.03.2018
- Einwilligungserklärung zum Datenschutz vom 07.09.2017
- Einwilligungserklärung zur Durchführung der Untersuchungen vom 21.03.2018
- Fragebogen zur Tagesschläfrigkeit undatiert
- Studienplan vom 28.03.2018
- Dokumentationsbogen vom 07.09.2017
- Anamnesebogen vom 08.09.2017
- Untersuchungsprotokoll vom 08.09.2017
- Einschluss- und Ausschlusskriterien vom 08.09.2017
- Probandenaufklärung vom 21.03.2018
- Teilnehmende Ärzte vom 07.09.2017
- CV Dr. Ulrich Schiefer vom 28.03.2018

Hinweis zur Datenschutzgrundverordnung:

Da das Vorhaben voraussichtlich über den 25.05.2018 hinaus dauern wird, wird die Datenschutzgrundverordnung der EU (DSGVO) auf das Projekt anzuwenden sein. In Bezug auf die datenschutzrechtliche Information und Einwilligungserklärung sollten daher bereits jetzt zusätzlich zu den bislang üblicherweise dargestellten Datenschutzaspekten insbesondere folgende Punkte beachtet werden:

a. Die in dem Projekt für die Datenverarbeitung verantwortliche Person ist zu benennen. Auch wenn diese Person gleichzeitig die Projektleitung übernehmen sollte, ist sie ggf. zusätzlich als für die Datenverarbeitung verantwortliche Person ausdrücklich zu nennen.
b. Der Name und die Kontaktdaten der zuständigen Datenschutzbeauftragten (lokal und Sponsor/Studienleitung) sind anzugeben.
c. Auf das Bestehen eines Beschwerderechts bei einer Datenschutz-Aufsichtsbehörde (Landesdatenschutzbeauftragte oder Bundesdatenschutzbeauftragte des Prüfzentrums, Landesdatenschutzbeauftragte des Sponsors/der Studienleitung) ist hinzuweisen. Die

zuständigen Datenschutz-Aufsichtsbehörden sind zu nennen. Die Information sollte für jedes Prüf-/Studienzentrum angepasst sein.

d. Die Betroffenen sind auf ihr Recht hinzuweisen, Auskunft (einschließlich unentgeltlicher Überlassung einer Kopie) über die sie betreffenden personenbezogenen Daten zu erhalten sowie ggf. deren Berichtigung oder Löschung zu verlangen.

Details zu Ihren Informationspflichten gegenüber den Studienteilnehmern entnehmen Sie bitte insbesondere den Artikeln 13 ff. DSGVO. Die Ethik-Kommission prüft die Angaben zu den zuständigen Datenschutzbeauftragten und Aufsichtsbehörden nicht auf Richtigkeit. Für die Angaben zu den lokalen Datenschutzbeauftragten und Aufsichtsbehörden reicht gegenüber der Ethik-Kommission die Angabe eines Platzhalters.

C Information material and forms

All information material for test subjects and case report forms used during the present work are attached as follows:

- Information material
- Consent declaration form for the participation in the study and for data protection
- Medical history form
- Case report form (CRF)
- In- and exclusion criteria list
- Documentation form for the main examination

Hochschule Aalen

Studien-ID: ☐☐☐ Probanden-ID: ☐☐☐
Geschlecht: ☐m ☐w Alter: _____
Untersuchungsdatum: ☐☐.☐☐.☐☐☐☐
Untersucher:__

Messung von Vigilanz und Qualität während statischer automatisierter Perimetrie (SAP) unter Zuhilfenahme der Methode der konstanten Stimuli (MoCS) und einer erhöhten Anzahl an Fangfragen

Probandenaufklärung

Sehr geehrte Probandin, sehr geehrter Proband,

Die Studie **„Messung von Vigilanz und Qualität während statischer automatisierter Perimetrie (SAP) unter Zuhilfenahme der Methode der konstanten Stimuli (MoCS) und einer erhöhten Anzahl an Fangfragen“** wird durchgeführt, um feststellen zu können, zu welchem Zeitpunkt eine Untersuchung des Gesichtsfeldes (Perimetrie) aufgrund von Müdigkeit des Patienten beendet werden sollte.

Sind Sie interessiert? Ich freue mich über Ihre Teilnahme.
Die Teilnahme an der Studie ist freiwillig. Ihnen entstehen durch eine Nichtteilnahme keine Nachteile. Sie haben das Recht, auch nach erklärter Einwilligung Ihre Einwilligung zu widerrufen und aus der Studie auszuscheiden.

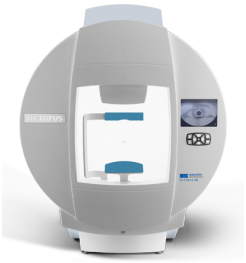
Ihre Daten werden in pseudonymisierter Form erhoben, verarbeitet und für die Dauer von 10 Jahren gespeichert. Zugriff auf Ihre Daten haben lediglich Angehörige des Kompetenzzentrums „Vision Research“ (Prof. Dr. med. Ulrich Schiefer, Dr. Michael Wörner, Judith Ungewiß) an der Hochschule Aalen. Zum Zweck einer Veröffentlichung werden die Daten lediglich in pseudonymisierter Form verwendet.

Für diese Studie wurde eine Wegeunfallversicherung bei der VMD Versicherungsdienst GmbH, Klingenbergstr. 4, 32758 Detmold, abgeschlossen.

Die Versicherungssumme beläuft sich auf folgende Leistungen:

- Ersatzleistung bei Invalidität: 100.000,00 €
- Ersatzleistung bei Tod: 50.000,00 €
- Bergungskosten: 15.000,00 €
- Kosmetische Operationen: 5.000,00 €

Überblick



Die Gesichtsfelduntersuchung wird an einem sogenannten Perimeter (siehe Abb. 1) durchgeführt. Während der Untersuchung wird mit einer integrierten Kamera die Pupille aufgezeichnet. Zudem wird die Herzrate (HR) mittels Brustgurt (siehe Abb. 2) erhoben.

Abb. 1: Perimeter

Abb. 2: Brustgurt zur Registrierung der Herzrate

Hintergrund

Das Gesichtsfeld ist der Bereich, den man sieht, ohne Augen und Kopf zu bewegen. Bei einem gesunden Menschen hat es eine Ausdehnung von etwa 200 Grad. Bei der Messung des Gesichtsfeldes werden zum einen die Außengrenzen bestimmt, zum Anderen wird untersucht, ob innerhalb des Gesichtsfeldes Ausfälle vorhanden sind. Dies ist notwendig, um bestimmte Erkrankungen (z. B. Grüner Star) diagnostizieren und deren Fortschreiten feststellen zu können.

Zur Untersuchung des Gesichtsfeldes dient die Perimetrie. Dazu werden dem Patienten mithilfe des Perimeters (siehe Abb. 1) Lichtreize verschiedener Größe und Helligkeit, verteilt über das Gesichtsfeld,

dargeboten. Sobald ein Lichtreiz gesehen wird, gibt der Patient dies mittels Druck auf einem Taster an.

Um einen verlässlichen Gesichtsfeld-Befund zu erhalten, muss der Patient wach und aufmerksam sein. Die Gesichtsfelduntersuchung ist aber sehr ermüdend, weshalb untersucht werden muss, wann die Untersuchung überhaupt durchgeführt werden kann. Dazu werden sogenannte "Fangfragen", das sind Lichtpunkte, die so hell sind, dass sie gesehen werden müssen oder so dunkel sind, dass sie nicht gesehen werden können, eingestreut. Werden die hellsten Punkte nicht gesehen oder die dunkelsten Punkte als "gesehen" angegeben, so wird deutlich, dass der Proband unkonzentriert ist. Diese Fangfragen können allerdings nur sehr selten eingestreut werden, da sie ansonsten die Dauer der Untersuchung zu stark verlängern würden. Daher kann die Frage, wann die Untersuchung beendet werden sollte, mithilfe der Fangfragen bislang nur sehr ungenau beantwortet werden.

Daher wird in dieser Studie testweise der Anteil an Fangfragen auf 50% erhöht. Zudem wird während der Untersuchung die Herzrate abgeleitet, um die Übereinstimmung des Müdigkeitslevels und der Antworten auf die Fangfragen überwachen zu können. Die Pupille wird während der Messung ebenfalls gefilmt. Aus diesen Videobildern kann ermittelt werden, wann die Pupille anfängt, sich regelmäßig zu weiten und zusammenzuziehen, ohne dass Änderungen des einfallenden Lichts vorhanden sind: Dies ist ebenfalls charakteristisch für den Eintritt von Müdigkeit.

Ablauf der Studie

Allgemein

Bitte versuchen Sie während der gesamten Gesichtsfelduntersuchung ruhig auf dem Stuhl zu sitzen und vermeiden Sie starke Kopfbewegung, so dass Sie immer mit der Stirn an der Stirnstütze aufliegen.

Voruntersuchungen

Vor den Haupttests werden folgende Voruntersuchungen von Prof. Dr. med. Ulrich Schiefer durchgeführt:

- Spaltlampenuntersuchung des vorderen Augenabschnittes
  Hierbei untersucht der zuständige Augenarzt Hornhaut, Bindehaut, Tränenfilm und Lidränder sowie deren Beschaffenheit und das Vorliegen etwaiger Entzündungen oder Reizungen. Die Augenlinse wird auf Trübungen hin überprüft.
- Spiegeln des hinteren Augenabschnittes

  Der Augenarzt betrachtet mittels Ophthalmoskop und Augenspiegel die Netzhaut des Probanden und beurteilt deren Zustand. Dazu werden Kriterien wie beispielsweise die Beschaffenheit der Blutgefäße oder der Papille herangezogen.
- Augenbeweglichkeitsuntersuchung

  Hier wird überprüft, ob der Proband gleichmäßig in alle Richtungen blicken kann. Dazu fixiert der Proband ein vom Untersucher dargebotenes Objekt, welches in acht Richtungen (oben, oben rechts, rechts, unten rechts, unten, unten links, links, oben links) bewegt wird. Mit dieser Untersuchung können etwaige Lähmungen und Ausfälle der Augenmuskeln diagnostiziert werden.
- Untersuchung der Augenstellung

  Der Augenarzt deckt mit einer Abdeckscheibe (Coverscheibe) wechselseitig ein Auge auf bzw. ab. So kann er erkennen, wie sich die Augen in Ruhestellung, also sobald sie kein Objekt mehr fixieren und während der Fixation eines Objektes verhalten. Anhand dieser Erkenntnisse kann der Untersucher feststellen, ob eine Fehlstellung der Augen vorhanden ist.

Frau Judith Ungewiß, M.Sc., führt folgende Messungen durch:

- Bestimmung der Sehschärfe

  Zur Bestimmung der Sehschärfe werden dem Probanden für jedes einzelne Auge auf einem Monitor Zahlen, die als Sehzeichen dienen, in Abstufungen immer kleiner werdend dargeboten. Diese werden vom Probanden laut vorgelesen, bis der Untersucher die Messung abbricht und die Sehschärfe ermittelt wurde.

- Test des räumlichen Sehens

  Der Test erfolgt in einer Prüfentfernung von 40cm. Der Studienteilnehmer wird gebeten, auf einer Prüfkarte erkennbare Objekte zu benennen und mitzuteilen. Hierüber erhält der Untersucher Aufschluss über das Vorhandensein und die Qualität des räumlichen Sehens des Studienteilnehmers.
- Messung des Augeninnendrucks (mit berührungslosem Druckmessgerät)

  Der Studienteilnehmer wird vor dem Messgerät positioniert und gebeten, auf einen Fixierpunkt zu schauen. Löst der Untersucher die Messung aus, so wird ein sanfter Luftstoß in Richtung des Auges des Probanden ausgegeben. Dieser Vorgang erfolgt drei Mal pro Auge. Anschließend wird der Wert des Augeninnendrucks auf dem Display des Geräts angelesen und notiert.
- Bestimmung des Führungsauges (sofern vorhanden)

  Zur Bestimmung des Führungsauges fixiert der Proband ein in der Ferne gelegenes Objekt mit beiden Augen. Nun deckt er das Objekt mit seinem am ausgestreckten Arm vorgehaltenen Daumen ab. Durch den Untersucher wird nun abwechselnd rechtes und linkes Auge des Probanden abgedeckt. Dabei beobachtet der Proband seine Seheindrücke und beschreibt diese, wodurch das Führungsauge ermittelt werden kann: Wird das geführte Auge abgedeckt, so ist das Objekt durch den Daumen verdeckt, wird das Führungsauge abgedeckt, so ist das Objekt nun nicht mehr durch den Daumen verdeckt.

Oben genannte Voruntersuchungen werden vorgenommen, um eine gute Sichtbarkeit der Lichtpunkte zu gewährleisten und Augenerkrankungen auszuschließen.

Hauptuntersuchung

Sie füllen einen Fragebogen zur Tagesschläfrigkeit („Epworth Sleepiness Scale“) aus. Dies nimmt in etwa 5-10 Minuten in Anspruch.

Dann legen Sie den Brustgurt zur Ableitung der Herzrate an.

Im Anschluss findet die Gesichtsfelduntersuchung statt. Dazu werden Sie am Perimeter positioniert. Im Perimeter befindet sich zentral eine Fixationsmarke (siehe Abb. 3), die Sie bitte während der gesamten Untersuchung ansehen. An vier verschiedenen Orten erscheinen nun nacheinander unterschiedlich helle Lichtpunkte (bitte sehen Sie diese nicht an, sondern bleiben Sie bei der Fixationsmarke!). Sobald Sie einen Lichtpunkt sehen, drücken Sie bitte den Taster.

Selbstverständlich dürfen Sie während der Untersuchung blinzeln. Sinnvollerweise tun Sie dies immer, nachdem Sie gerade einen Lichtpunkt gesehen haben. Da zwischen zwei Lichtpunkten immer eine ausreichend lange Pause ist, werden Sie so keinen Lichtpunkt verpassen.

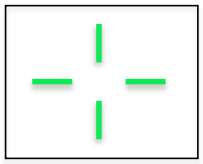


Abb. 3: Fixationsmarke

Die Untersuchung dauert ca. 45 Minuten. Während dieser Zeit sind Sie niemals alleine in Untersuchungsraum. Die anwesende Studiendurchführende kann Sie auf Ihren Wunsch hin jederzeit über den Fortschritt des Experiments in Kenntnis setzen.

Vermutlich werden Sie während des Experiments müde werden – das ist in Ordnung und so gewollt. Bitte setzen Sie das Experiment trotzdem fort.

Lediglich bei vollständigem Einschlafen werden Sie von der Studiendurchführenden geweckt werden.

Nach Abschluss des Experiments legen Sie den Brustgurt ab.

Nebenwirkungen

Es sind keine Nebenwirkungen bekannt, die durch die durchgeführten Tests entstehen könnten.

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Untersuchungsdatum: ☐☐.☐☐.☐☐☐☐
Untersucher:__

Risiken

Durch die Spaltlampenuntersuchung kann es zu einem kurzzeitigen Blendgefühl kommen, ansonsten sind für die Untersuchungen keine Risiken bekannt.

Zeitaufwand

Der Zeitaufwand beläuft sich auf zwei Termine zu jeweils etwa einer Stunde. Der erste Termin ist vorgesehen für die Voruntersuchung bei Prof. Dr. med. Ulrich Schiefer, die Voruntersuchungen durch Frau Judith Ungewiß und die Erhebung der medizinischen Vorgeschichte. Am zweiten Termin erfolgen die Befragung mit dem Fragebogen „Epworth Sleepiness scale“ und die Gesichtsfelduntersuchung mit Ableitung der Herzrate.

Probandenaufklärung_Diss._JU_V2CLEAN_2018-05-04.doc

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Geschlecht: ☐m ☐w Alter: _____
Untersuchungsdatum: ☐☐.☐☐.☐☐☐☐
Untersucher:__

Das Aufklärungsgespräch hat geführt:

☐ **Prof. Dr. med Ulrich Schiefer**
ulrich.schiefer@hs-aalen.de

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Fax: +49- 7071 29-5061
www.sehbahn.de
http://www.uni-tuebingen.de

Erklärung der aufklärenden Person

Hiermit erkläre ich, den/die o.g. Teilnehmer/in am _____ über Wesen, Bedeutung, Tragweite und Risiken der o.g. Studie mündlich und schriftlich aufgeklärt und ihm/ihr eine Ausfertigung dieser Probandenaufklärung sowie der Einwilligungserklärung übergeben zu haben.

_____ _____
Ort, Datum Unterschrift der aufklärenden Person

_____ _____
Ort, Datum Unterschrift des/der Teilnehmer/in

Einwilligungserklärung_Diss._JU_V2_2018_05_04.doc
Studien-ID: ☐☐☐ Probanden-ID: ☐☐☐
Geschlecht: ☐m ☐w Alter: _____
Untersuchungsdatum: ☐☐.☐☐.☐☐☐☐
Untersucher:_____

Messung von Vigilanz und Qualität während statischer automatisierter Perimetrie (SAP) unter Zuhilfenahme der Methode der konstanten Stimuli (MoCS) und einer erhöhten Anzahl an Fangfragen

Einwilligungserklärung zur Durchführung der Untersuchungen

Hiermit willige ich ein,

dass zum Zwecke der Studie **"Messung von Vigilanz und Qualität während statischer automatisierter Perimetrie (SAP) unter Zuhilfenahme der Methode der konstanten Stimuli (MoCS) und einer erhöhten Anzahl an Fangfragen"** folgende Messungen / Untersuchungen durchgeführt werden dürfen:

1. Bestimmung der Sehschärfe (mit und ohne Brille)
2. Bestimmung der Brillenglasstärke (Refraktion)
3. Bestimmung des Führungsauges
4. Mikroskopische Untersuchung des vorderen Augenabschnitts
5. Untersuchung der Netzhaut mit dem Augenspiegel
6. Messung des Augeninnendrucks (mit berührungslosem Druckmessgerät)
7. Messung zur Augenstellung
8. Messung zur Augenbeweglichkeit
9. Perimetrische Untersuchung
10. Ableitung der Herzrate

Einwilligungserklärung zum Datenschutz

Sehr geehrte Probandin, sehr geehrter Proband,

Für das Erstellen einer wissenschaftlichen Studie werden persönliche Daten und medizinische Befunde über Sie erhoben. Die Weitergabe, Speicherung und Auswertung ihrer persönlichen Daten erfolgt nach gesetzlichen Bestimmungen. Für die Teilnahme an oben genannter Studie werden folgende Einwilligungen vorausgesetzt:

Hiermit willige ich ein,
dass zum Zweck der Studie: „**Messung von Vigilanz und Qualität während statischer automatisierter Perimetrie (SAP) unter Zuhilfenahme der Methode der konstanten Stimuli (MoCS) und einer erhöhten Anzahl an Fangfragen“** die folgenden personenbezogenen Daten von mir erhoben und mit einem Verschlüsselungscode versehen gespeichert werden:

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Studien-ID: ☐☐☐ Probanden-ID: ☐☐☐
Geschlecht: ☐m ☐w Alter: _____
Untersuchungsdatum: ☐☐.☐☐.☐☐☐☐
Untersucher:_____

1. Geschlecht
2. Geburtsdatum
3. Sehschärfe
4. Brillenkorrektion
5. Augenbezogene Befunde
6. Allgemeinbefunde

Diese Daten dürfen nur mit einem Verschlüsselungscode versehen auf elektronischen Datenträgern gespeichert und verarbeitet werden. Ebenfalls bin ich damit einverstanden, dass meine Daten, in anonymer Form und ohne Rückschlüsse auf meine Person, veröffentlicht werden.

Die Teilnahme an der Studie ist freiwillig. Ihnen entstehen durch eine Nichtteilnahme keine Nachteile. Sie haben das Recht, auch nach erklärter Einwilligung Ihre Einwilligung zu widerrufen und aus der Studie auszuscheiden.

Ihre Daten werden in pseudonymisierter Form erhoben, verarbeitet und für die Dauer von 10 Jahren gespeichert. Zugriff auf Ihre Daten und die Verantwortung dafür haben lediglich Angehörige des Kompetenzzentrums „Vision Research“ (Prof. Dr. med. Ulrich Schiefer, Dr. Michael Wörner, Judith Ungewiß) an der Hochschule Aalen. Die verantwortliche Datenschutzbeauftragte der Hochschule Aalen ist Frau Britta Seitz, erreichbar unter datenschutz@hs-aalen.de. Auf das Bestehen eines Beschwerderechts bei der Datenschutz-Aufsichtsbehörde (Landesbeauftragter für Datenschutz und Informationsfreiheit Jörg Klingbeil, Königstrasse 10a, 70173 Stuttgart) wird hiermit hingewiesen. Sie haben das Recht, Auskunft (einschließlich unentgeltlicher Überlassung einer Kopie) über die Sie betreffenden personenbezogenen Daten zu erhalten sowie ggf. deren Berichtigung oder Löschung zu verlangen. Zum Zweck einer Veröffentlichung werden die Daten lediglich in pseudonymisierter Form verwendet.

Name: _____

Geburtsdatum: _____

Ort, Datum Unterschrift

Die Arbeitsgruppe „Vision Research“ sichert Ihnen den ordnungsgemäßen Umgang gemäß Datenschutz-Grundverordnung (DSGVO) mit Ihren zur Verfügung gestellten Daten zu. Zudem wird eine Weitergabe an externe Dritte ausgeschlossen.

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Anamnesebogen_Diss._JU_2017-09-08.docx
Studien-ID: ☐☐☐ Probanden-ID: ☐☐☐
Geschlecht: ☐m ☐w Alter: _____
Untersuchungsdatum: ☐☐.☐☐.☐☐☐☐
Untersucher:_____

Anamnesebogen

Augenanamnese	Ja	Nein	Falls ja, ab welchem Lebensjahr bzw. wann wurde Erstdiagnose gestellt?	Welches Auge ist betroffen? R/L	Anmerkungen
1. Brillenträger?	☐	☐	☐☐. Lj.		
2. Kontaktlinsenträger?	☐	☐	☐☐. Lj		
3. Sehen Sie auf beiden Augen mit Korrektion gleich gut?	☐	☐			
4. Schielen bekannt?	☐	☐	☐☐. Lj	R ☐ L ☐	
5. Sind Sie schwachsichtig? (Amblyopie)?	☐	☐	☐☐. Lj	R ☐ L ☐	
6. Augenbewegungsstörungen bzw. Doppelbilder?	☐	☐			
7. Grauer Star (Katarakt)?	☐	☐	☐☐. Lj	R ☐ L ☐	
8. Grüner Star (Glaukom)?	☐	☐	☐☐. Lj	R ☐ L ☐	
9. Netzhauterkrankungen? (z.B. Netzhautablösung,..)	☐	☐	☐☐. Lj	R ☐ L ☐	
10. Makulaerkrankungen?	☐	☐	☐☐. Lj	R ☐ L ☐	

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Geschlecht: ☐m ☐w Alter: _____
Untersuchungsdatum: ☐☐.☐☐.☐☐☐☐
Untersucher:_____

Augenanamnese	**Ja**	**Nein**	**Falls ja, ab welchem Lebensjahr bzw. wann wurde Erstdiagnose gestellt?**	**Welches Auge ist betroffen? R/L**	**Anmerkungen**
11. Schwere chronische Augenentzündungen?	☐	☐	☐☐. Lj	R ☐ L ☐	
12. Augenverletzungen?	☐	☐	☐☐. Lj	R ☐ L ☐	
13. Augenoperationen?	☐	☐	☐☐. Lj	R ☐ L ☐	
14. Augenmedikamente? (Tropfen/Salben)	☐	☐	☐☐. Lj	R ☐ L ☐	
15. Sind in Ihrer Familie Augenerkrankungen bekannt? (z.B. hohe Fehlsichtigkeiten, Glaukom [Grüner Star], Katarakt [Grauer Star], Netzhautablösung, Farbsehstörungen,….)	☐	☐			

Allgemeinanamnese	**Ja**	**Nein**	**Falls ja, ab welchem Lebensjahr bzw. wann wurde Erstdiagnose gestellt?**	**Anmerkungen**
1. Herz-Kreislauferkrankung?	☐	☐	☐☐. Lj	
2. Andere Organerkrankung? (z.B. Leber, Niere, Magen,..)	☐	☐		
3. Neurologische Erkrankungen? (z.B. Schlaganfall, Epilepsie)	☐	☐	☐☐. Lj	

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Anamnesebogen_Diss._JU_2017-09-08.docx
Studien-ID: ☐☐☐ Probanden-ID: ☐☐☐
Geschlecht: ☐m ☐w Alter: _____
Untersuchungsdatum: ☐☐.☐☐.☐☐☐☐
Untersucher:_____

Allgemeinanamnese	**Ja**	**Nein**	**Falls ja, ab welchem Lebensjahr bzw. wann wurde Erstdiagnose gestellt?**	**Anmerkungen**
4. Stoffwechselerkrankung? (z.B. Blutzucker, Schilddrüse, Fettstoffwechsel,..)	☐	☐	☐☐. Lj	_____ _____ _____
5. Seelische Erkrankungen?	☐	☐	☐☐. Lj	_____ _____
6. Schwangerschaft?	☐	☐		_____ _____
7. Medikamenteneinnahme?	☐	☐	☐☐. Lj	_____ _____
8. Medikamente, die die Reaktionszeit beeinflussen?	☐	☐	☐☐. Lj	_____ _____
9. Andere Erkankungen?	☐	☐	☐☐. Lj	_____ _____
10. Haben Sie Allergien?	☐	☐		_____ _____

Sonstige Anmerkungen:

_____

_____

CRF_Diss._JU_2017-09-08.docx

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Geschlecht: ☐m ☐w Alter: _____
Untersuchungsdatum: ☐☐.☐☐.☐☐☐☐
Untersucher: _____

Untersuchungsprotokoll

Augenstellung und Augenbeweglichkeit

	RA Intakt/Unauffällig	RA Gestört/Auffällig	LA Intakt/Unauffällig	LA Gestört/Auffällig	Bemerkungen
Augenstellung	☐	☐	☐	☐	
Augenbeweglichkeit	☐	☐	☐	☐	

Pupillen (Efferenz und Afferenz)

Pupillen	Ja	Nein	RA auffällig	LA auffällig	
Pupillen rund	☐	☐	☐	☐	
Pupillen zentriert	☐	☐	☐	☐	
In Helligkeit und Dunkelheit isokor?	☐	☐			
--Anisokorie?					☐ R > L ☐ R < L
--Bei Dunkelheit zunehmend?	☐	☐			Dilatationsdefizit
--Bei Helligkeit zunehmend?	☐	☐			Kontraktionsdefizit

RAPD?	☐	☐	☐ __ , __ logE	☐ __ , __ logE	
Sonstige Anmerkungen					

Vorderer Augenabschnitt Spaltlampe (WQ900, Haag Streit, Köniz)

	RA Intakt/Unauffällig	RA Gestört/Auffällig	LA Intakt/Unauffällig	LA Gestört/Auffällig	Bemerkungen
Bindehaut					
Hornhaut	☐	☐	☐	☐	
Vorderkammer	☐	☐	☐	☐	
Vorderkammertiefe temporale Peripherie (Grad 1-., nach W. van Herick)	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4		☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4		
Irisfarbe					
Iris/Pupille	☐	☐	☐	☐	
Linse	☐	☐	☐	☐	
Glaskörper	☐	☐	☐	☐	
Intraokular reizfrei?	☐	☐	☐	☐	

Augenhintergund BETA 200 S LED Ophthalmoskop, Heine, Herrsching

	RA		LA	
	Intakt/Unauffällig	Gestört / Auffällig	Intakt/Unauffällig	Gestört / Auffällig
Papille randscharf?	☐	☐	☐	☐
Papille vital gefärbt?	☐	☐	☐	☐
Zentrale Exkavation?	☐	☐	☐	☐
CDR:				
ISNT Regel erfüllt?	☐	☐	☐	☐
Papillenrand / Nervenfaserschicht	☐	☐	☐	☐
Makula?	☐	☐	☐	☐
	Ausprägungsgrad		Ausprägungsgrad	
Wallreflex	☐ + ☐ (+) ☐ Ø		☐ + ☐ (+) ☐ Ø	
Foveolarreflex	☐ + ☐ (+) ☐ Ø		☐ + ☐ (+) ☐ Ø	
	Intakt/Unauffällig	Gestört / Auffällig	Intakt/Unauffällig	Gestört / Auffällig
Zentrale Fixation?	☐	☐	☐	☐
Exzentrischer Fixationsort:				
Gefäße?	☐	☐	☐	☐
a : v =				
Peripherie?	☐	☐	☐	☐
Bemerkungen				

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Ein-_Ausschlusskriterien_Diss._JU_2017-09-08.docx
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Geschlecht: ☐m ☐w Alter: _____
Untersuchungsdatum: ☐☐.☐☐.☐☐☐☐
Untersucher:__

Einschluss- und Ausschlusskriterien

Einschlusskriterien:

☐ Mindestalter: 18 Jahre
☐ Vorliegen einer unterzeichneten Einverständniserklärung

Ausschlusskriterien:

Allgemein:

☐ Epilepsie (potentielle Anfalls-Triggerung durch Flickerreize)/psychiatrische Erkrankungen
☐ Medikamente, die Reaktionszeit beeinflussen

Ophthalmologisch:

☐ Amblyopie (Schwachsichtigkeit)
☐ Schielen (auch zeitweilig = intermittierend)
☐ Stereowinkel gemessen mit Lang ≥ 600“ in 40 cm
☐ Augenbewegungsstörungen
☐ Augenzittern (Nystagmus)
☐ operative Augeneingriffe, die weniger als 3 Monate zurückliegen
☐ pupillenverengende Medikamente
☐ schwerwiegende Augenverletzungen
☐ Hinweise auf Sehnerven- oder Sehbahnerkrankungen
☐ Erkrankungen der Netzhautregion des schärfsten Sehens (Makula-Erkrankung)

==========

Erfüllt der Proband alle Kriterien, um an der Studie teilzunehmen?

Ja ☐ Nein ☐

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Untersuchungsdatum: ☐☐.☐☐.☐☐☐☐
Untersucher:_____

Dokumentationsbogen

Bisherige Korrektionswerte

☐Brille ☐Kontaktlinsen

	Sphäre	Zylinder	Achse	$Visus_{cc}$	$Visus_{sc}$
Rechtes Auge					
Linkes Auge					

Bemerkungen: _____

_____

Aktuelle Refraktion

	Sphäre	Zylinder	Achse	Visus		IOP Uhrzeit
Rechtes Auge						
Linkes Auge						

Bemerkungen: _____

_____

Angaben zum untersuchten Auge

Führungsauge (Rosenbach): ☐RA ☐LA ☐nicht eindeutig
untersuchtes Auge: ☐RA ☐LA

Perimetrie ☐mit Nahglas
☐ohne Nahglas
eingesetzes Nahglas zur Perimetrie: sph ☐☐,☐☐ cyl ☐☐,☐☐ A ☐☐☐°

Dokumentationsbogen_Diss._JU_2018-04-10.doc
Studien-ID: ☐☐☐ Probanden-ID: ☐☐☐
Geschlecht: ☐m ☐w Alter: _____
Untersuchungsdatum: ☐☐.☐☐.☐☐☐☐
Untersucher:_____

Besonderheiten während der Messung

Kommunikation mit ProbandIn:

Uhrzeit	Aktion

Sonstige:

_____

_____

_____

_____

_____

_____

_____

_____

D Epworth Sleepiness Scale (ESS)

Questionnaire for the Epworth Sleepiness Scale (ESS) according to (Johns 1991), taken from the Website of the German Sleep Society (Deutsche Gesellschaft für Schlafforschung und Schlafmedizin (DGSM) 2007), in German language (see next page).

Code:_____

Fragebogen zur Tagesschläfrigkeit

(Epworth Sleepiness Scale)

Datum: .....

Die folgende Frage bezieht sich auf Ihr normales Alltagsleben in der letzten Zeit:

Für wie wahrscheinlich halten Sie es, daß Sie in einer der folgenden Situationen einnicken oder einschlafen würden, - sich also nicht nur müde fühlen?

Auch wenn Sie in der letzten Zeit einige dieser Situationen nicht erlebt haben, versuchen Sie sich trotzdem vorzustellen, wie sich diese Situationen auf Sie ausgewirkt hätten.

Benutzen Sie bitte die folgende Skala, um für jede Situation eine möglichst genaue Einschätzung vorzunehmen und kreuzen Sie die entsprechende Zahl an:

0 = würde *niemals* einnicken
1 = *geringe* Wahrscheinlichkeit einzunicken
2 = *mittlere* Wahrscheinlichkeit einzunicken
3 = *hohe* Wahrscheinlichkeit einzunicken

Situation	Wahrscheinlichkeit einzunicken
Im Sitzen lesend	⓪ ① ② ③
Beim Fernsehen	⓪ ① ② ③
Wenn Sie passiv (als Zuhörer) in der Öffentlichkeit sitzen (z.B. im Theater oder bei einem Vortrag)	⓪ ① ② ③
Als Beifahrer im Auto während einer einstündigen Fahrt ohne Pause	⓪ ① ② ③
Wenn Sie sich am Nachmittag hingelegt haben, um auszuruhen	⓪ ① ② ③
Wenn Sie sitzen und sich mit jemand unterhalten	⓪ ① ② ③
Wenn Sie nach dem Mittagessen (ohne Alkohol) ruhig dasitzen	⓪ ① ② ③
Wenn Sie als Fahrer eines Autos verkehrsbedingt einige Minuten halten müssen	⓪ ① ② ③
Bitte nicht ausfüllen Summe	

E Publication of *pilot study 1*: abstract and poster

The following pages show the publication of *pilot study 1* as abstract and poster (Ungewiss et al. 2016).

Monitoring quality and vigilance during automated static perimetry
A proof-of-concept-study using video-pupillography, heart rate recording, and an increased number of catch trials

Judith Ungewiss[1], Ulrich Schiefer[1,2,3], Thomas Kübler[1,4]
[1] Competence Center Vision Research, University of Applied Sciences, Aalen, Germany
[2] Department for Ophthalmology, University of Tuebingen, Germany
[3] Research Institute for Ophthalmology, University of Tuebingen, Germany
[4] Computer Engineering Department, University of Tuebingen, Germany

Purpose
To monitor quality and vigilance by video-pupillography and heart rate recording during automated static perimetry.

Materials and methods
Method of constant stimuli was used to assess differential luminance sensitivity with the OCTOPUS 900 perimeter (Haag-Streit AG, Koeniz, Switzerland) using OPI (Open Perimetry Interface): Stimulus intensity was varied in nine steps between 0.04 and 160 cd/m^2 with a background luminance of 10 cd/m^2. Altogether, 1,560 stimuli were presented in approximately 48 minutes. An increased rate of false-positive and false-negative catch trials was implemented (40% each). Pupil data were extracted from the built-in camera. Heart rate was recorded with the H7 heart rate monitor and chest strap (Polar Elektro GmbH, Buettelborn, Germany).
The quality of visual field testing was defined by the response behavior to catch trials. An "agreement index" was determined, relating periods with increased variabilities of (i) pupil diameter, (ii) heart rate, and (iii) reaction time to periods with increased number of false responses to catch trials. The agreement index was calculated as the ratio between *event overlap* and *total event occurrence* periods.

Results
Sufficient data were obtained from five subjects (3 male, 2 female; age range from 25 to 58 years). Agreement indices are:

Tab. 1: Agreement indices

	Subject 1	**Subject 2**	**Subject 3**	**Subject 4**	**Subject 5**
Period with increased no. of false responses to catch trials	17.6 min.	2.9 min.	2.0 min.	27.7 min.	0 min.
Pupil diameter variability	0.35	0.33	0.10	0.70	0
Heart rate variability	0	0	0	0.03	0
Reaction time variability	0.32	0.41	0	0.08	0

Pupil diameter variability showed the highest agreement indices, whereas reaction time and heart rate variabilities showed low or no agreement.

Conclusions
In this study, pupil diameter variability was closer related to response behavior to catch trials than heart rate and reaction time variabilities. Pupil diameter variability can be considered as an indicator for decreasing quality of subjects' responses, thereby allowing a termination criterion of a perimetric session before its considerable contamination due to vigilance-related issues.

IPS 2016 – Udine

Monitoring quality and vigilance during automated static perimetry

A proof-of-concept study using video-pupillography, heart rate recording, and an increased number of catch trials

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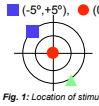
Purpose

To monitor quality and vigilance by video-pupillography and heart rate recording during automated static perimetry.

Methods

Location of stimuli

(-5°,+5°), (0°,0°), (3°,-6°)



Stimulus size

size III = 25.7'

Fig. 1: Location of stimuli (RE)

MoCS (Method of constant stimuli)

- 1,560 stimuli (approx. 48 min.)
- nine luminance levels between 0.04 and 160 cd/m² (i.e. -39 dB − -3 dB)
- 8-fold repetition of each stimulus intensity in randomized order at three locations (see Fig. 1)

Catch trials

false-pos. & false-neg.: 40 % each

Fig. 2: OCTOPUS 900 perimeter

OCTOPUS 900 Perimeter

HAAG-STREIT Inc., Köniz, Switzerland

Background luminance: 10 cd/m²

Fig. 3: H7 heart rate monitor, chest strap and app

Heart rate monitoring

H7 heart rate monitor, chest strap and app, Polar Elektro GmbH, Buettelborn, Germany

Results

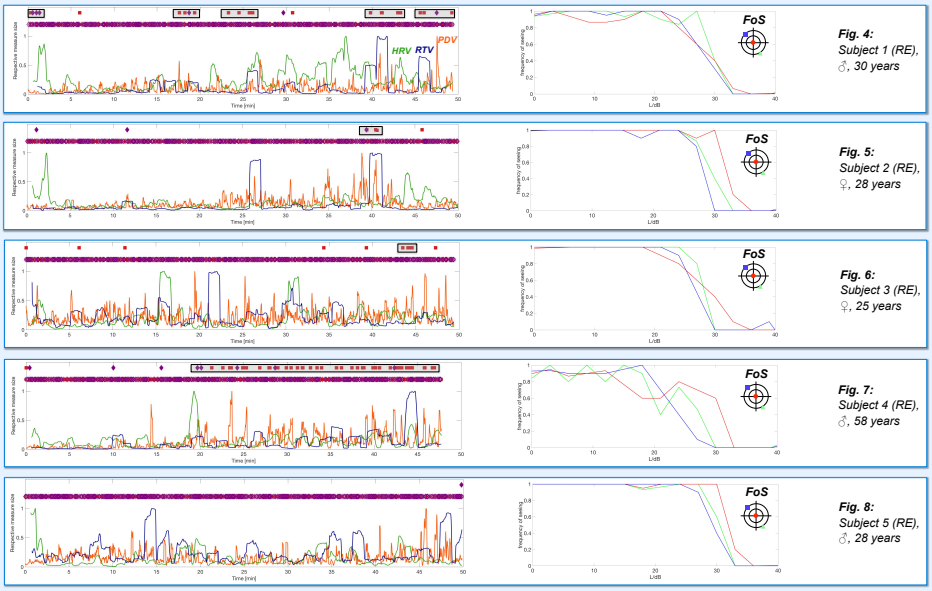


Fig. 4: *Subject 1 (RE), ♂, 30 years*

Fig. 5: *Subject 2 (RE), ♀, 28 years*

Fig. 6: *Subject 3 (RE), ♀, 25 years*

Fig. 7: *Subject 4 (RE), ♂, 58 years*

Fig. 8: *Subject 5 (RE), ♂, 28 years*

Figs. 4 – 8:

left: *pupil diameters variabilities (PDV, orange), heart rate variabilities (HRV, green) and reaction time variabilities (RTV, dark blue) over time, normed to [0;1] by their maximum;*
false neg. catch trials, correct responses;
false neg. responses;
false pos. catch trials, correct responses;
false pos. responses;
periods with increased no. of false responses to catch trials (at least 3 false responses within 2 min.) are highlighted in grey

right: *frequency of seeing curves (the related stimulus locations are color labeled as in **Fig. 1**)*

Agreement of measured parameters and increased number of false responses to catch trials

Tab. 1: *Periods with increased no. of false responses to catch trials and agreement indices, calculated as ratio between event overlap (either pupil diameter variability, heart rate variability or reaction time variability and the periods with increased no. of false [i.e. false-pos. OR false-neg.] responses to catch trials) and total event occurence periods (all parameters mentioned below)*

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5
Period with increased no. of false responses to catch trials [min.]	17.6	2.9	2.0	27.7	0.0
Pupil diameter variability	0.35	0.33	0.10	0.70	0.00
Heart rate variability	0.00	0.00	0.00	0.03	0.00
Reaction time variability	0.32	0.41	0.00	0.08	0.00

Conclusions

- Pupil diameter variability is closer related to response behaviour regarding catch trials than to heart rate or to reaction time variabilities.
- Pupil diameter variability can be considered as an indicator for decreasing quality of subjects' responses.
- Perimetric quality can be enhanced by terminating the session before its considerable contamination due to vigilance-related issues.

Subjects

- 5 subjects (RE, each)
- 2 females, 3 males
- age: 25 to 58 years
- sph ametropia: 0.00 to -5.00 dpt
- cyl ametropia: 0.00 to -2.75 dpt
- else, ophthalmologically normal
- informed consent

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Haag-Streit Inc., Servier Inc.

F Individual result documents

All individual result documents are attached.

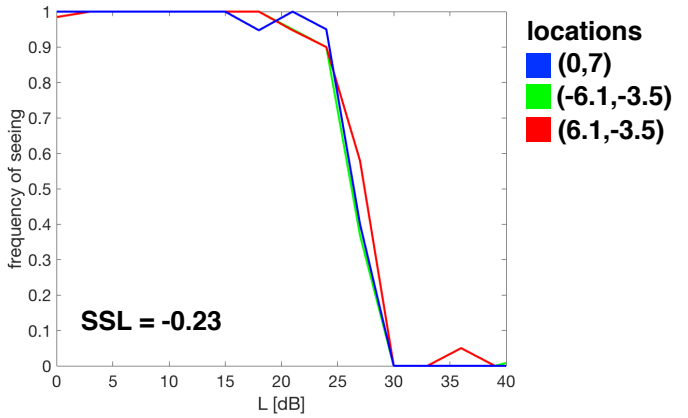
The following abbreviations apply:

BR	blink rate
BRV	blink rate variability
f	female
FOS	frequency of seeing
HR	heart rate
HRV	heart rate variability
HRVHF	heart rate variability (high frequency band)
HRVLF	heart rate variability (low frequency band)
m	male
no.	number
OSAS	obstructive sleep apnea syndrome
PD	pupil diameter
PDV	pupil diameter variability
PF	height of the palpebral fissure
PFV	variability of the palpebral fissure height
RT	response time
RTV	response time variability
SSL	slope steepness

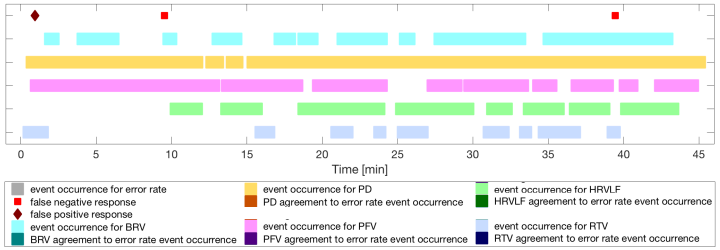
subject ID	**001**
age	**46**
gender	**f**
ESS score	**7**
total no. of errors	**3**

sleep disorders:
none

FOS curve



Agreement plot

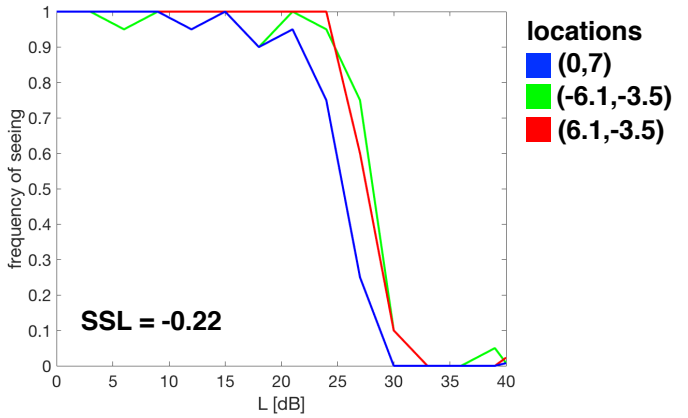


Individual results of false responses to catch trials and all related parameters

subject ID	**002**
age	**43**
gender	**m**
ESS score	**7**
total no. of errors	**6**

sleep disorders:
none

FOS curve



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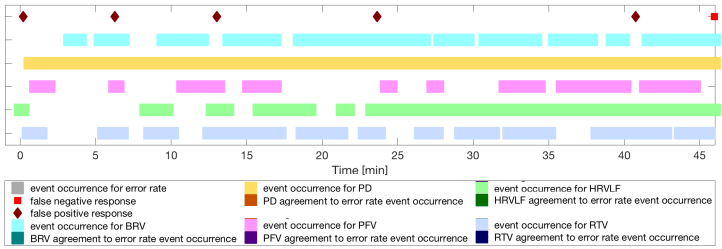
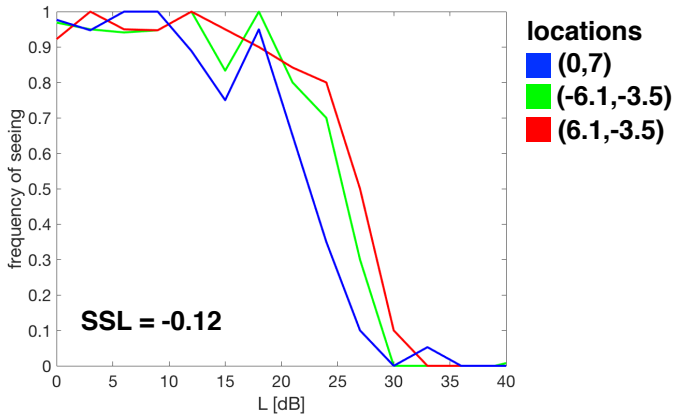


Individual results of false responses to catch trials and all related parameters

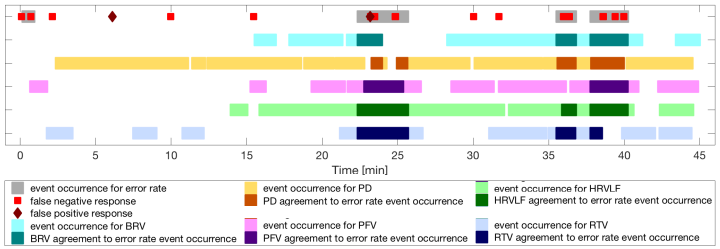
subject ID	**003**
age	**24**
gender	**m**
ESS score	**7**
total no. of errors	**19**

sleep disorders:
none

FOS curve



Agreement plot

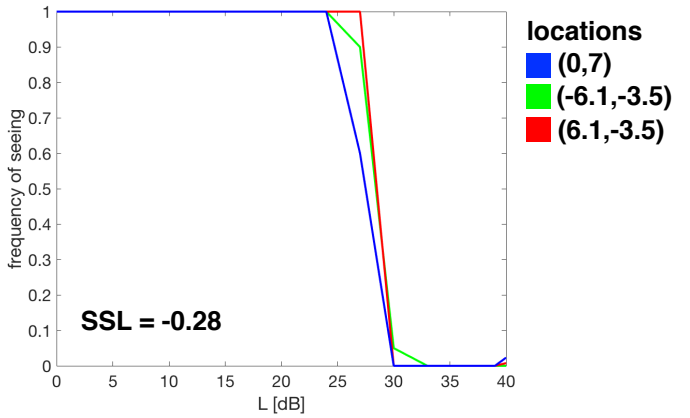


Individual results of false responses to catch trials and all related parameters

subject ID	**006**
age	**45**
gender	**f**
ESS score	**3**
total no. of errors	**4**

sleep disorders:
none

FOS curve



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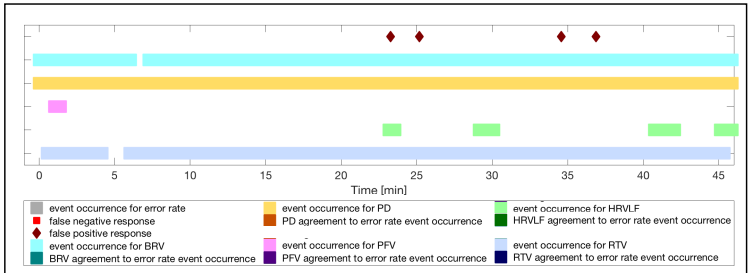
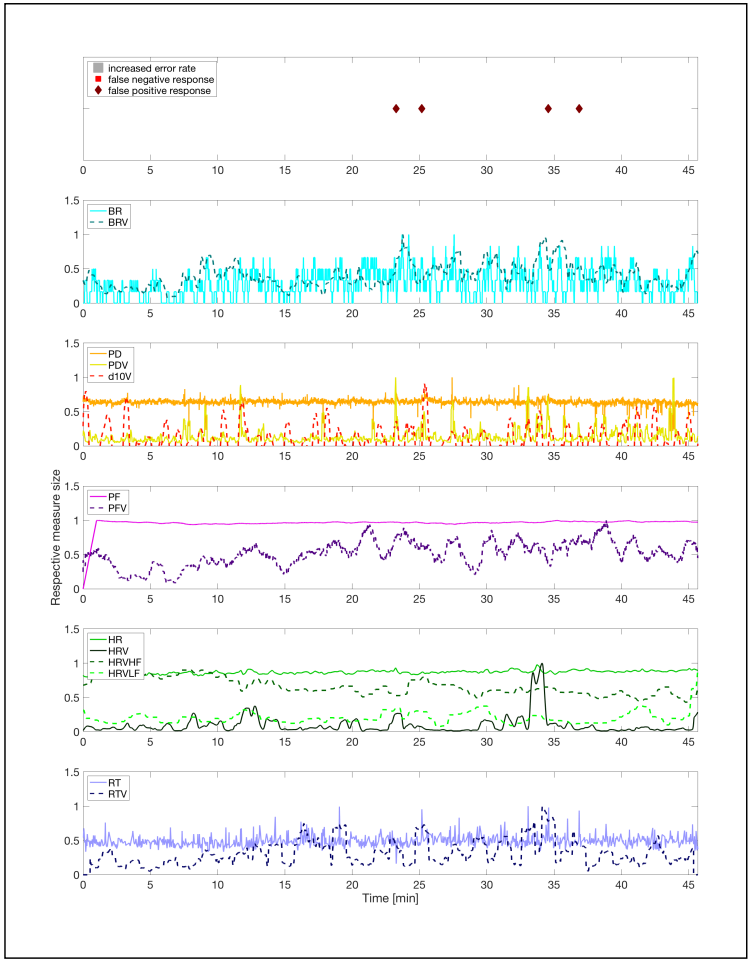


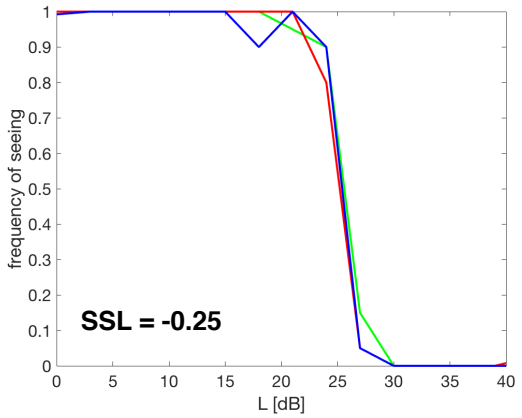
Individual results of false responses to catch trials and all related parameters



subject ID	**013**
age	**43**
gender	**f**
ESS score	**11**
total no. of errors	**2**

sleep disorders:
test subject reported to suffer from short breathing interruptions during the afternoon nap

FOS curve



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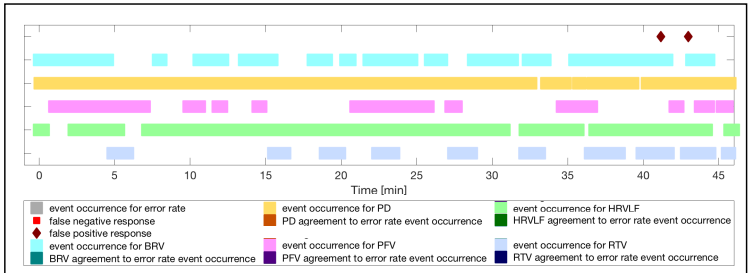
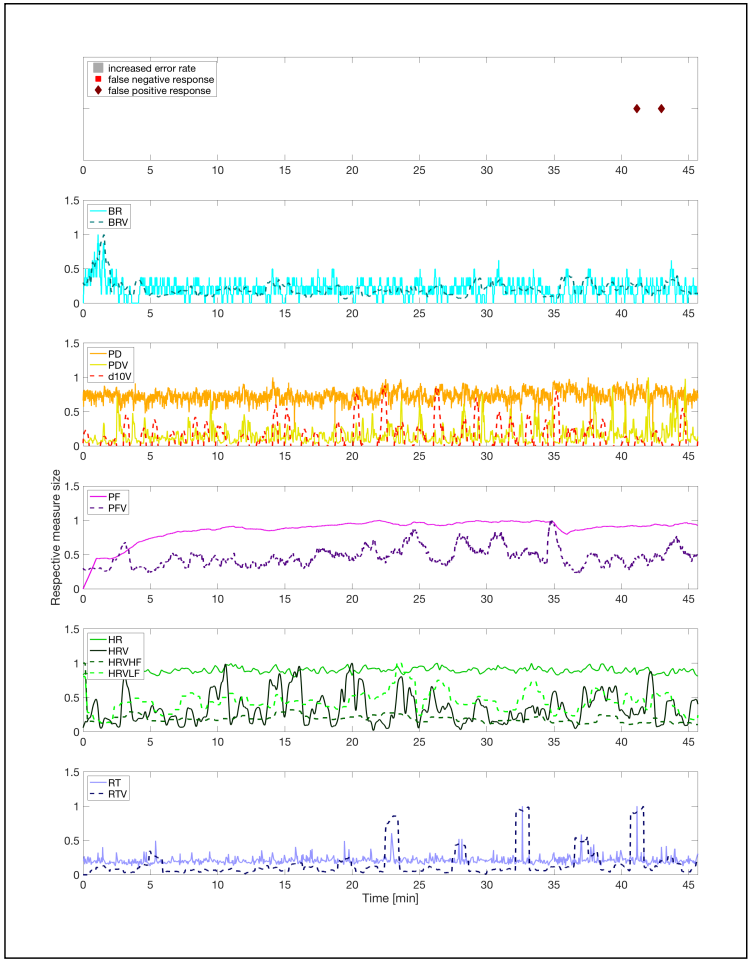


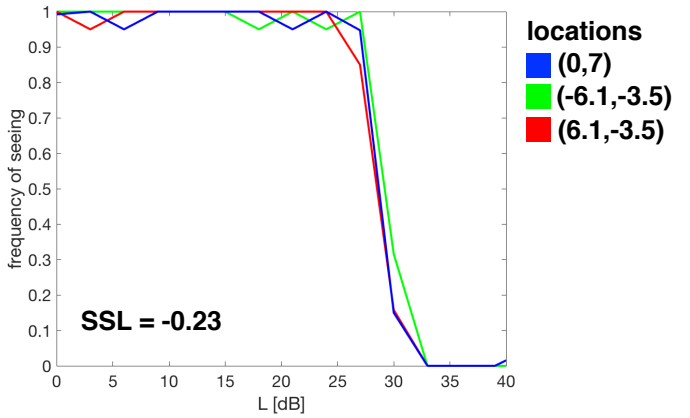
Individual results of false responses to catch trials and all related parameters



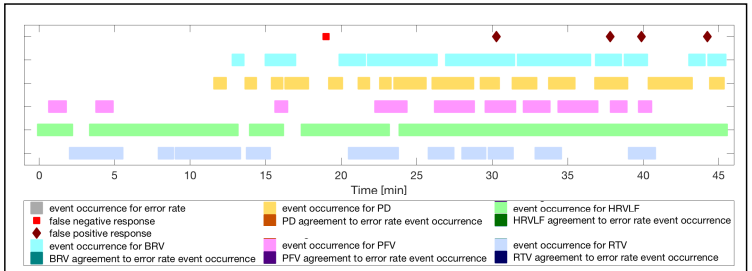
subject ID	**015**
age	**25**
gender	**f**
ESS score	**12**
total no. of errors	**5**

sleep disorders:
none

FOS curve



Agreement plot

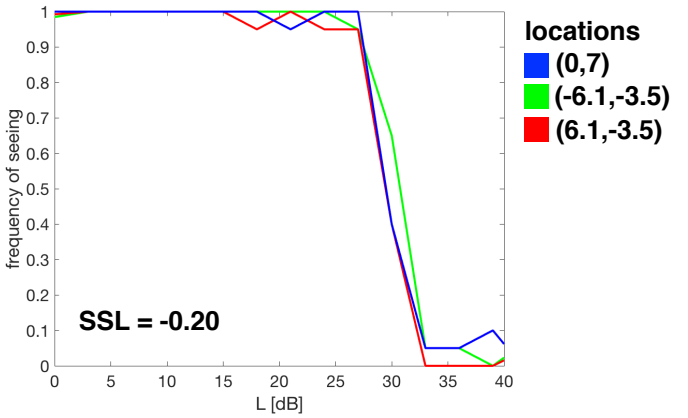


Individual results of false responses to catch trials and all related parameters

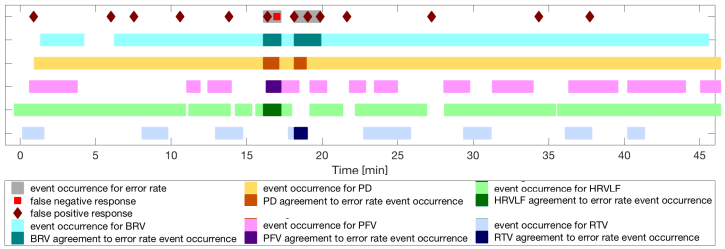
subject ID	**019**
age	**29**
gender	**m**
ESS score	**14**
total no. of errors	**14**

sleep disorders:
none

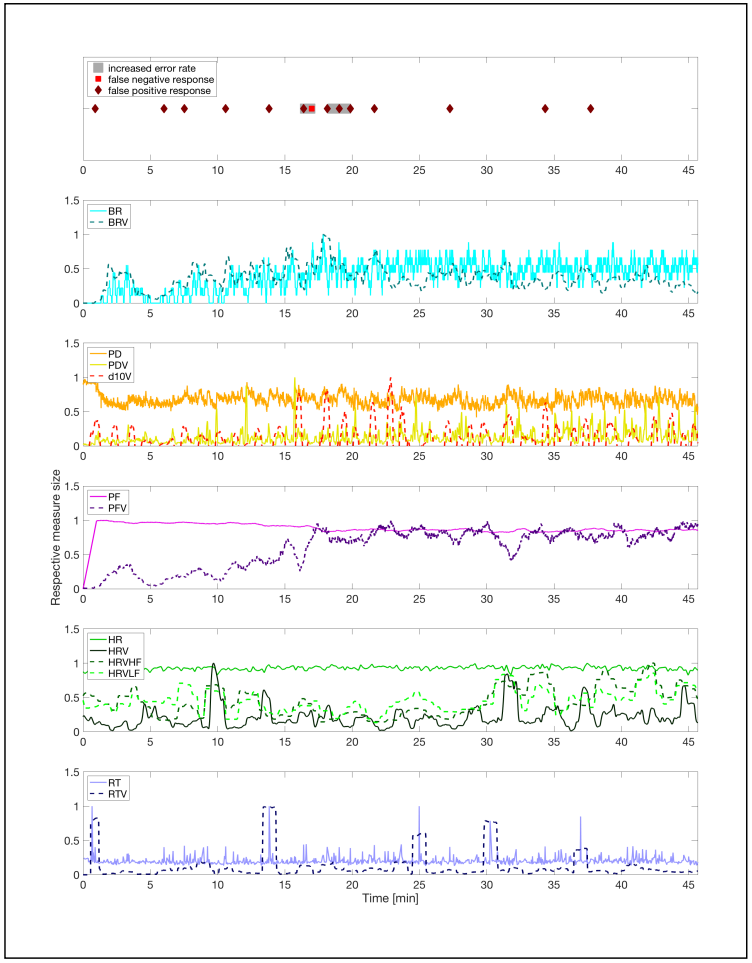
FOS curve



Agreement plot



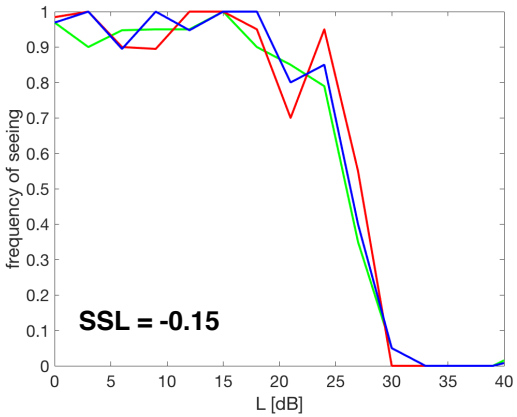
Individual results of false responses to catch trials and all related parameters



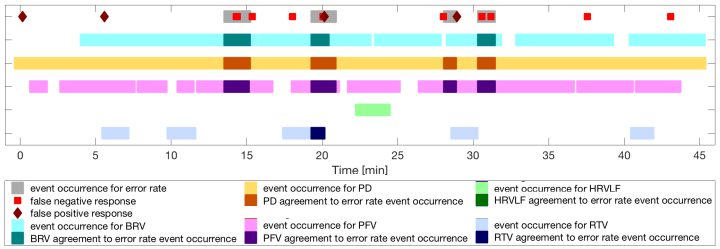
subject ID	**021**
age	**62**
gender	**m**
ESS score	**5**
total no. of errors	**14**

sleep disorders:
obstructive sleep apnea syndrome (OSAS)

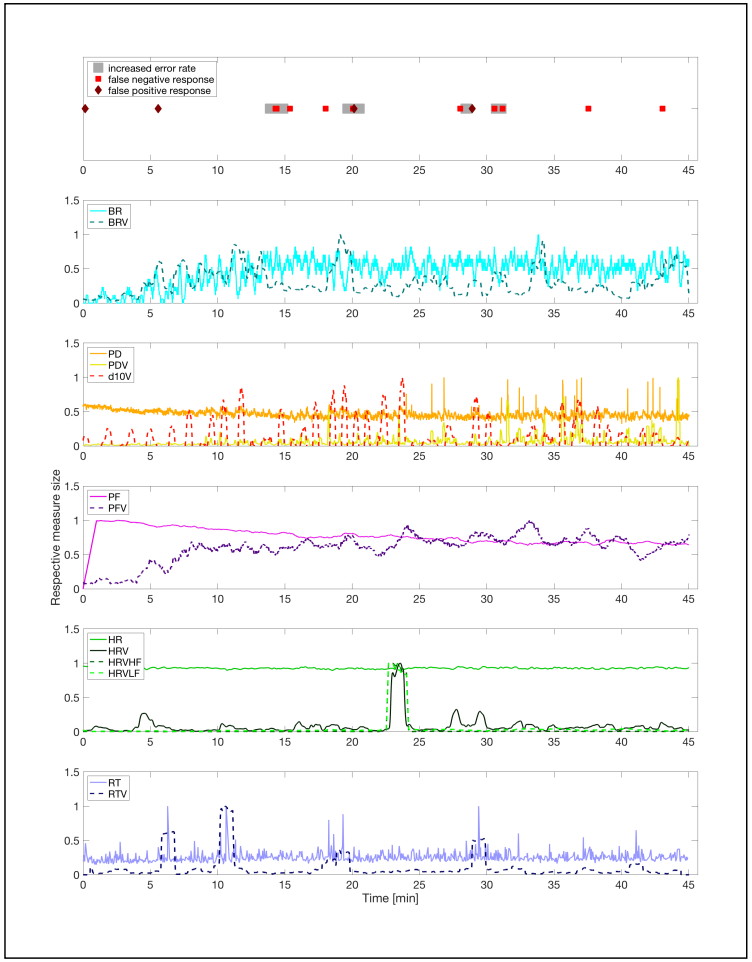
FOS curve



Agreement plot



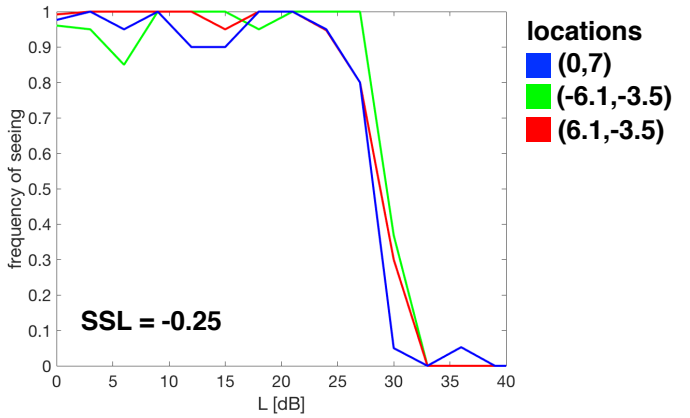
Individual results of false responses to catch trials and all related parameters



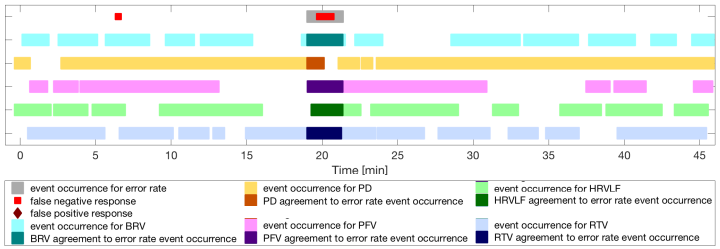
subject ID	**025**
age	**22**
gender	**f**
ESS score	**6**
total no. of errors	**10**

sleep disorders:
none

FOS curve



Agreement plot

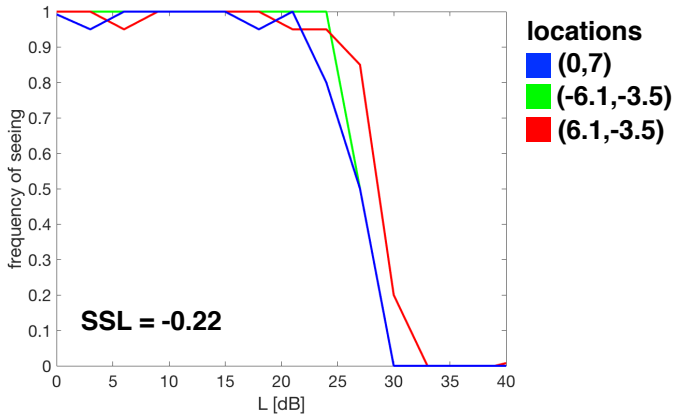


Individual results of false responses to catch trials and all related parameters

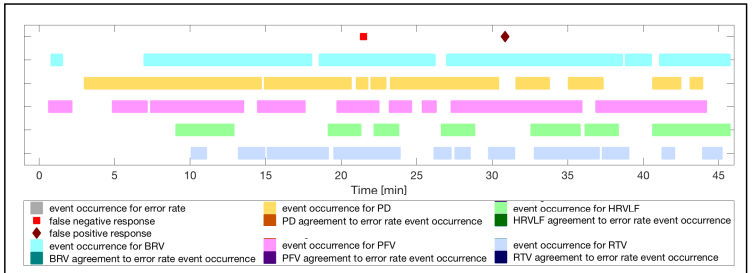
subject ID	**028**
age	**45**
gender	**f**
ESS score	**10**
total no. of errors	**2**

sleep disorders:
none

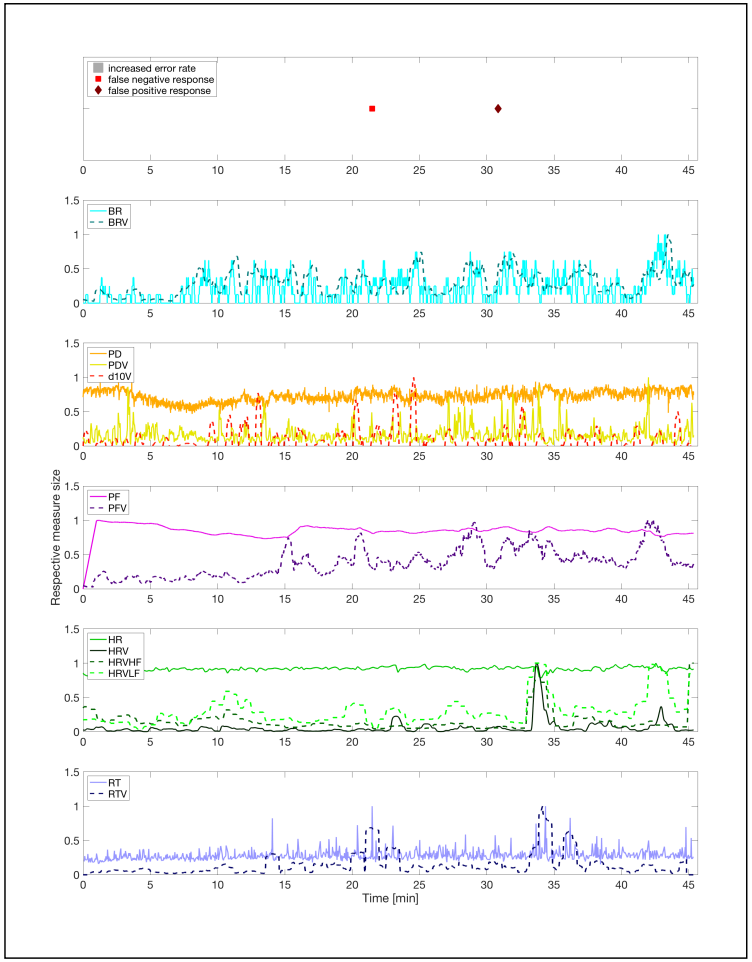
FOS curve



Agreement plot



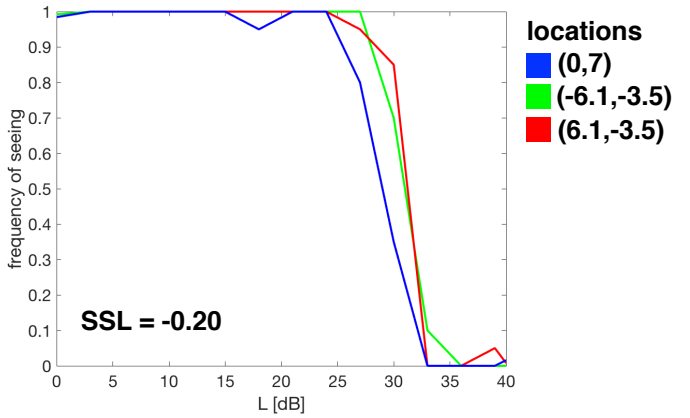
Individual results of false responses to catch trials and all related parameters



subject ID	**030**
age	**22**
gender	**f**
ESS score	**3**
total no. of errors	**7**

sleep disorders:
none

FOS curve



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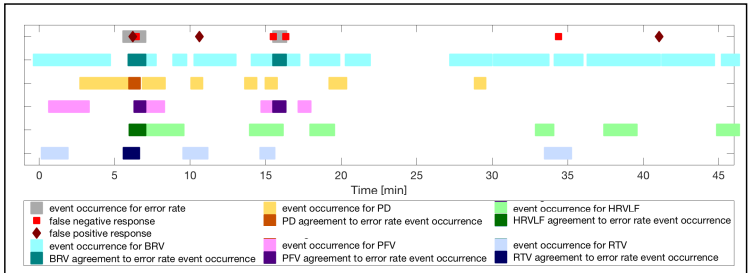
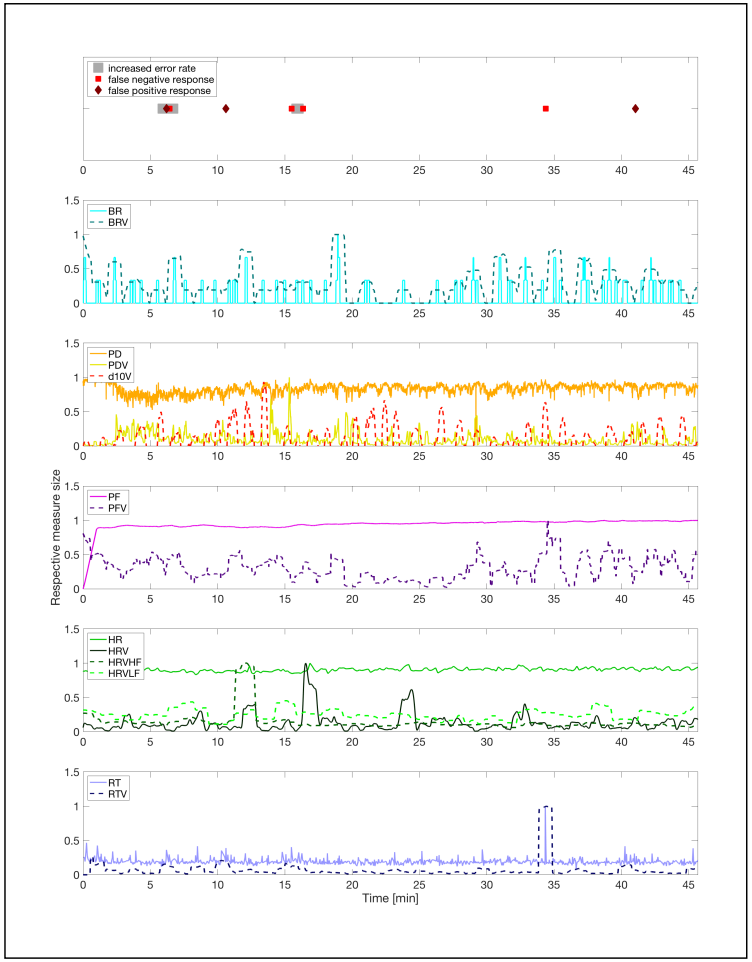


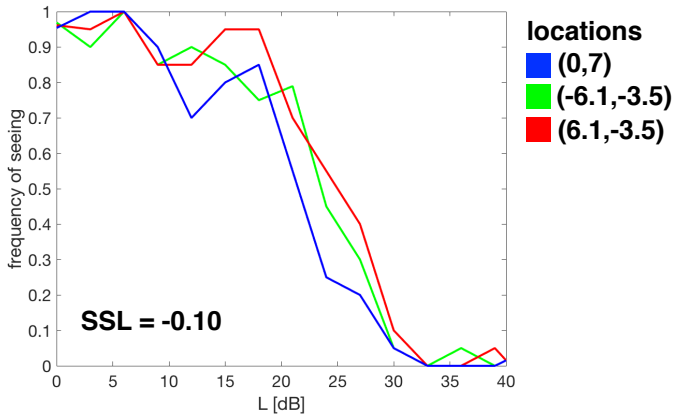
Individual results of false responses to catch trials and all related parameters



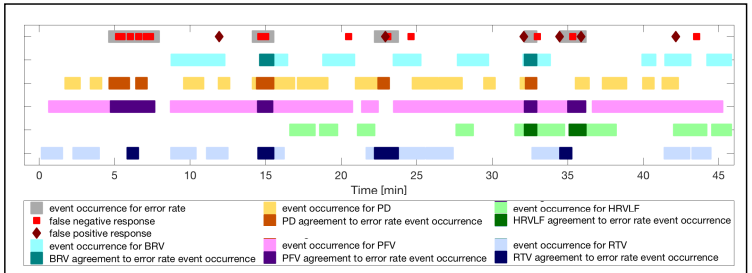
subject ID	**031**
age	**22**
gender	**f**
ESS score	**4**
total no. of errors	**20**

sleep disorders:
none

FOS curve



Agreement plot

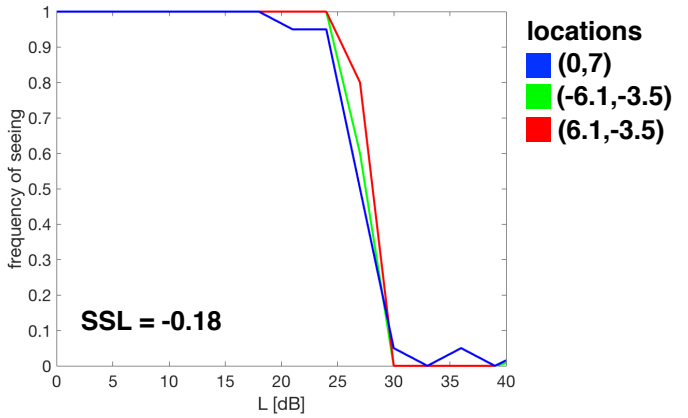


Individual results of false responses to catch trials and all related parameters

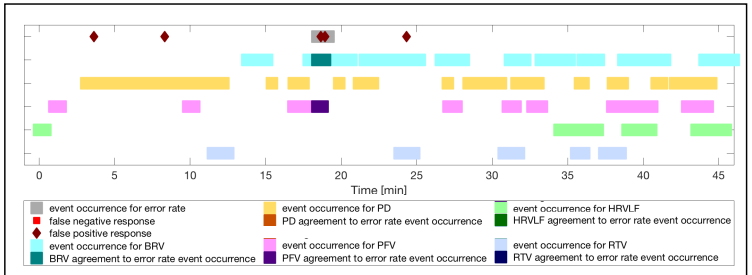
subject ID	**035**
age	**43**
gender	**m**
ESS score	**7**
total no. of errors	**5**

sleep disorders:
none

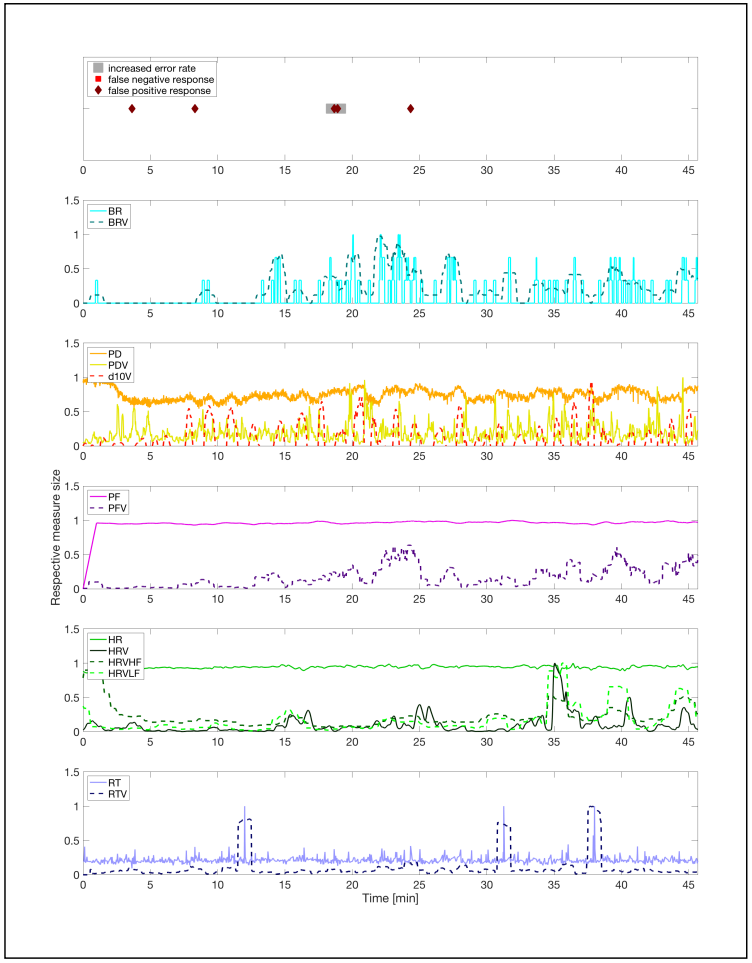
FOS curve



Agreement plot



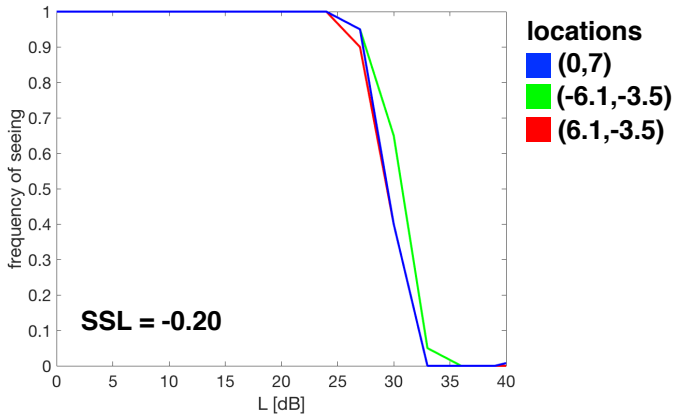
Individual results of false responses to catch trials and all related parameters



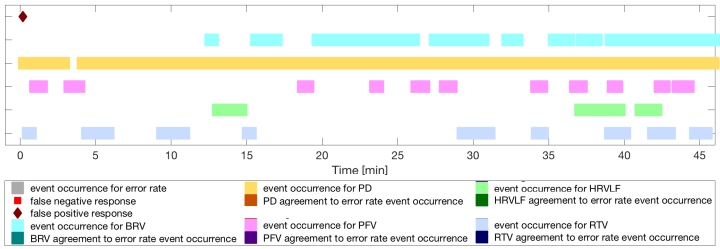
subject ID	**038**
age	**55**
gender	**f**
ESS score	**6**
total no. of errors	**1**

sleep disorders:
none

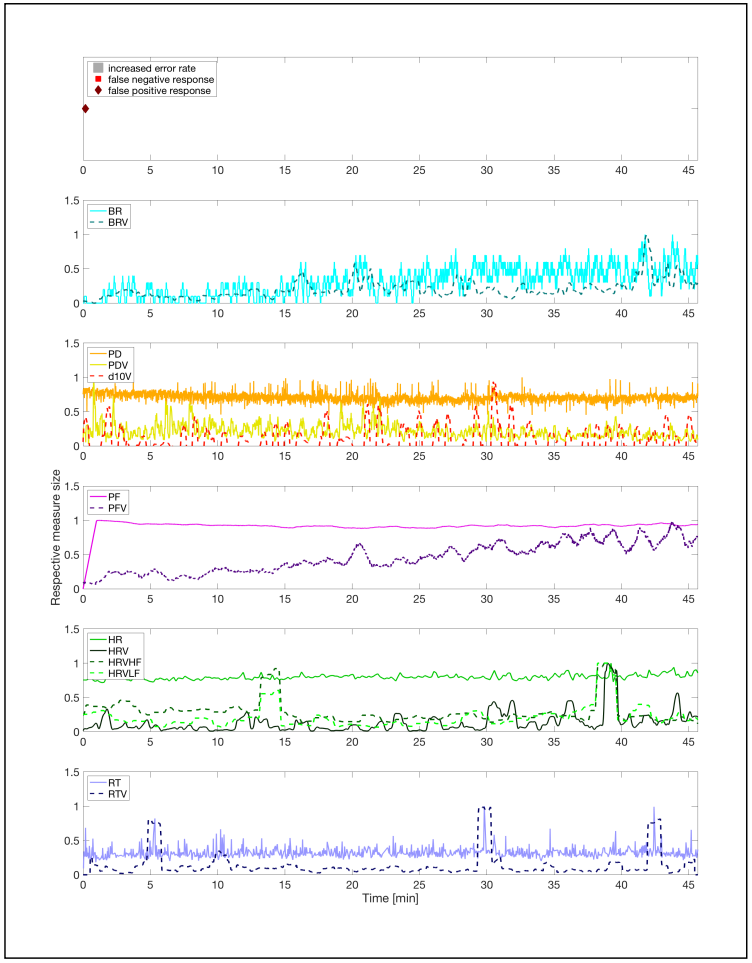
FOS curve



Agreement plot



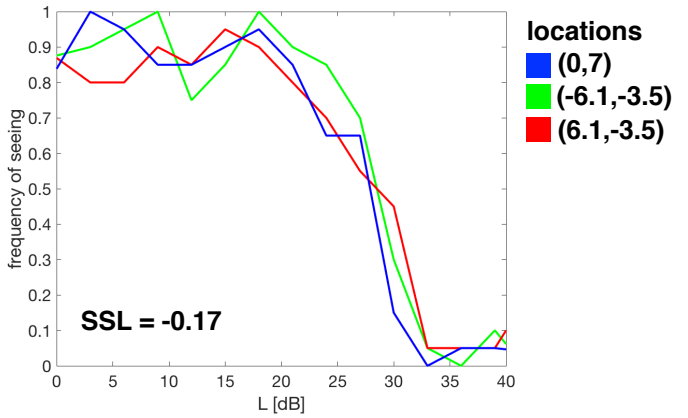
Individual results of false responses to catch trials and all related parameters



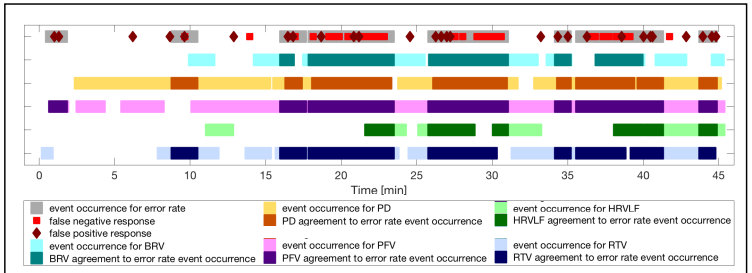
subject ID	**040**
age	**56**
gender	**f**
ESS score	**6**
total no. of errors	**79**

sleep disorders:
none

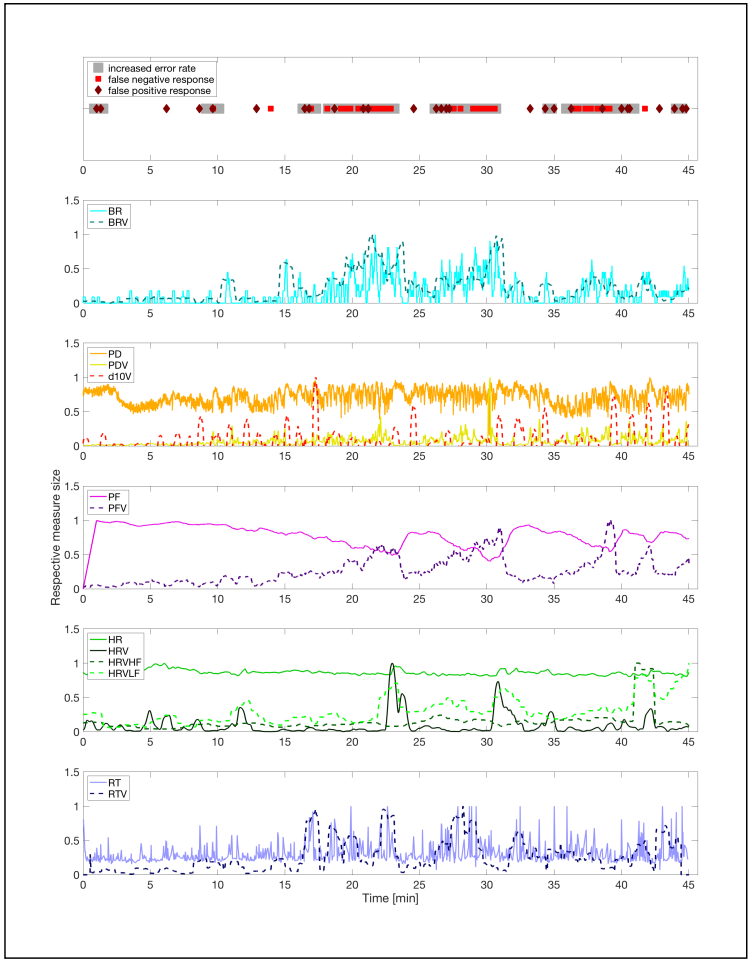
FOS curve



Agreement plot



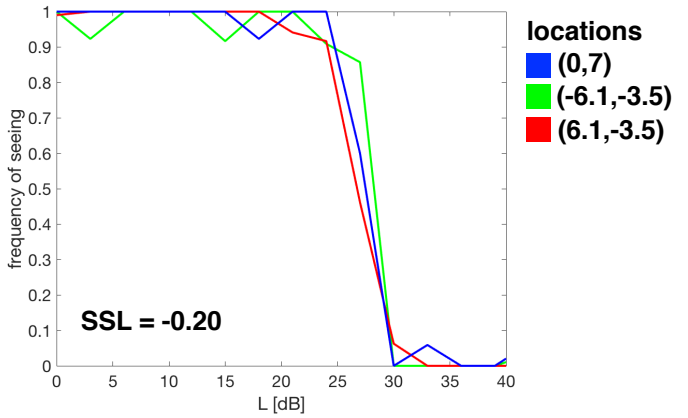
Individual results of false responses to catch trials and all related parameters



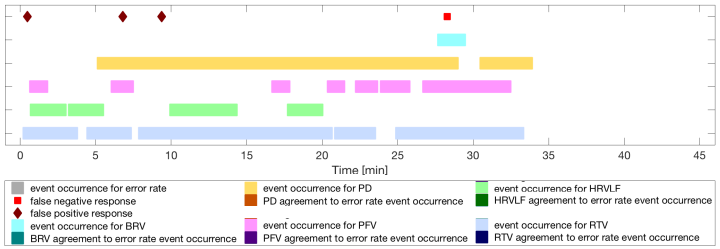
subject ID	**044**
age	**63**
gender	**f**
ESS score	**11**
total no. of errors	**4**

sleep disorders:
none

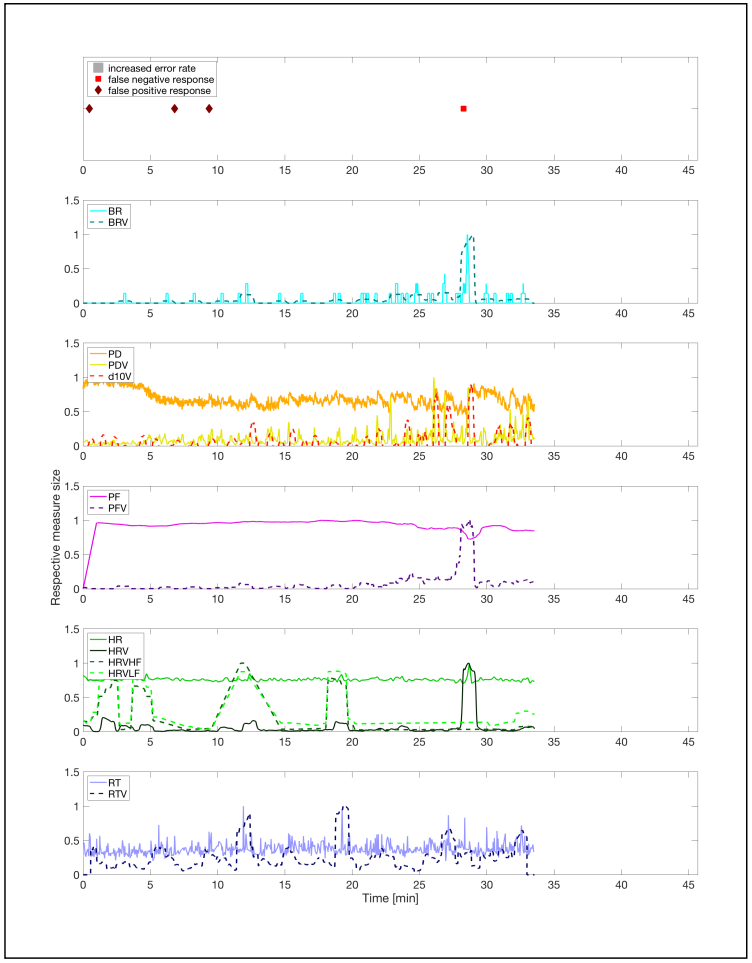
FOS curve



Agreement plot



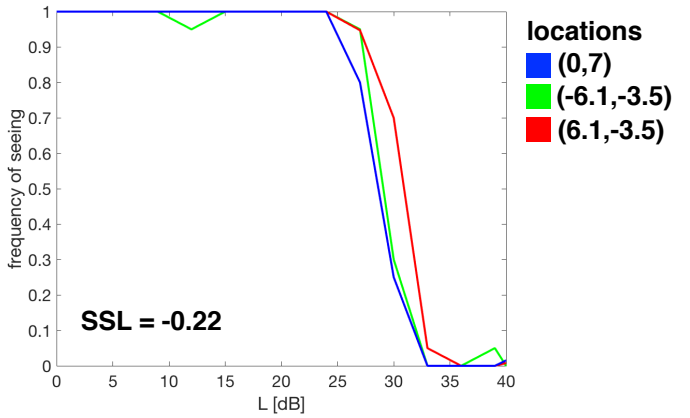
Individual results of false responses to catch trials and all related parameters



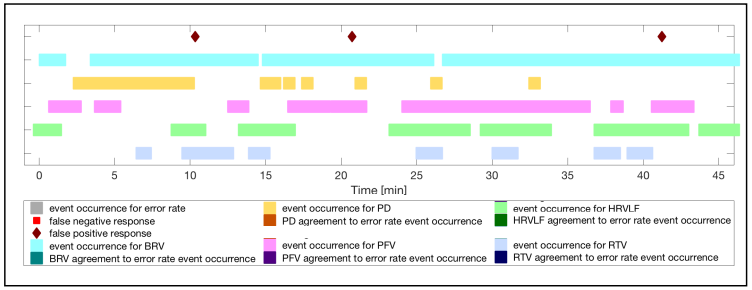
subject ID	**046**
age	**50**
gender	**m**
ESS score	**10**
total no. of errors	**3**

sleep disorders:
none

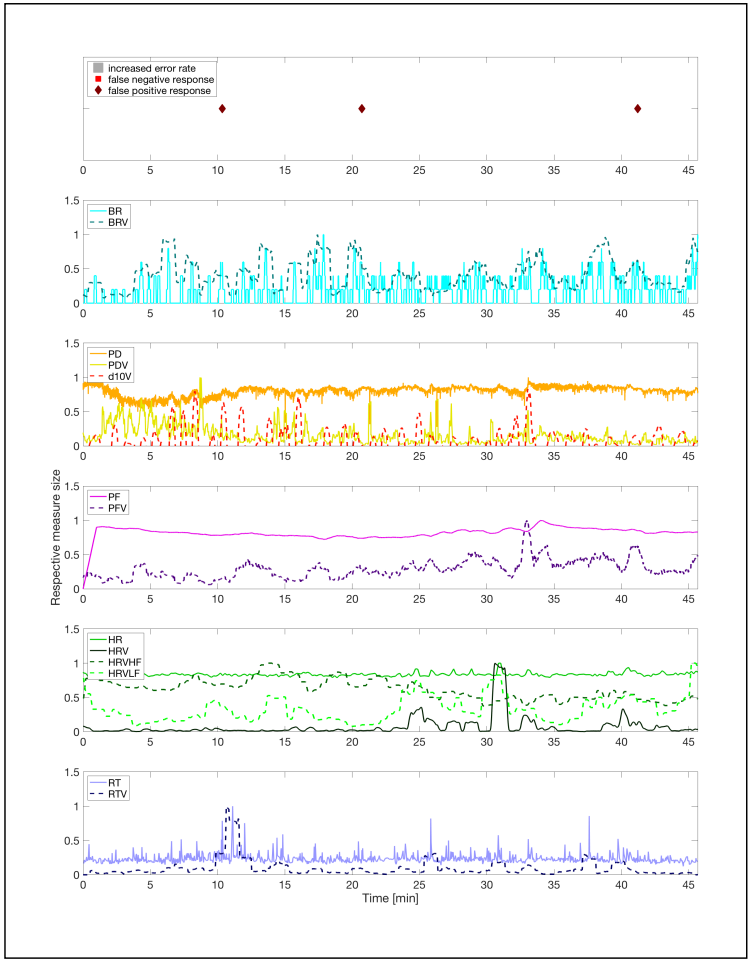
FOS curve



Agreement plot



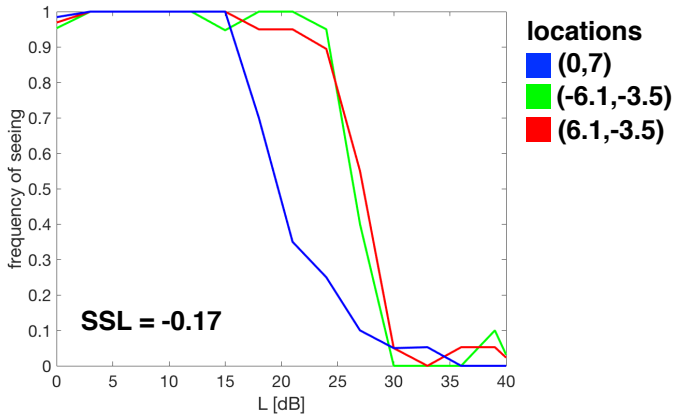
Individual results of false responses to catch trials and all related parameters



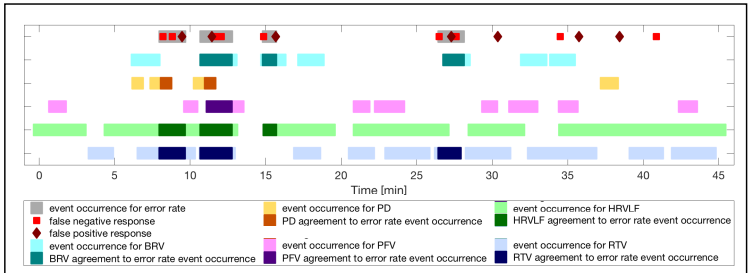
subject ID	**047**
age	**63**
gender	**f**
ESS score	**5**
total no. of errors	**18**

sleep disorders:
none

FOS curve



Agreement plot

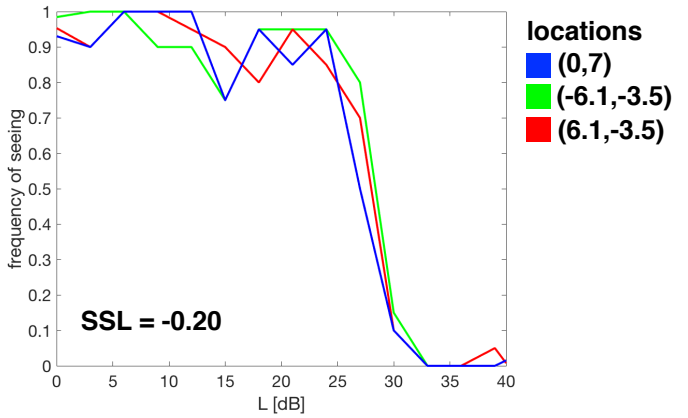


Individual results of false responses to catch trials and all related parameters

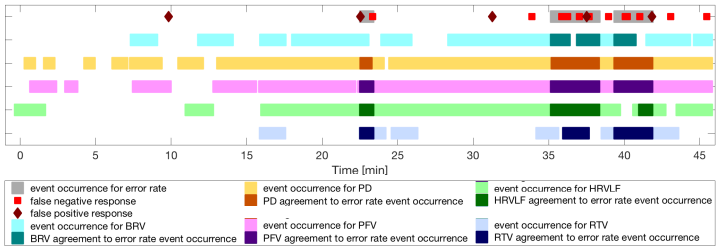
subject ID	**056**
age	**45**
gender	**f**
ESS score	**10**
total no. of errors	**18**

sleep disorders:
none

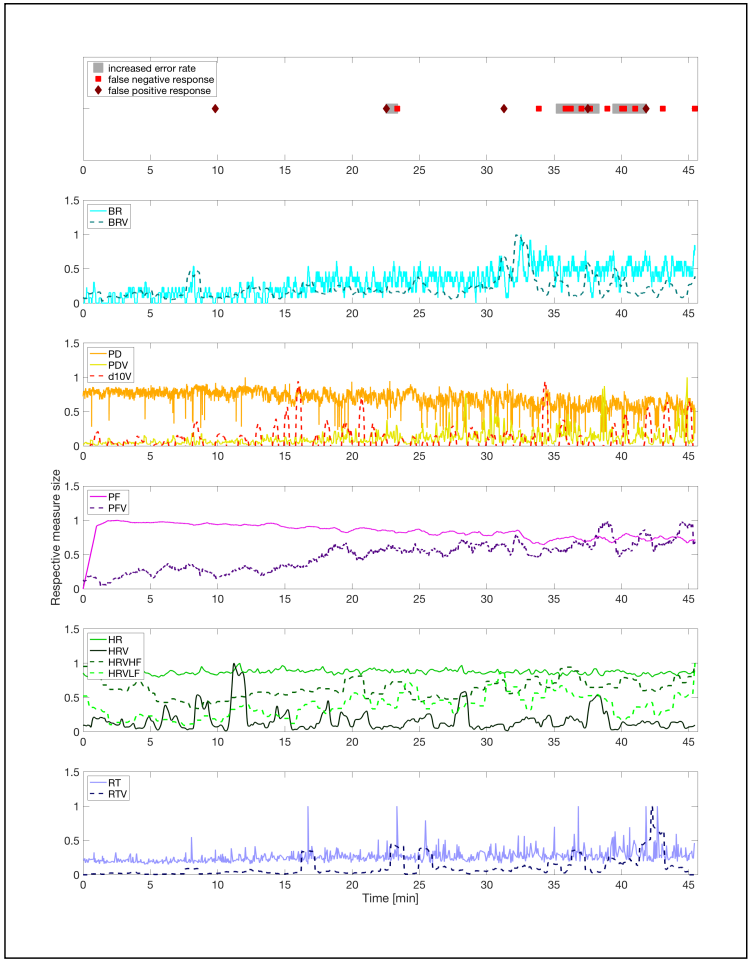
FOS curve



Agreement plot



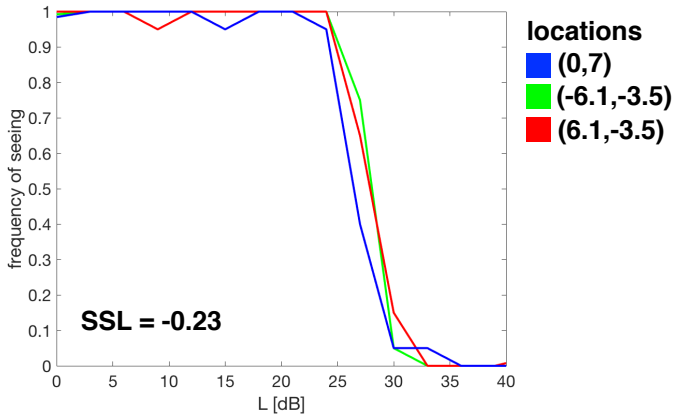
Individual results of false responses to catch trials and all related parameters



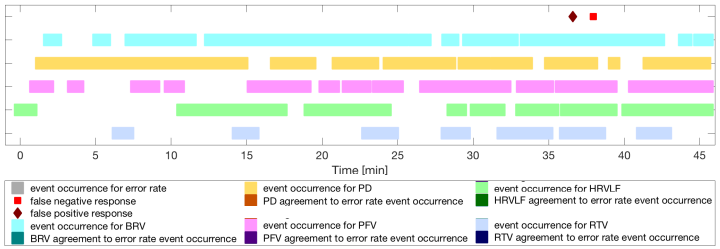
subject ID	**059**
age	**40**
gender	**f**
ESS score	**8**
total no. of errors	**2**

sleep disorders:
none

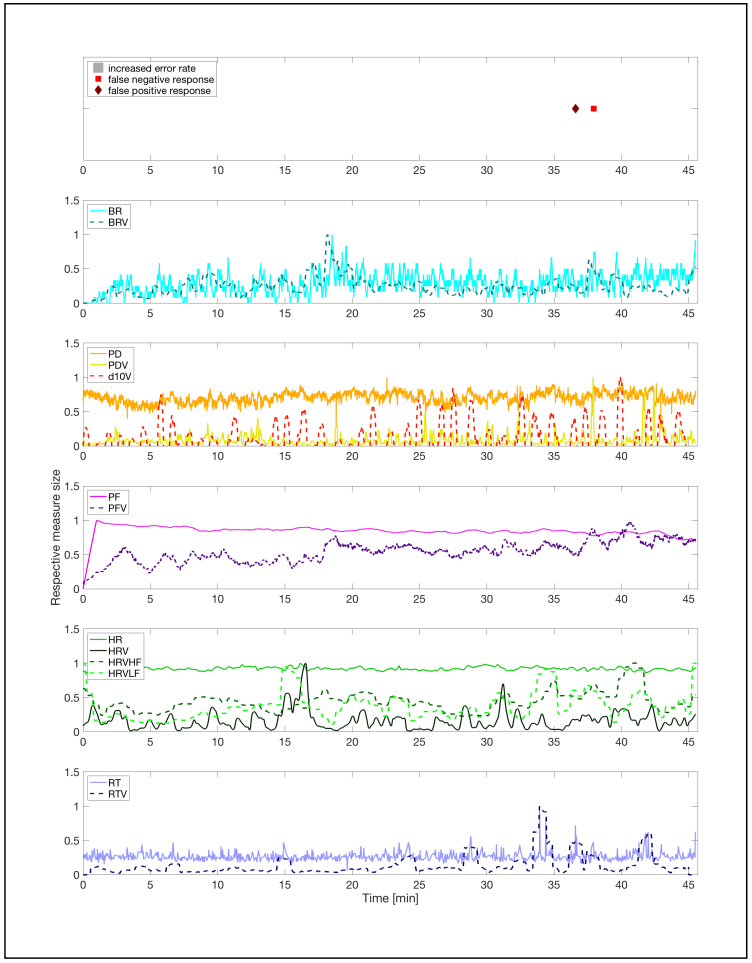
FOS curve



Agreement plot



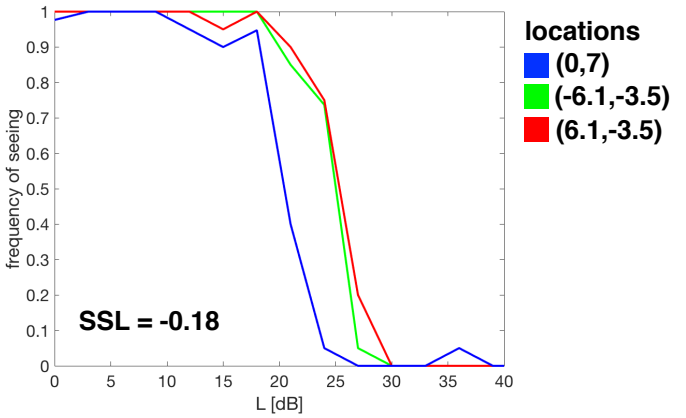
Individual results of false responses to catch trials and all related parameters



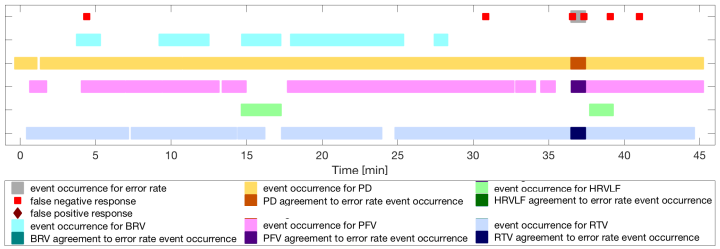
subject ID	**060**
age	**67**
gender	**m**
ESS score	**10**
total no. of errors	**6**

sleep disorders:
none

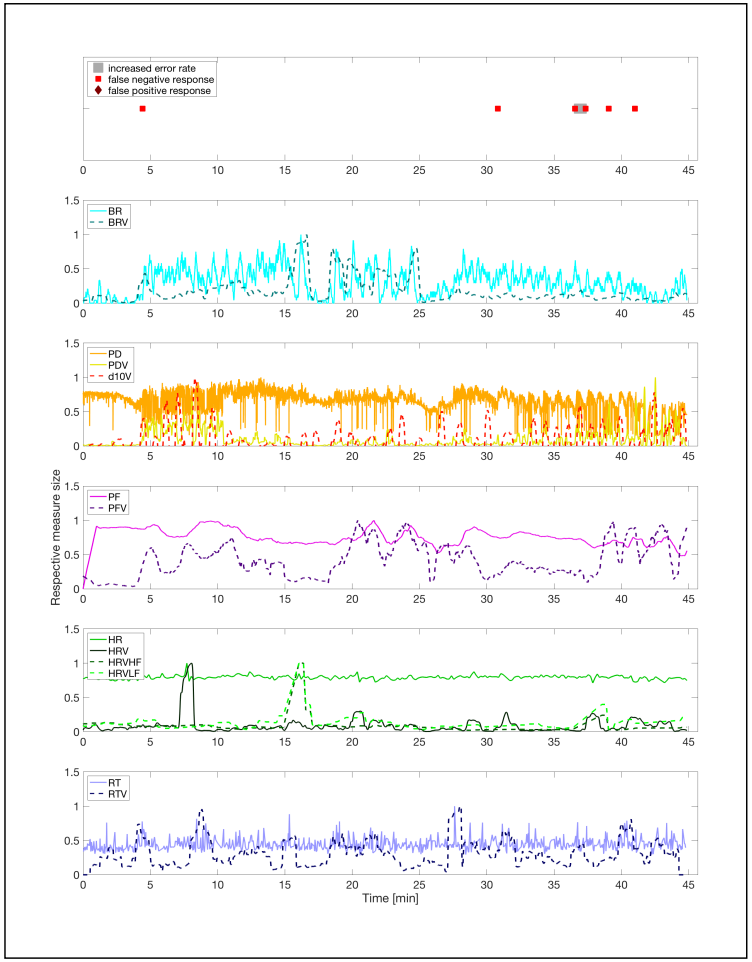
FOS curve



Agreement plot



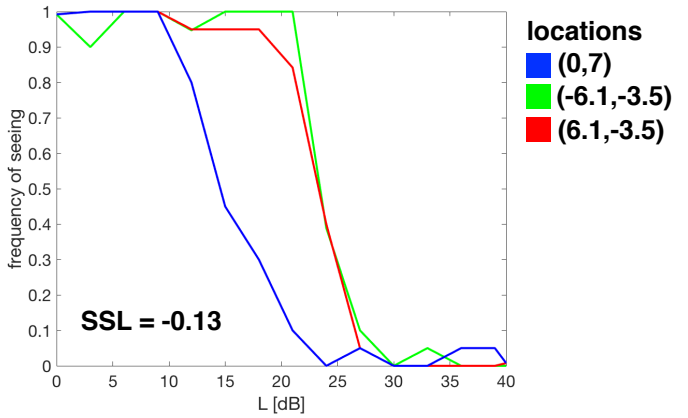
Individual results of false responses to catch trials and all related parameters



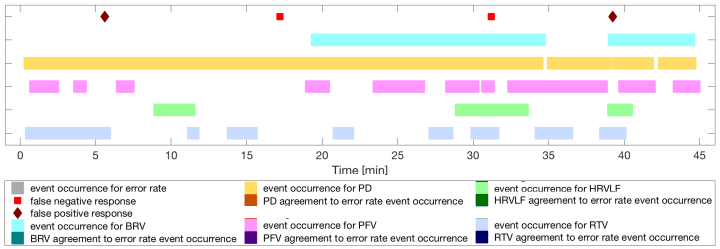
subject ID	**065**
age	**69**
gender	**f**
ESS score	**6**
total no. of errors	**4**

sleep disorders:
none

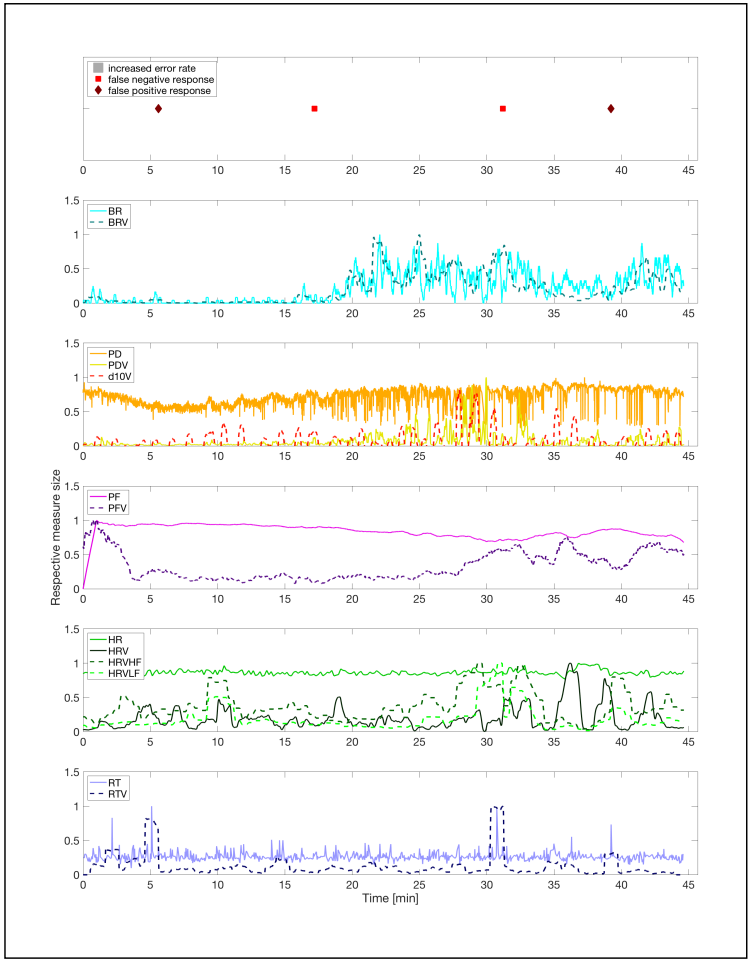
FOS curve



Agreement plot



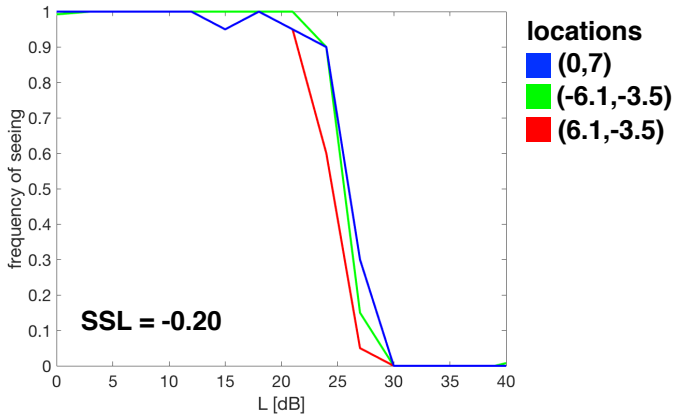
Individual results of false responses to catch trials and all related parameters



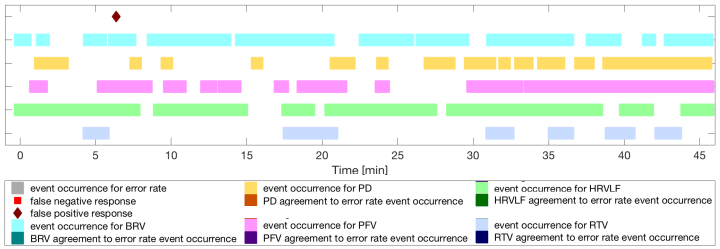
subject ID	**068**
age	**67**
gender	**f**
ESS score	**6**
total no. of errors	**1**

sleep disorders:
none

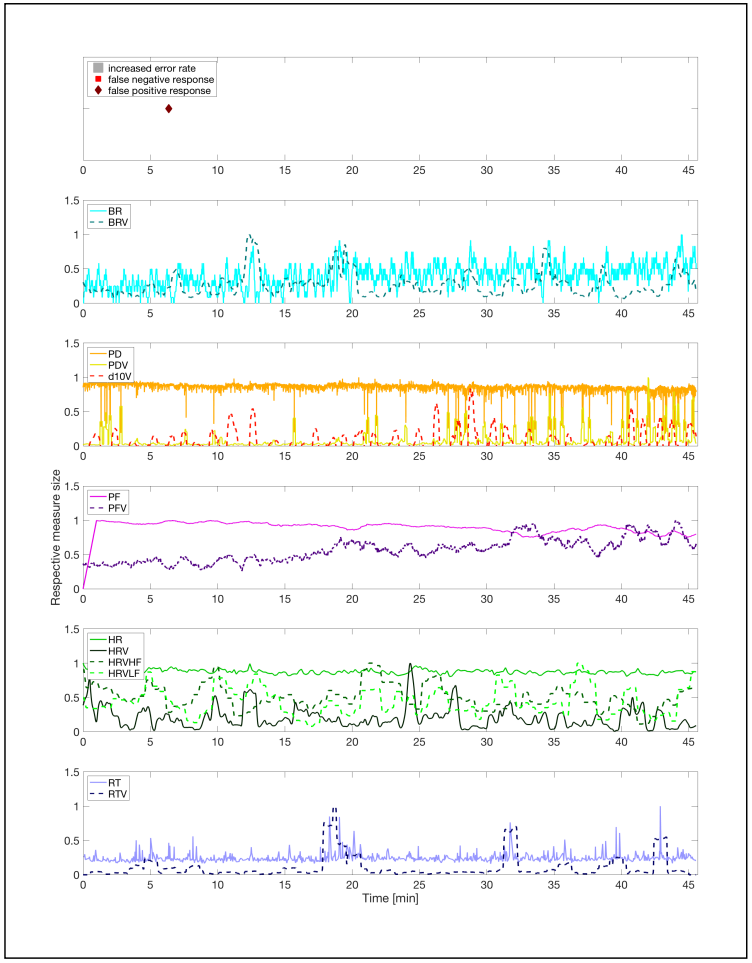
FOS curve



Agreement plot



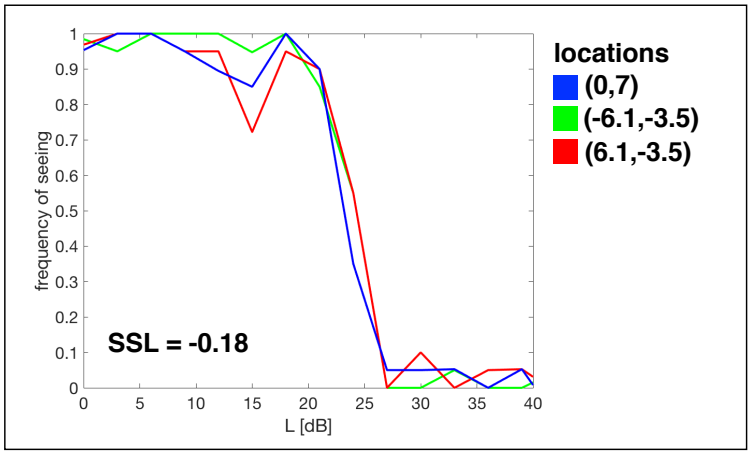
Individual results of false responses to catch trials and all related parameters



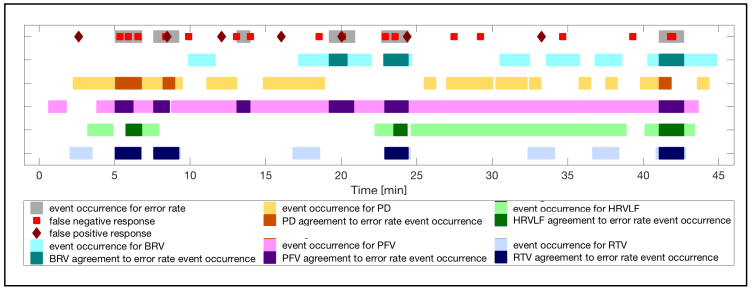
subject ID	**069**
age	**69**
gender	**m**
ESS score	**5**
total no. of errors	**24**

sleep disorders:
obstructive sleep apnea syndrome (OSAS)

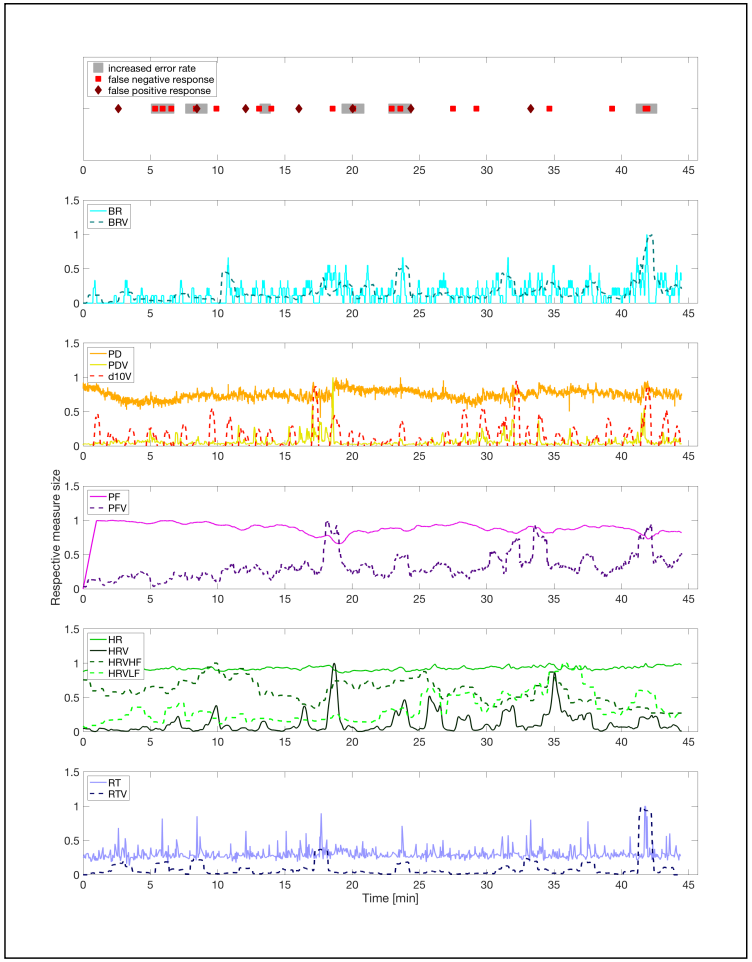
FOS curve



Agreement plot



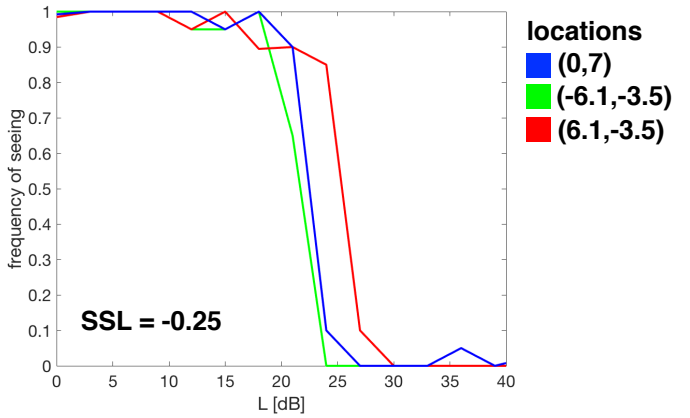
Individual results of false responses to catch trials and all related parameters



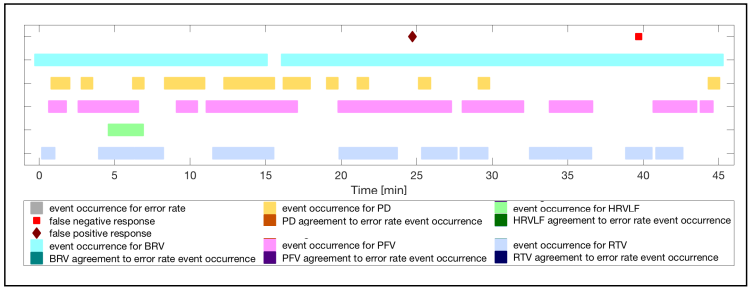
subject ID	**070**
age	**70**
gender	**f**
ESS score	**4**
total no. of errors	**2**

sleep disorders:
none

FOS curve



Agreement plot

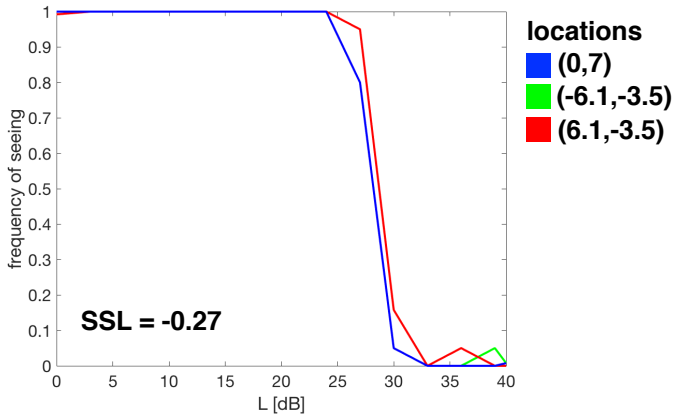


Individual results of false responses to catch trials and all related parameters

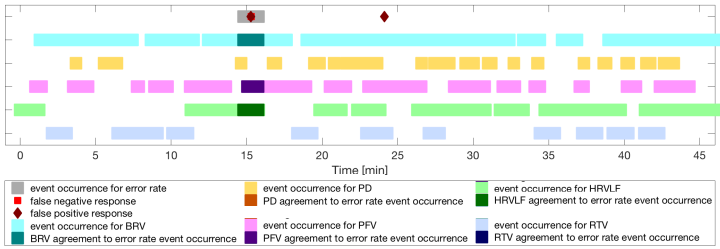
subject ID	**074**
age	**50**
gender	**f**
ESS score	**3**
total no. of errors	**3**

sleep disorders:
none

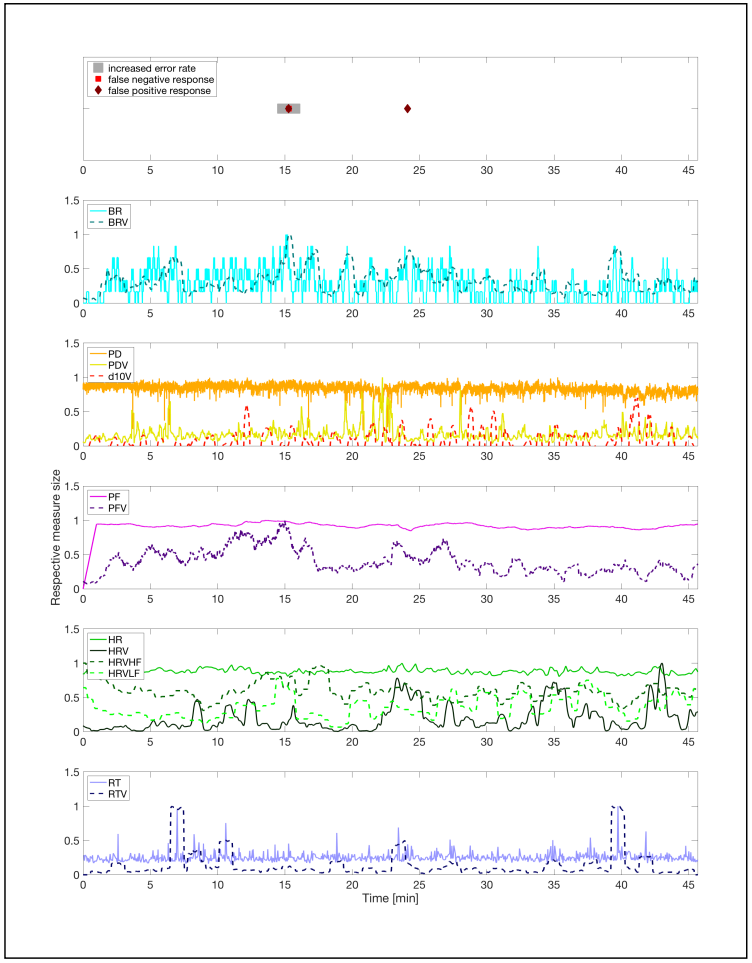
FOS curve



Agreement plot



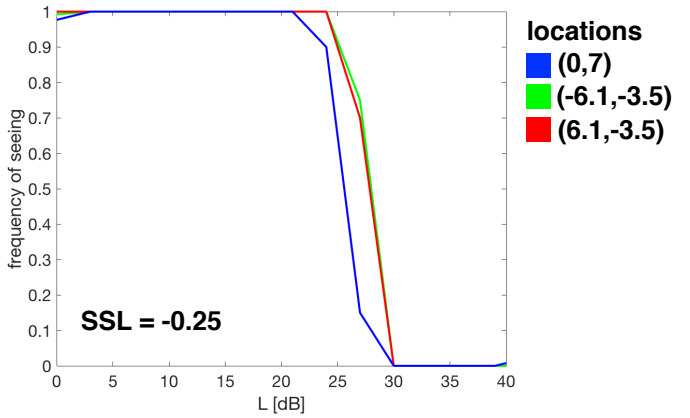
Individual results of false responses to catch trials and all related parameters



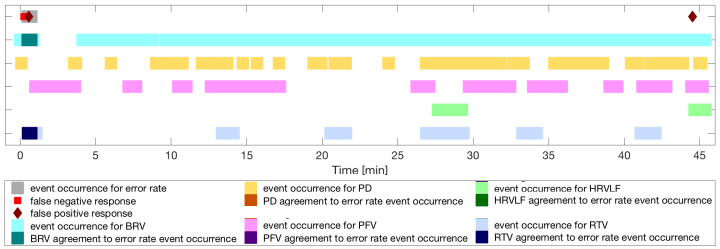
subject ID	**078**
age	**67**
gender	**f**
ESS score	**5**
total no. of errors	**3**

sleep disorders:
none

FOS curve



Agreement plot

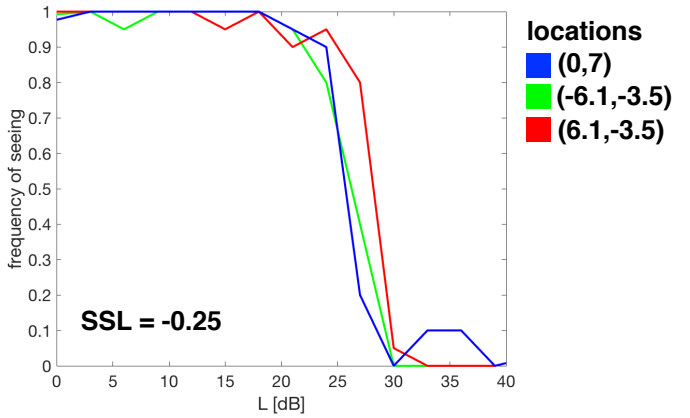


Individual results of false responses to catch trials and all related parameters

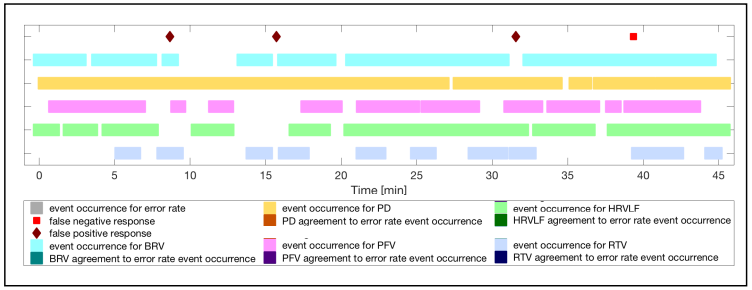
subject ID	**080**
age	**62**
gender	**f**
ESS score	**9**
total no. of errors	**4**

sleep disorders:
none

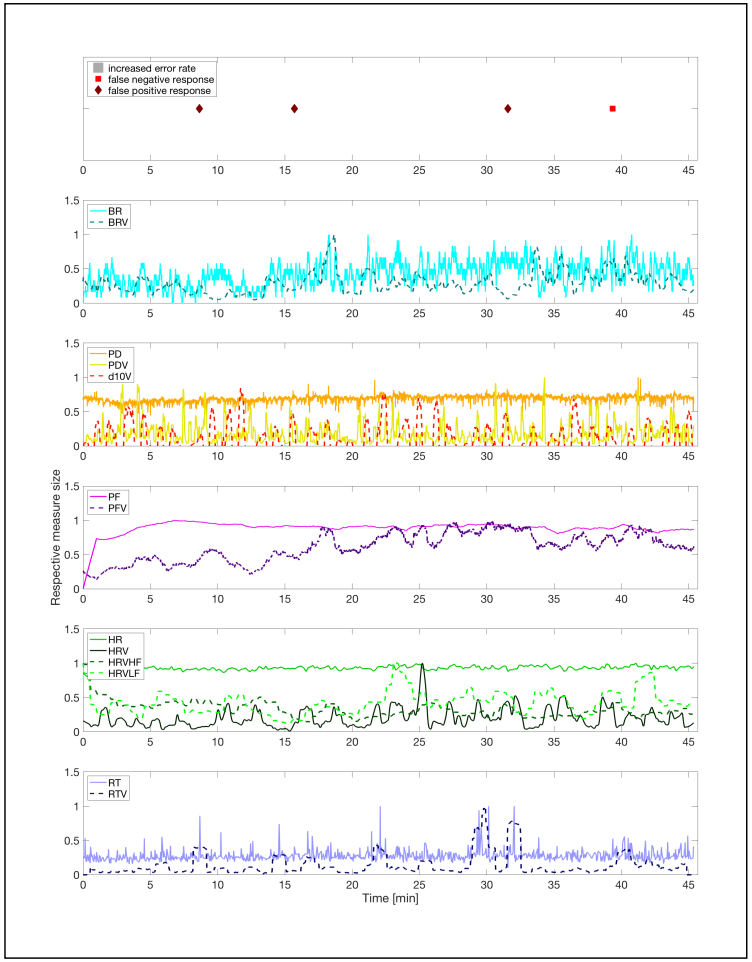
FOS curve



Agreement plot



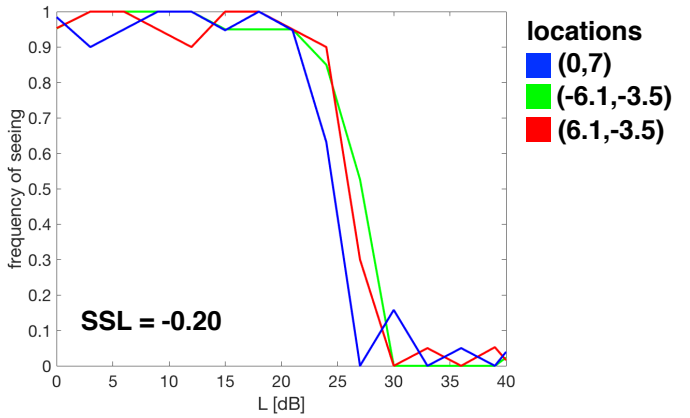
Individual results of false responses to catch trials and all related parameters



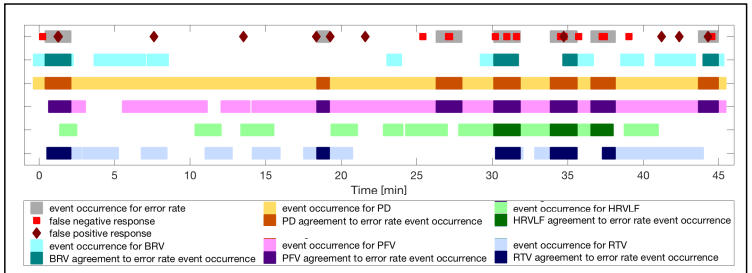
subject ID	**082**
age	**47**
gender	**f**
ESS score	**10**
total no. of errors	**25**

sleep disorders:
none

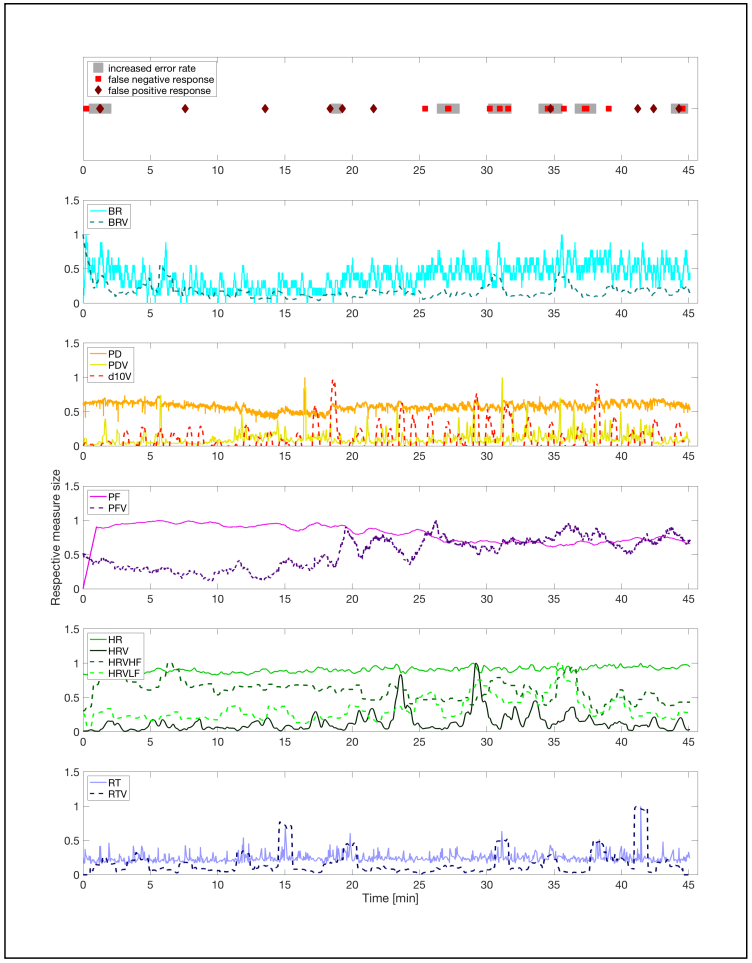
FOS curve



Agreement plot



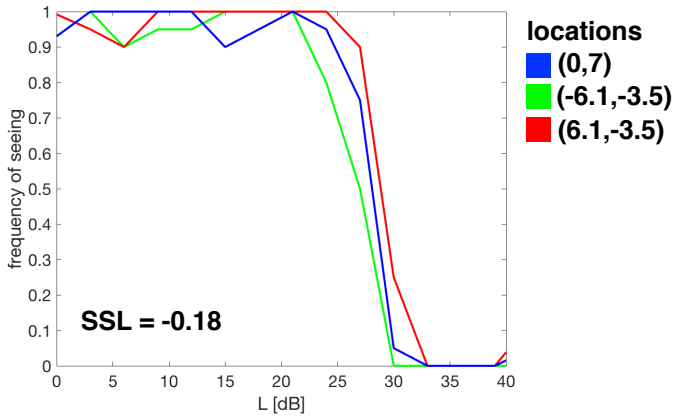
Individual results of false responses to catch trials and all related parameters



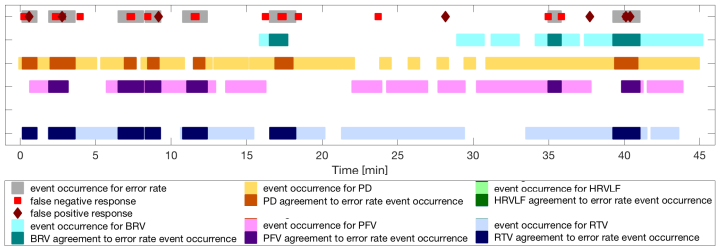
subject ID	**084**
age	**64**
gender	**f**
ESS score	**5**
total no. of errors	**26**

sleep disorders:
none

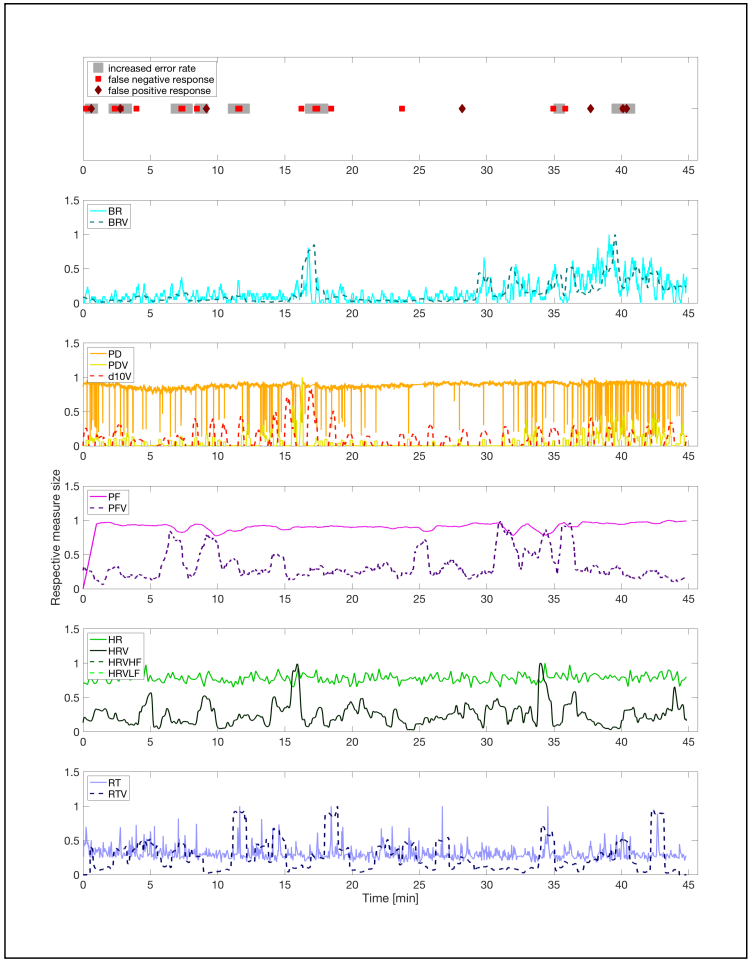
FOS curve



Agreement plot



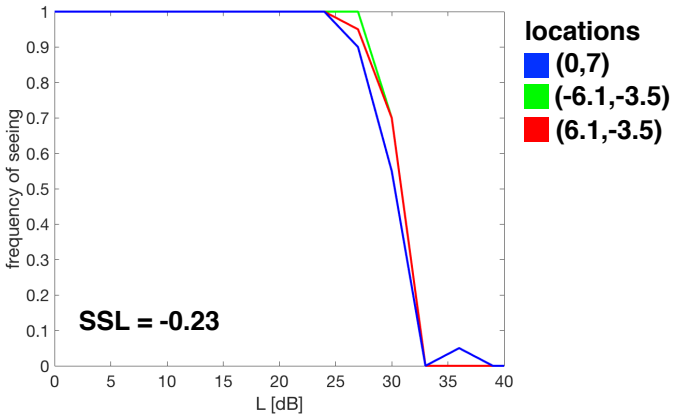
Individual results of false responses to catch trials and all related parameters



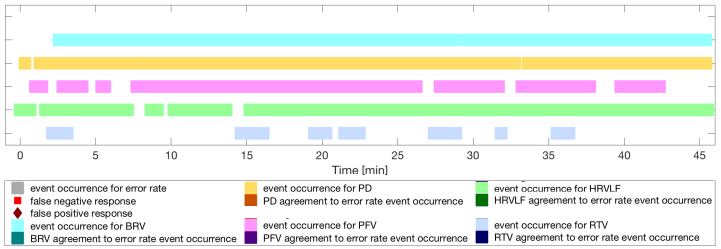
subject ID	**090**
age	**27**
gender	**m**
ESS score	**1**
total no. of errors	**0**

sleep disorders:
none

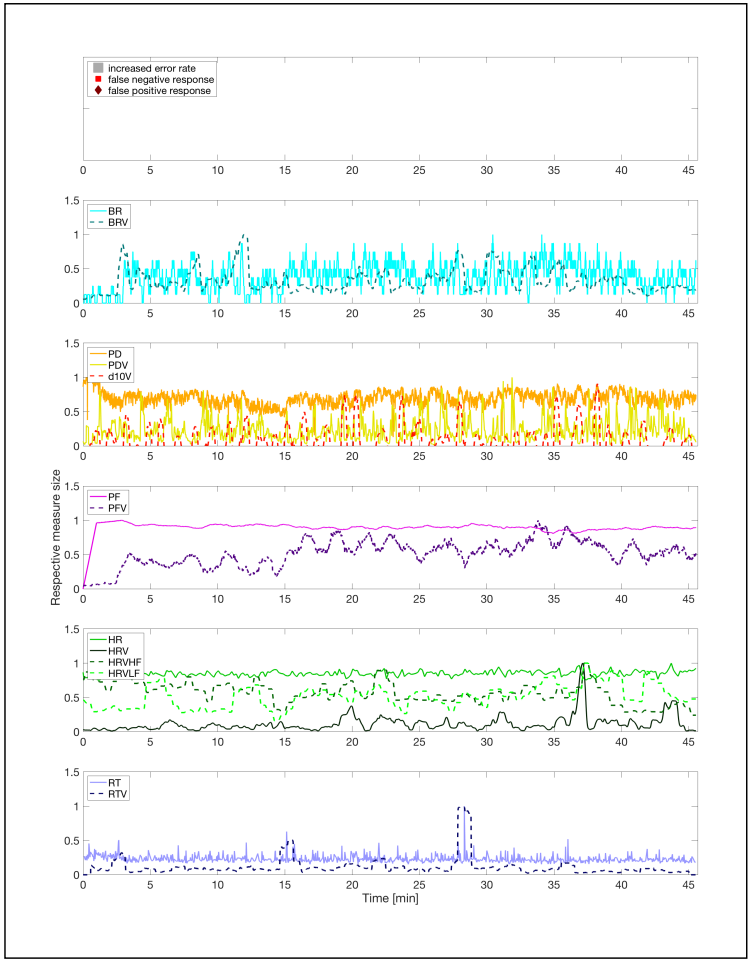
FOS curve



Agreement plot



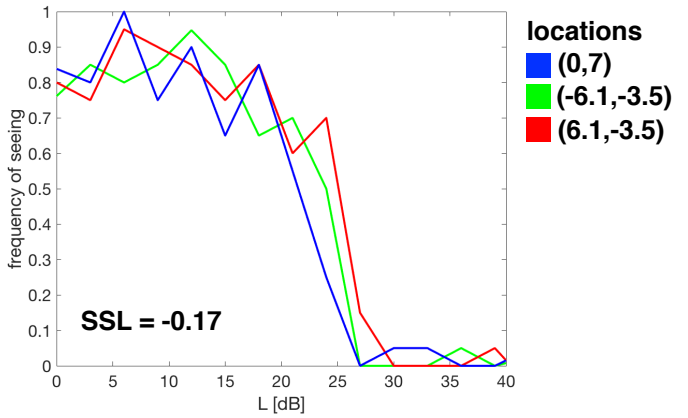
Individual results of false responses to catch trials and all related parameters



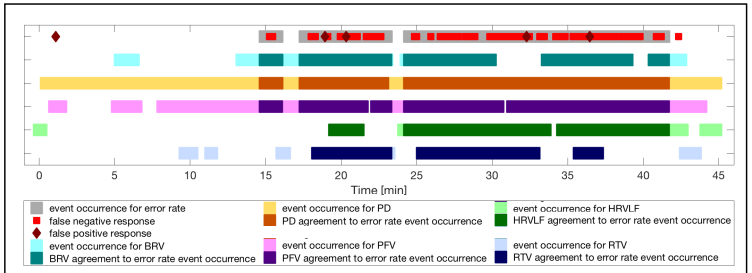
subject ID	**091**
age	**61**
gender	**f**
ESS score	**15**
total no. of errors	**82**

sleep disorders:
none

FOS curve



Agreement plot

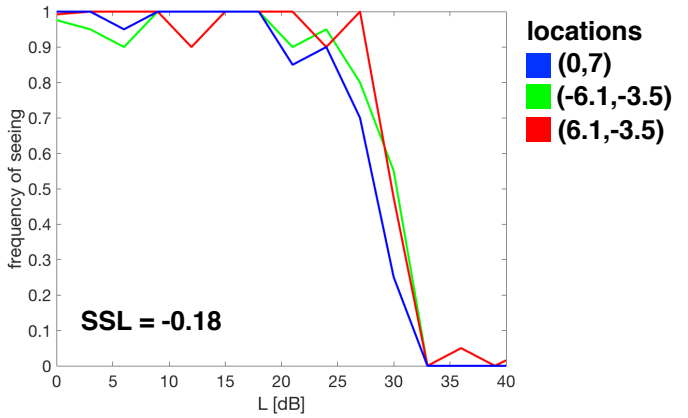


Individual results of false responses to catch trials and all related parameters

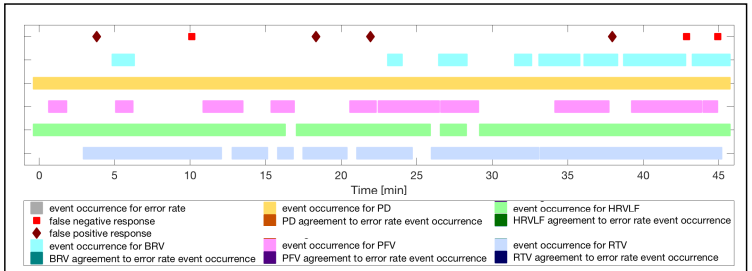
subject ID	**092**
age	**27**
gender	**f**
ESS score	**7**
total no. of errors	**7**

sleep disorders:
none

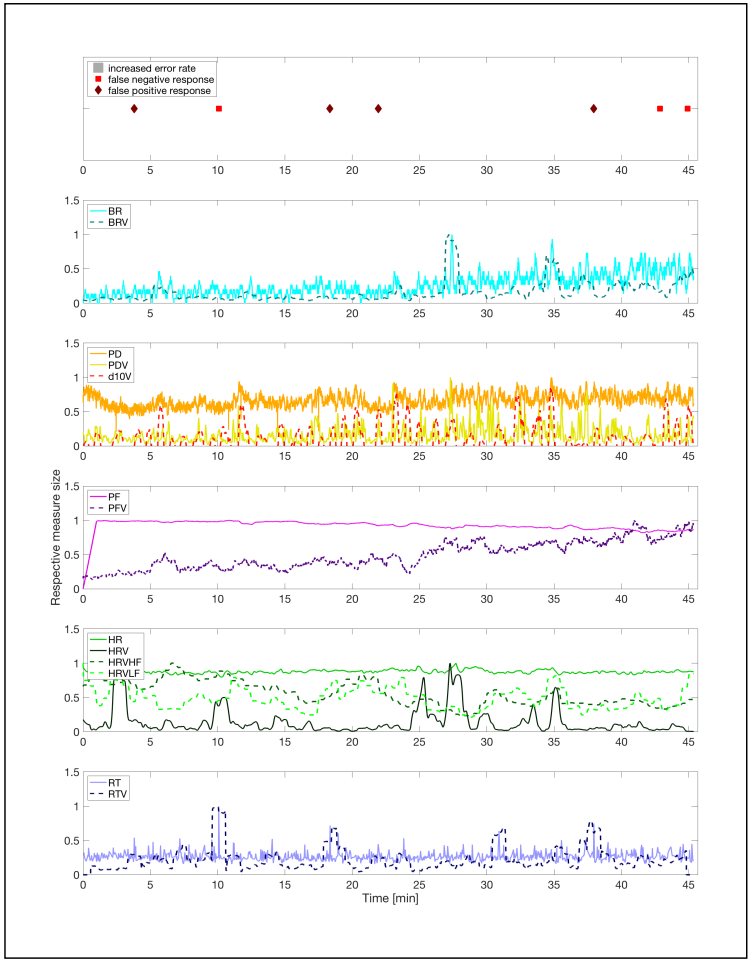
FOS curve



Agreement plot



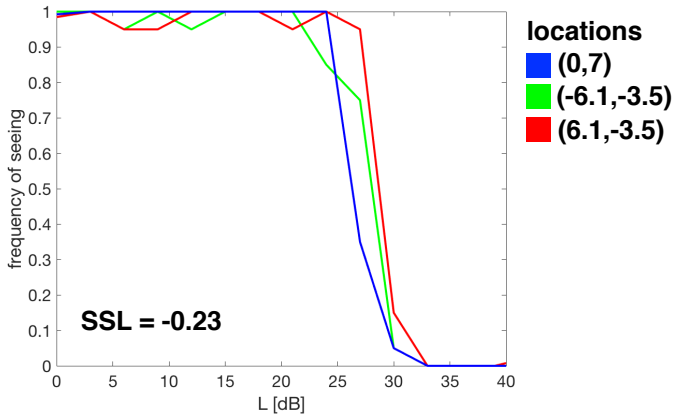
Individual results of false responses to catch trials and all related parameters



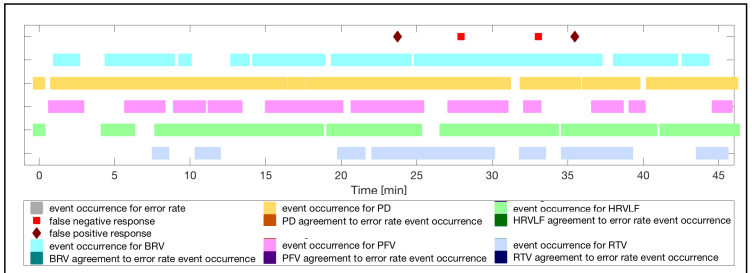
subject ID	**093**
age	**26**
gender	**m**
ESS score	**12**
total no. of errors	**4**

sleep disorders:
none

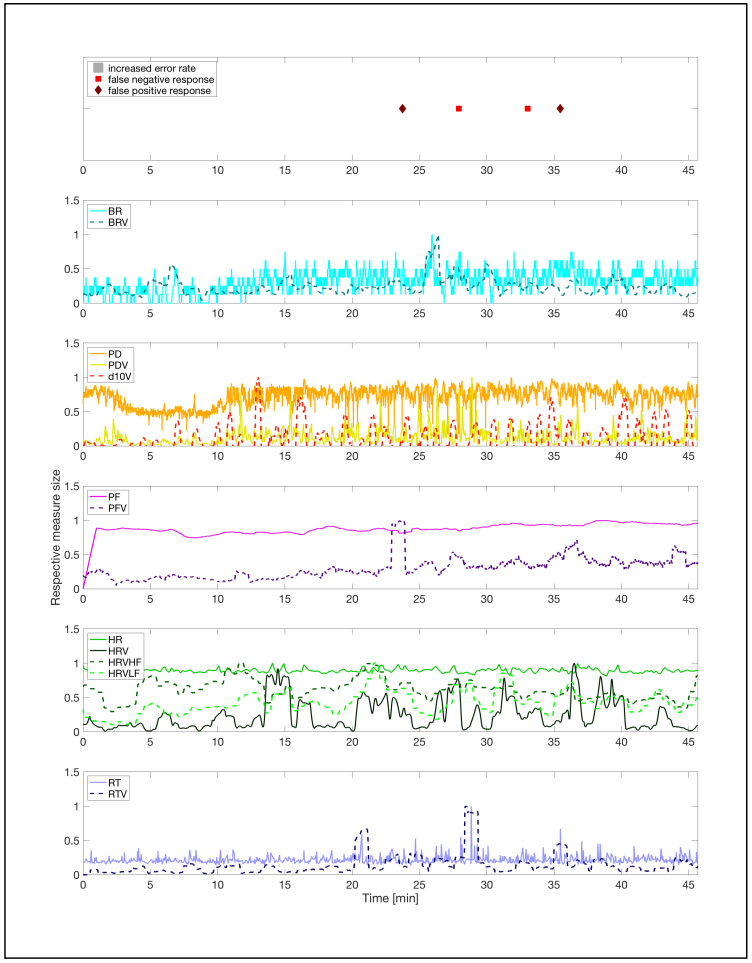
FOS curve



Agreement plot



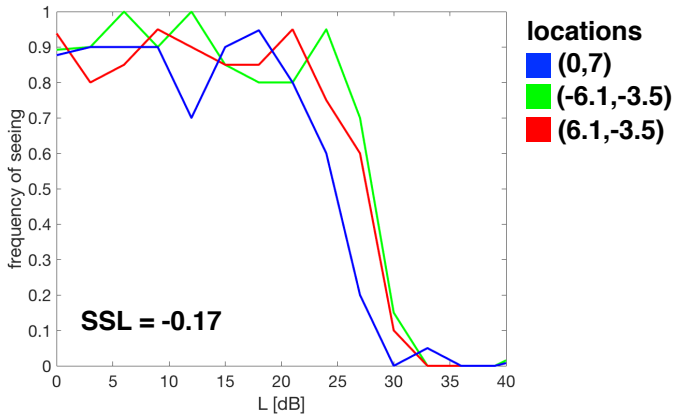
Individual results of false responses to catch trials and all related parameters



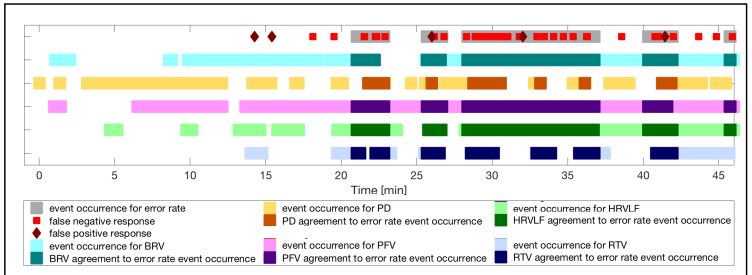
subject ID	**094**
age	**31**
gender	**m**
ESS score	**8**
total no. of errors	**43**

sleep disorders:
none

FOS curve



Agreement plot

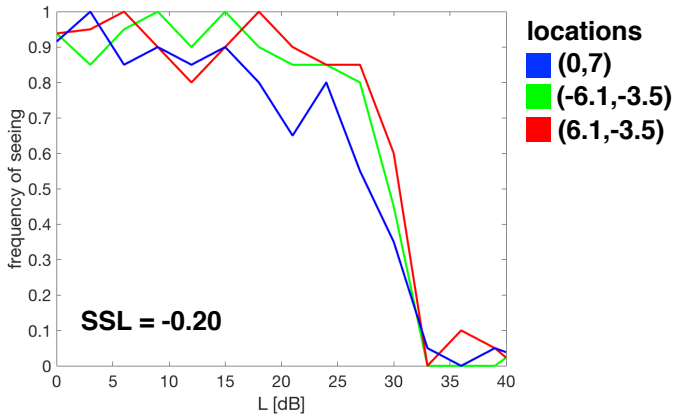


Individual results of false responses to catch trials and all related parameters

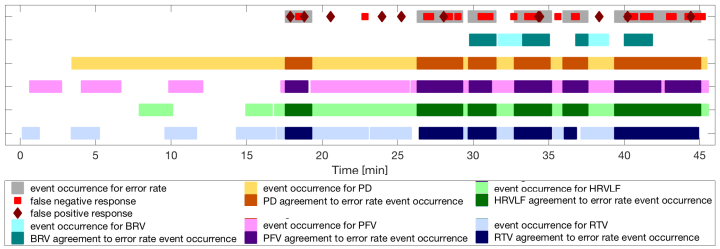
subject ID	**095**
age	**23**
gender	**f**
ESS score	**12**
total no. of errors	**39**

sleep disorders:
none

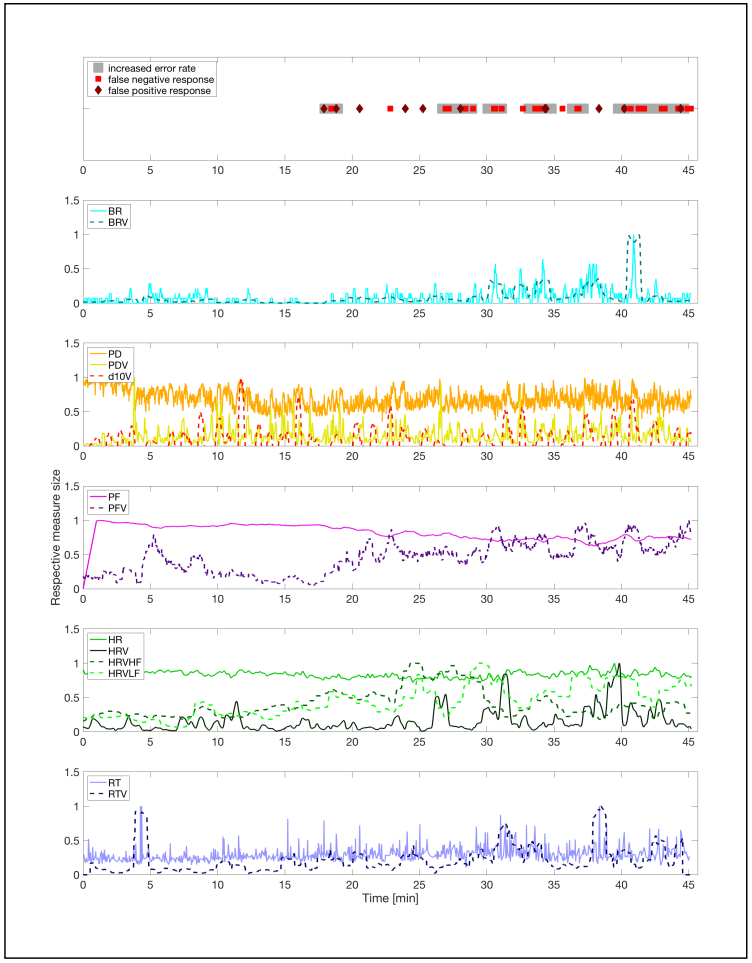
FOS curve



Agreement plot



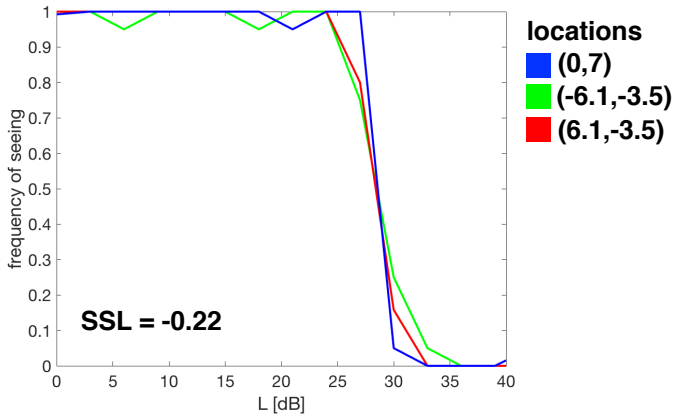
Individual results of false responses to catch trials and all related parameters



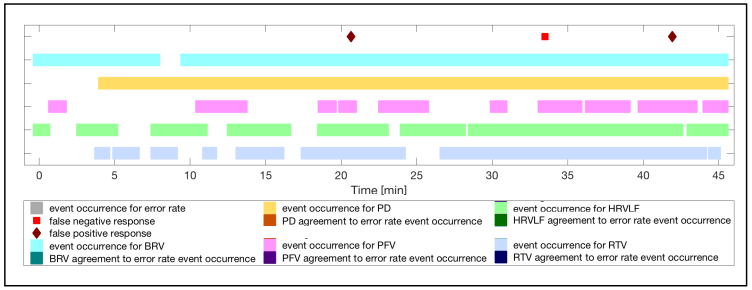
subject ID	**096**
age	**47**
gender	**m**
ESS score	**3**
total no. of errors	**3**

sleep disorders:
none

FOS curve



Agreement plot

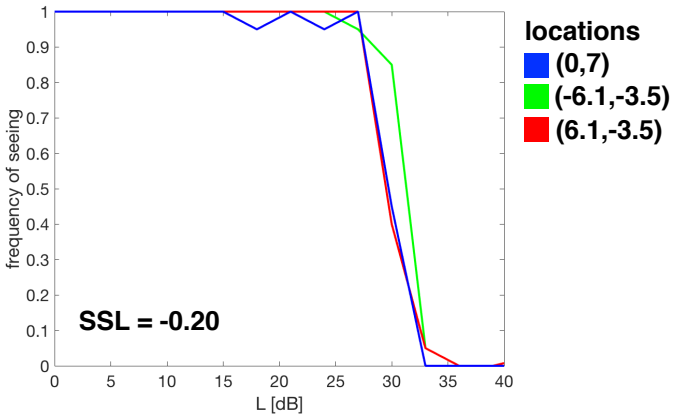


Individual results of false responses to catch trials and all related parameters

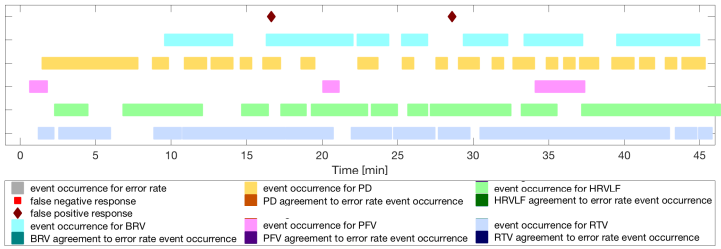
subject ID	**097**
age	**23**
gender	**f**
ESS score	**9**
total no. of errors	**2**

sleep disorders:
none

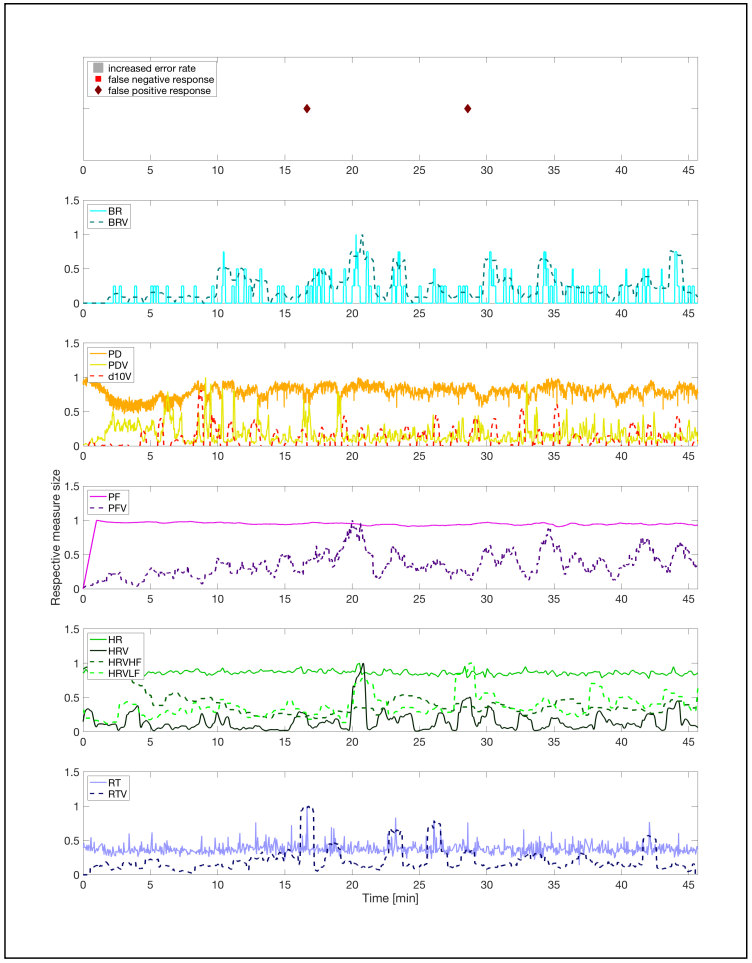
FOS curve



Agreement plot



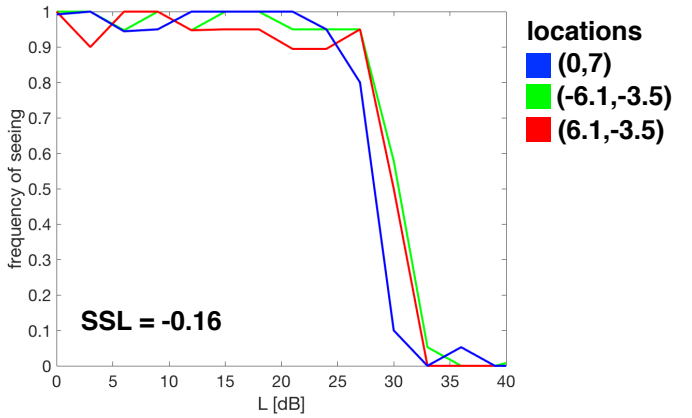
Individual results of false responses to catch trials and all related parameters



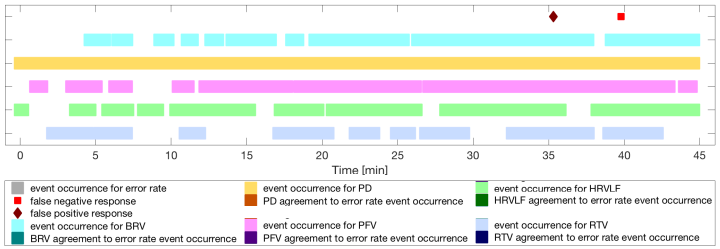
subject ID	**098**
age	**26**
gender	**f**
ESS score	**10**
total no. of errors	**2**

sleep disorders:
none

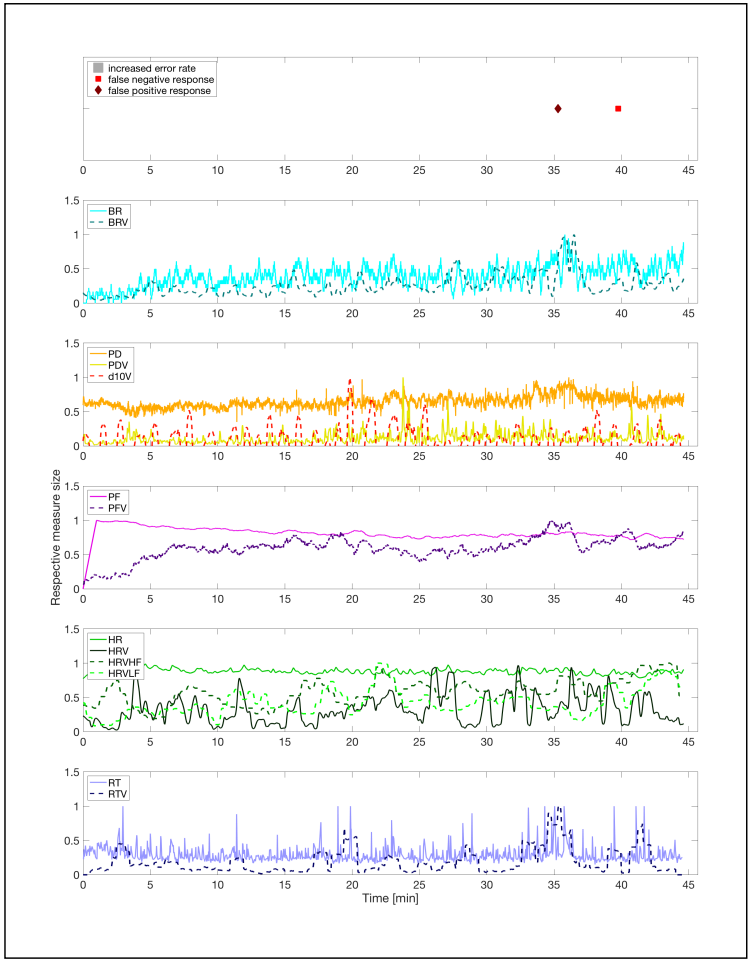
FOS curve



Agreement plot



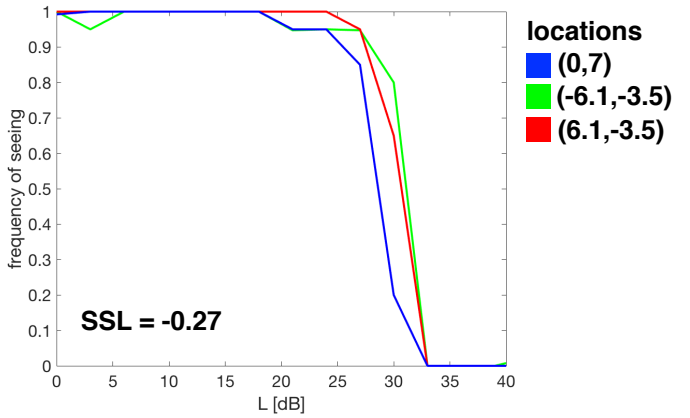
Individual results of false responses to catch trials and all related parameters



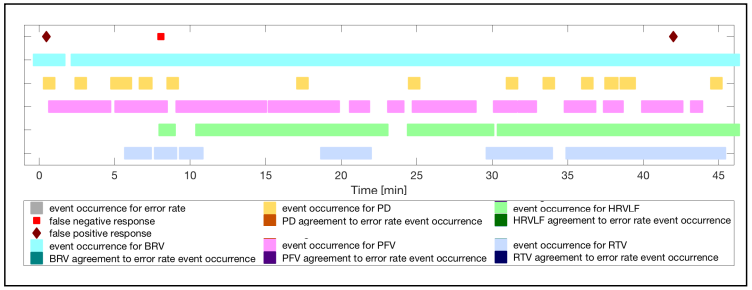
subject ID	**099**
age	**23**
gender	**m**
ESS score	**10**
total no. of errors	**3**

sleep disorders:
none

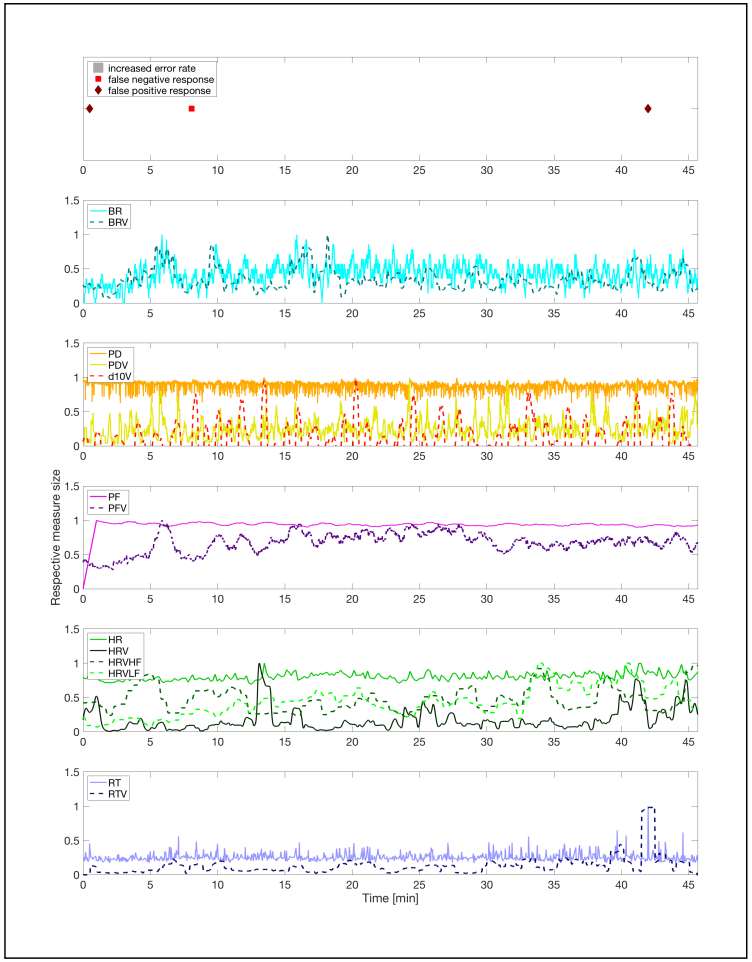
FOS curve



Agreement plot



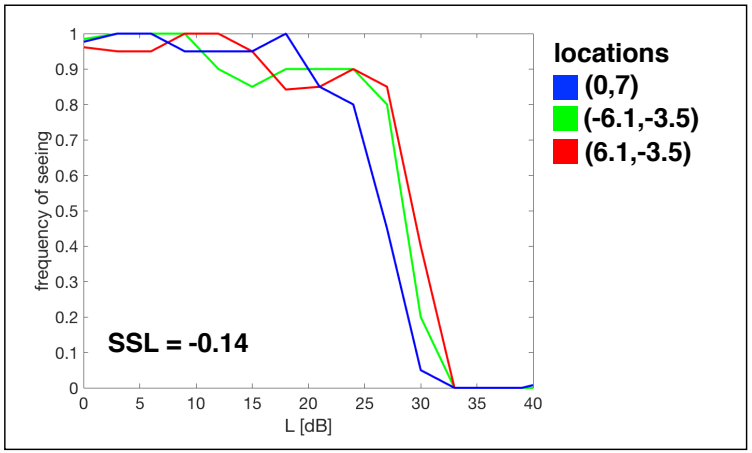
Individual results of false responses to catch trials and all related parameters



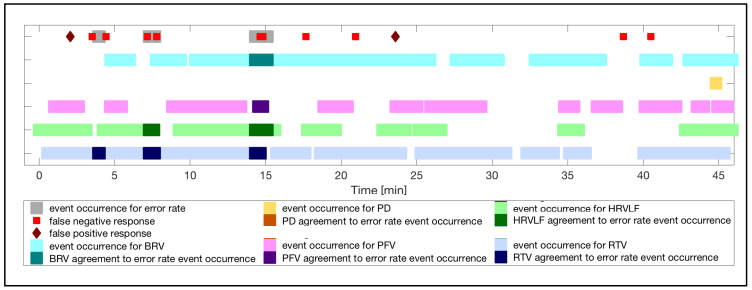
subject ID	**100**
age	**26**
gender	**f**
ESS score	**3**
total no. of errors	**12**

sleep disorders:
none

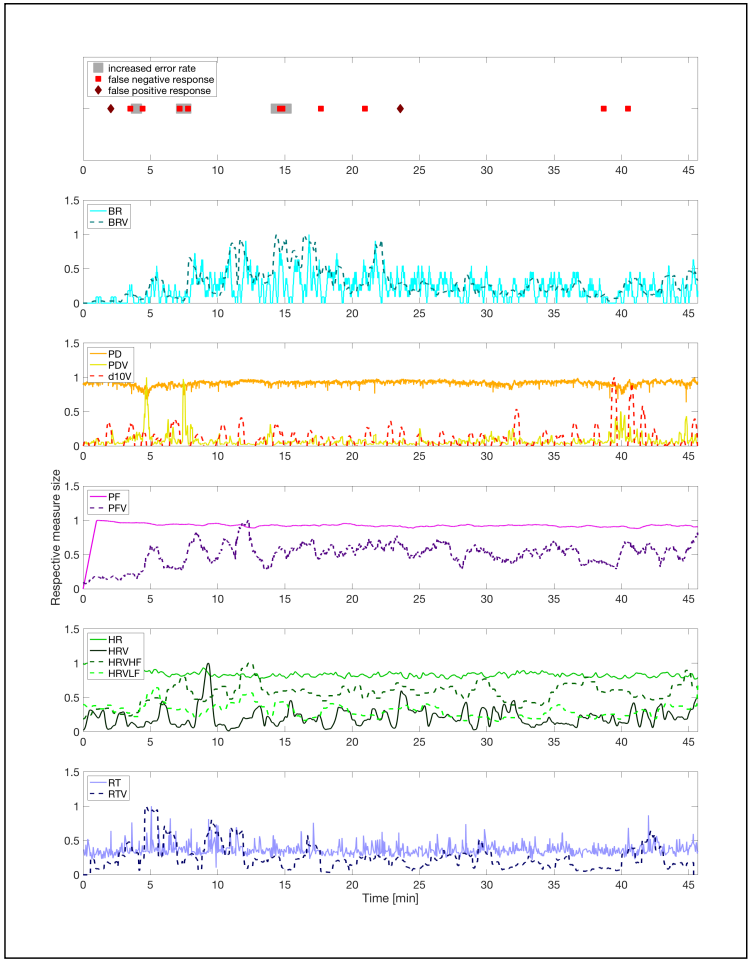
FOS curve



Agreement plot



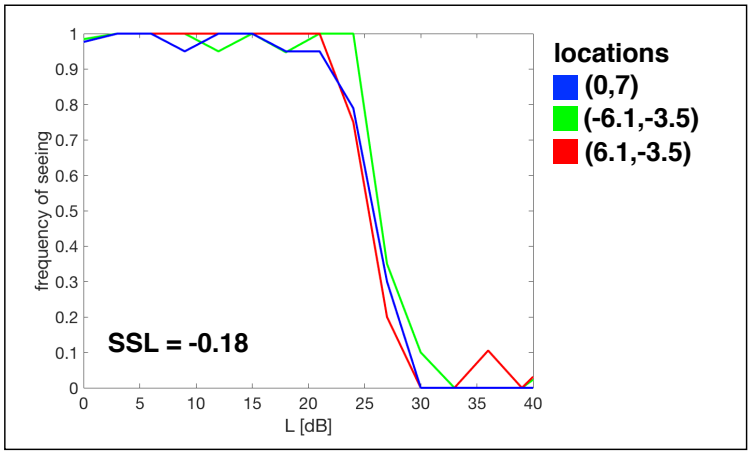
Individual results of false responses to catch trials and all related parameters



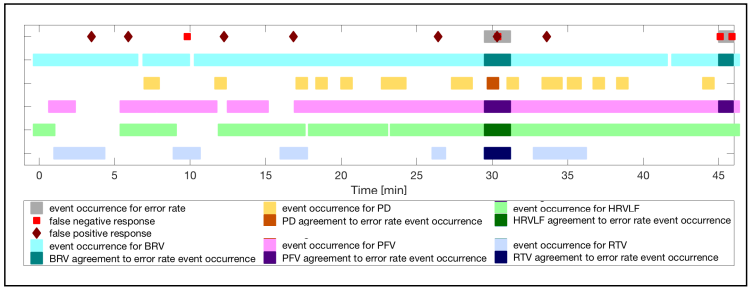
subject ID	**101**
age	**28**
gender	**m**
ESS score	**6**
total no. of errors	**9**

sleep disorders:
none

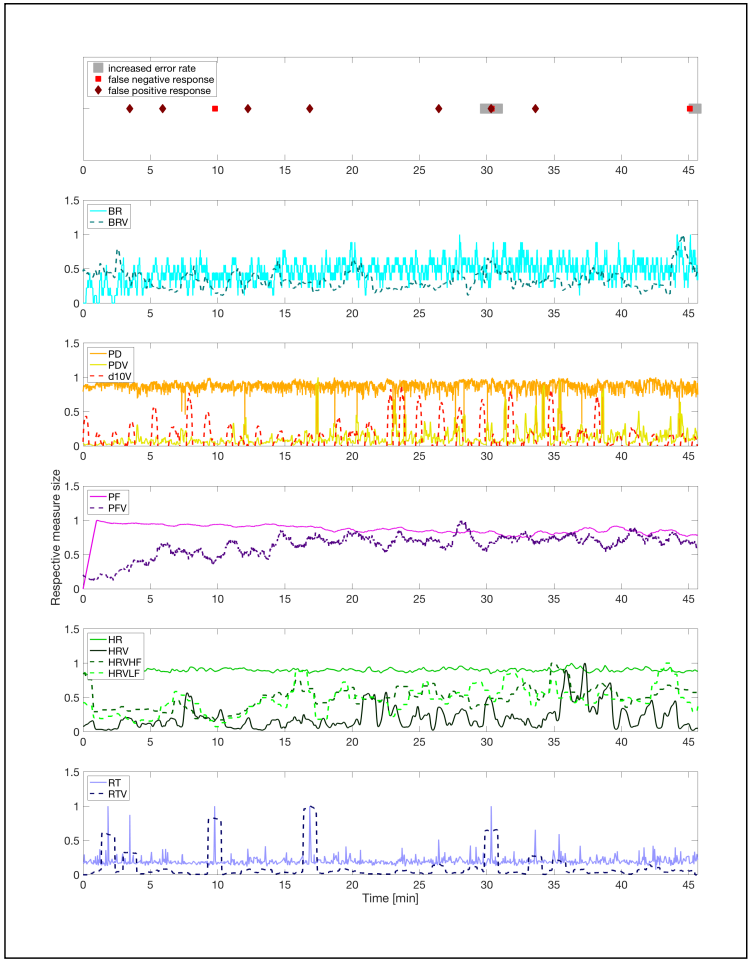
FOS curve



Agreement plot



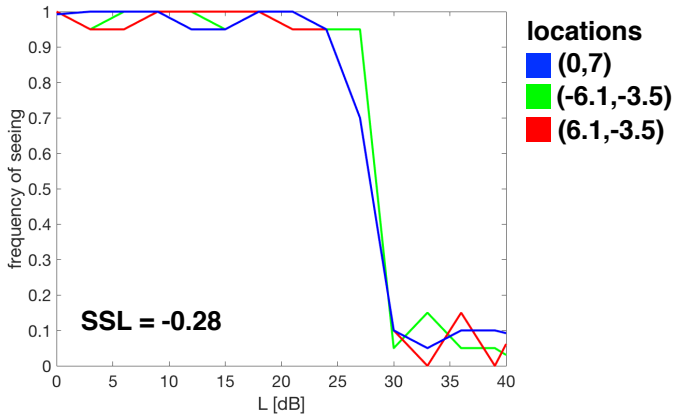
Individual results of false responses to catch trials and all related parameters



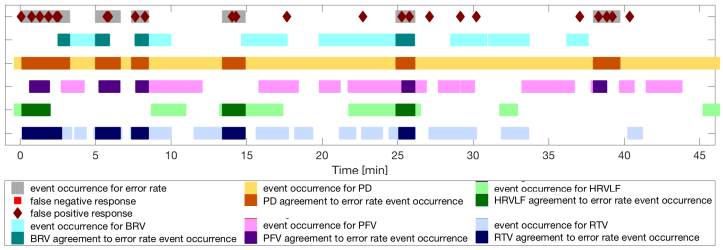
subject ID	**102**
age	**74**
gender	**f**
ESS score	**5**
total no. of errors	**24**

sleep disorders:
none

FOS curve



Agreement plot

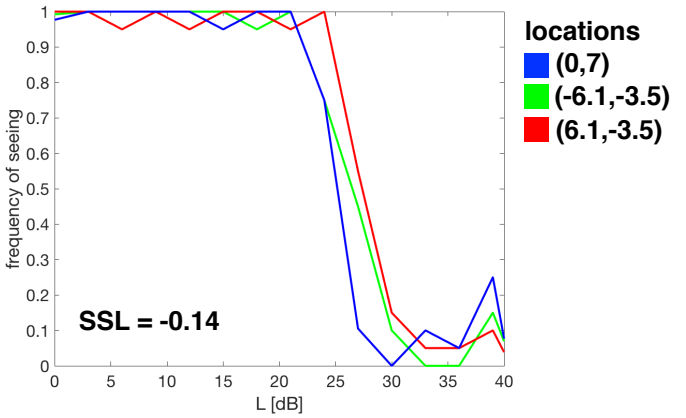


Individual results of false responses to catch trials and all related parameters

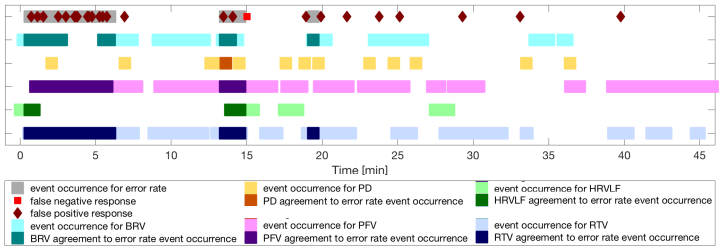
subject ID	**103**
age	**76**
gender	**m**
ESS score	**6**
total no. of errors	**27**

sleep disorders:
none

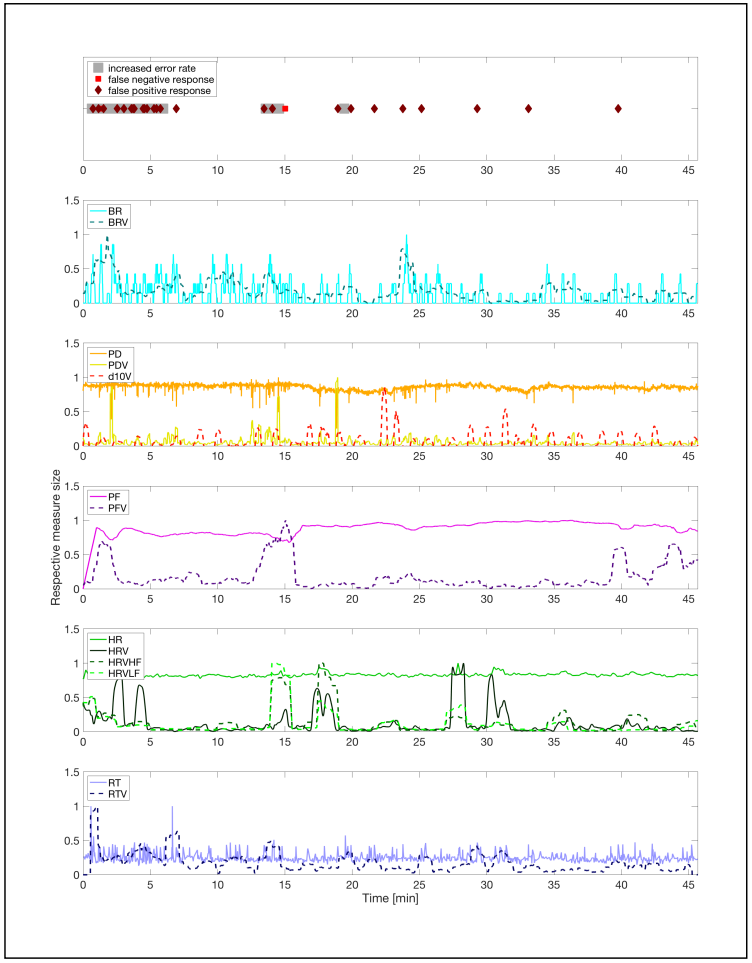
FOS curve



Agreement plot



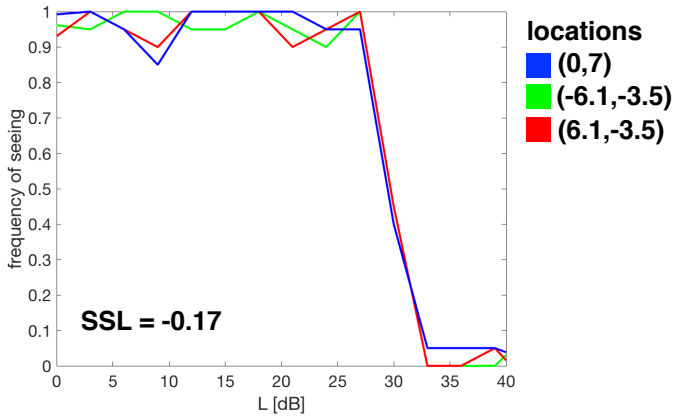
Individual results of false responses to catch trials and all related parameters



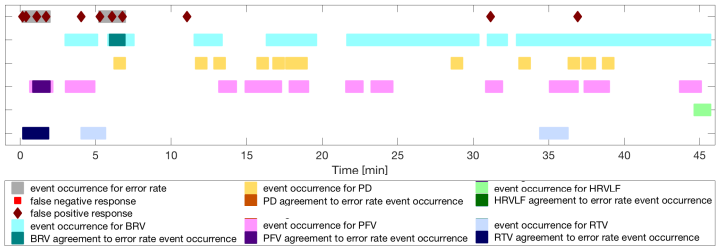
subject ID	**104**
age	**52**
gender	**f**
ESS score	**7**
total no. of errors	**11**

sleep disorders:
none

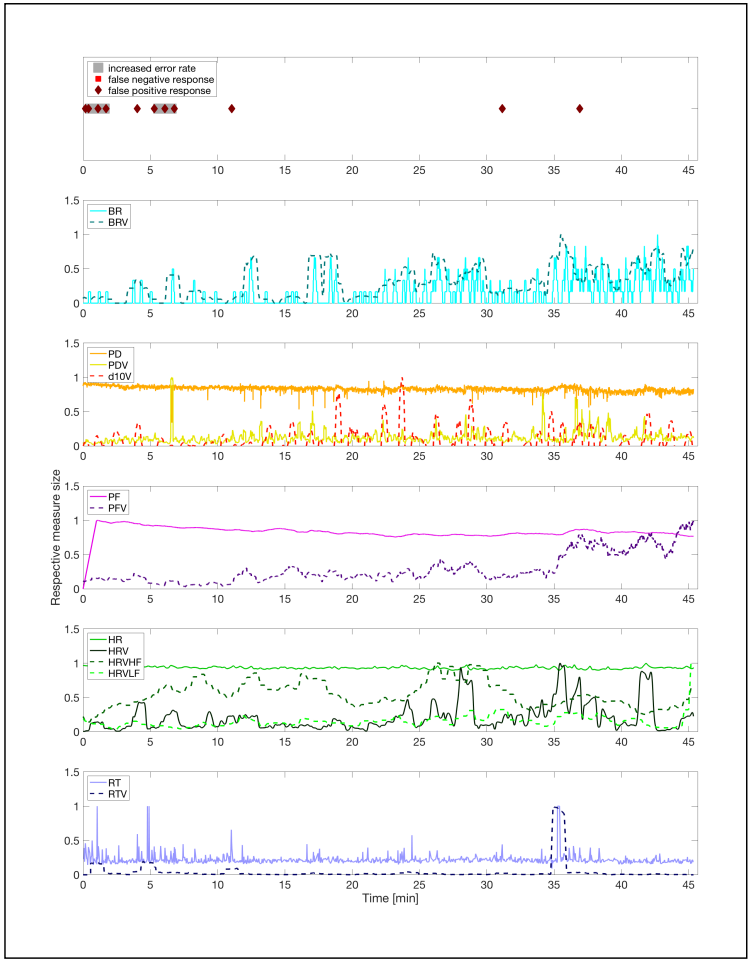
FOS curve



Agreement plot



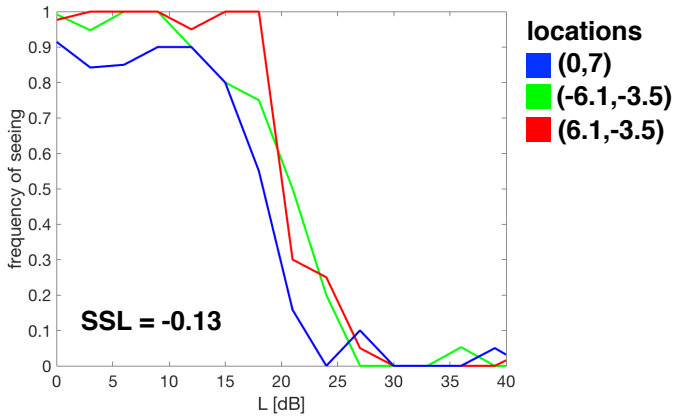
Individual results of false responses to catch trials and all related parameters



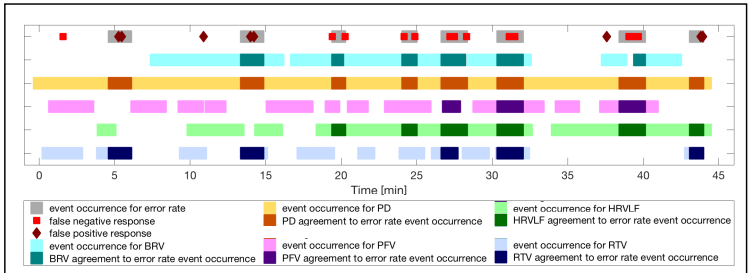
subject ID	**105**
age	**73**
gender	**f**
ESS score	**1**
total no. of errors	**22**

sleep disorders:
none

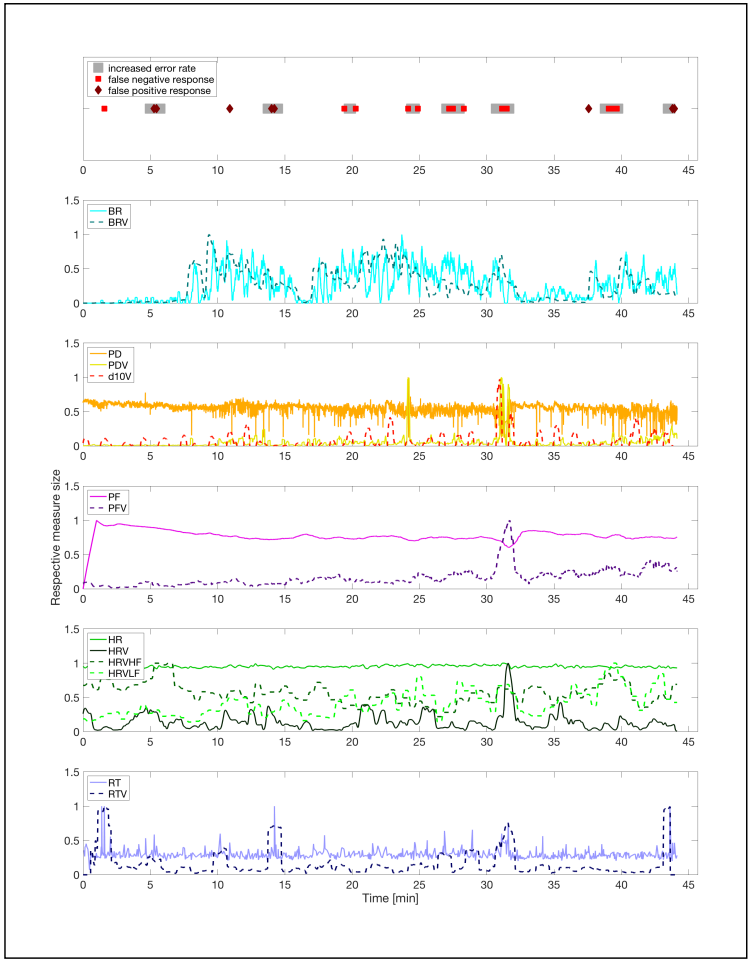
FOS curve



Agreement plot



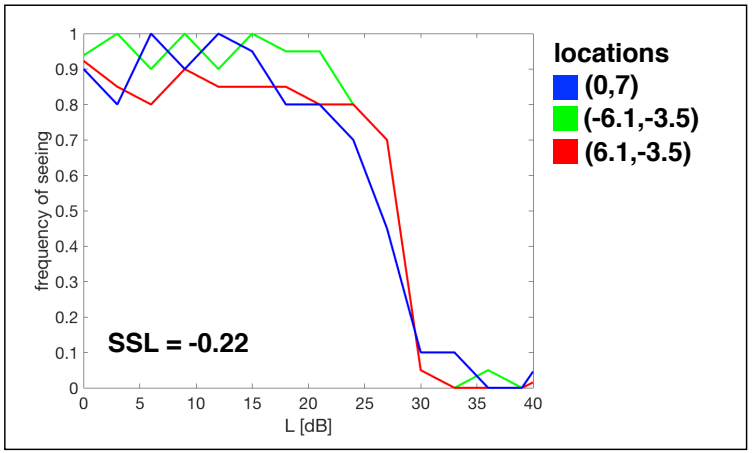
Individual results of false responses to catch trials and all related parameters



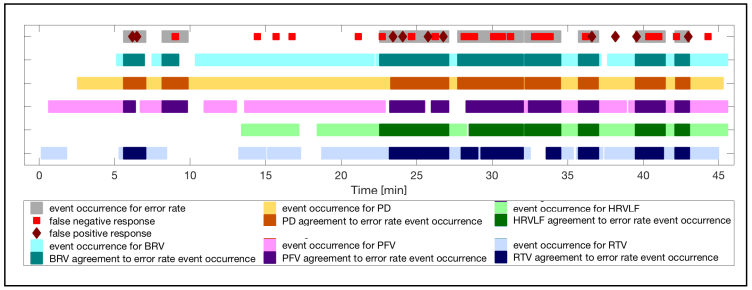
subject ID	**106**
age	**58**
gender	**m**
ESS score	**11**
total no. of errors	**44**

sleep disorders:
none

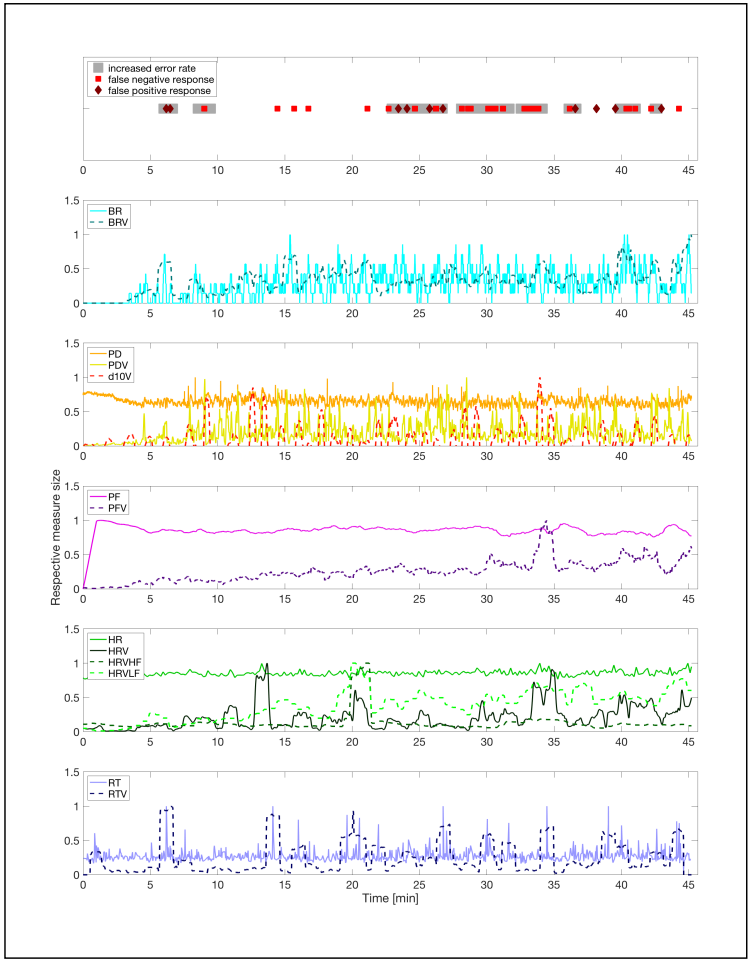
FOS curve



Agreement plot



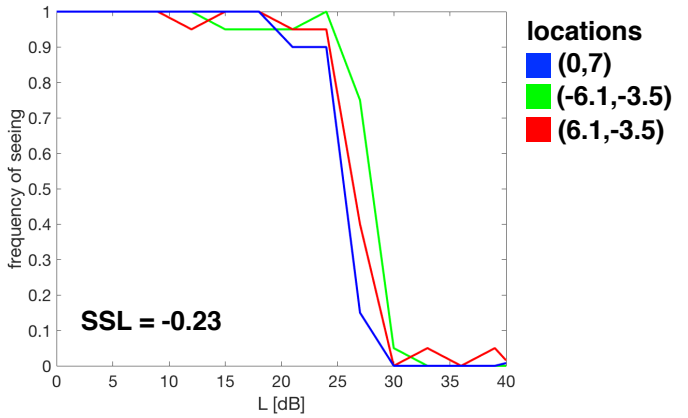
Individual results of false responses to catch trials and all related parameters



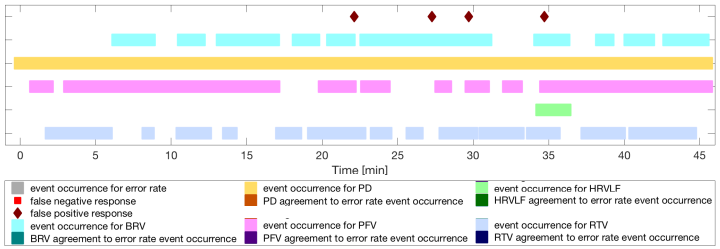
subject ID	**107**
age	**78**
gender	**m**
ESS score	**6**
total no. of errors	**4**

sleep disorders:
none

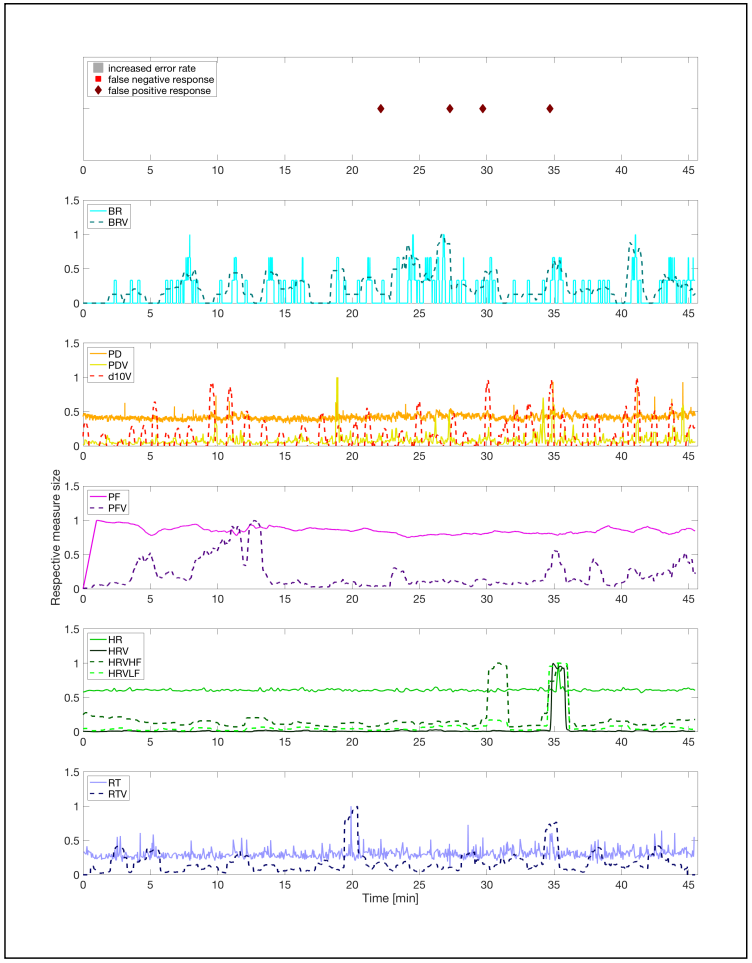
FOS curve



Agreement plot



Individual results of false responses to catch trials and all related parameters

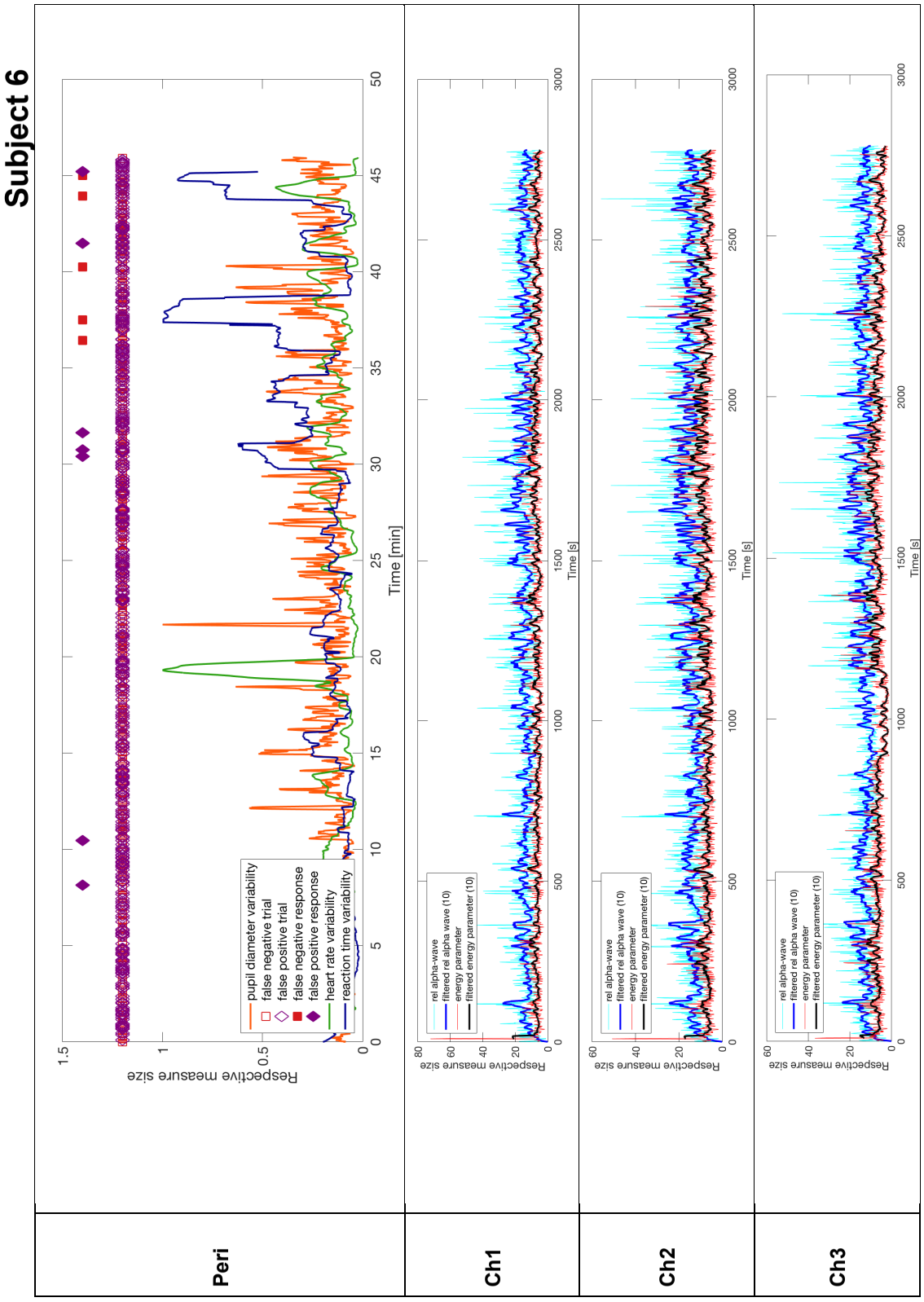


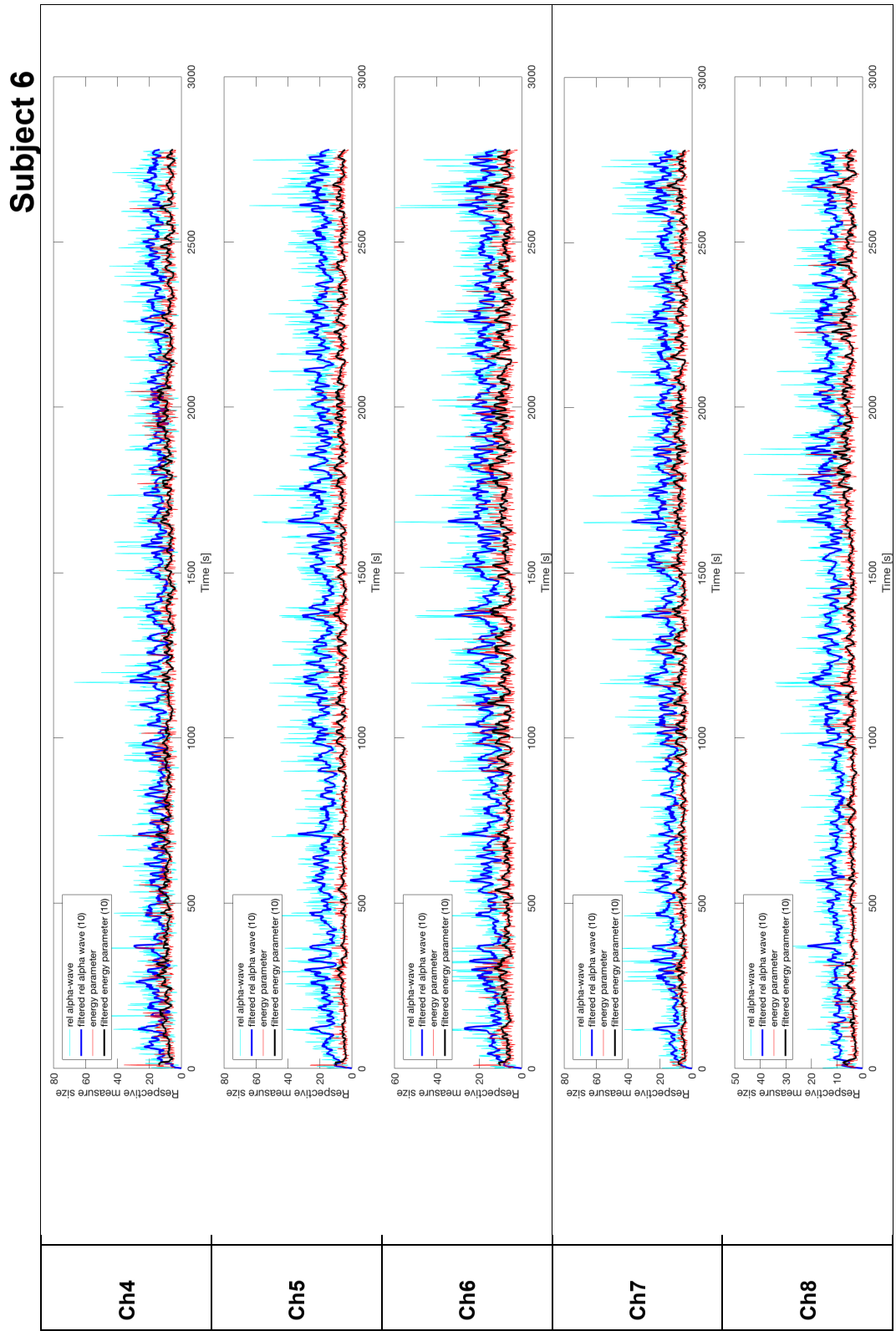
G Results of EEG data evaluation for *pilot study 2*

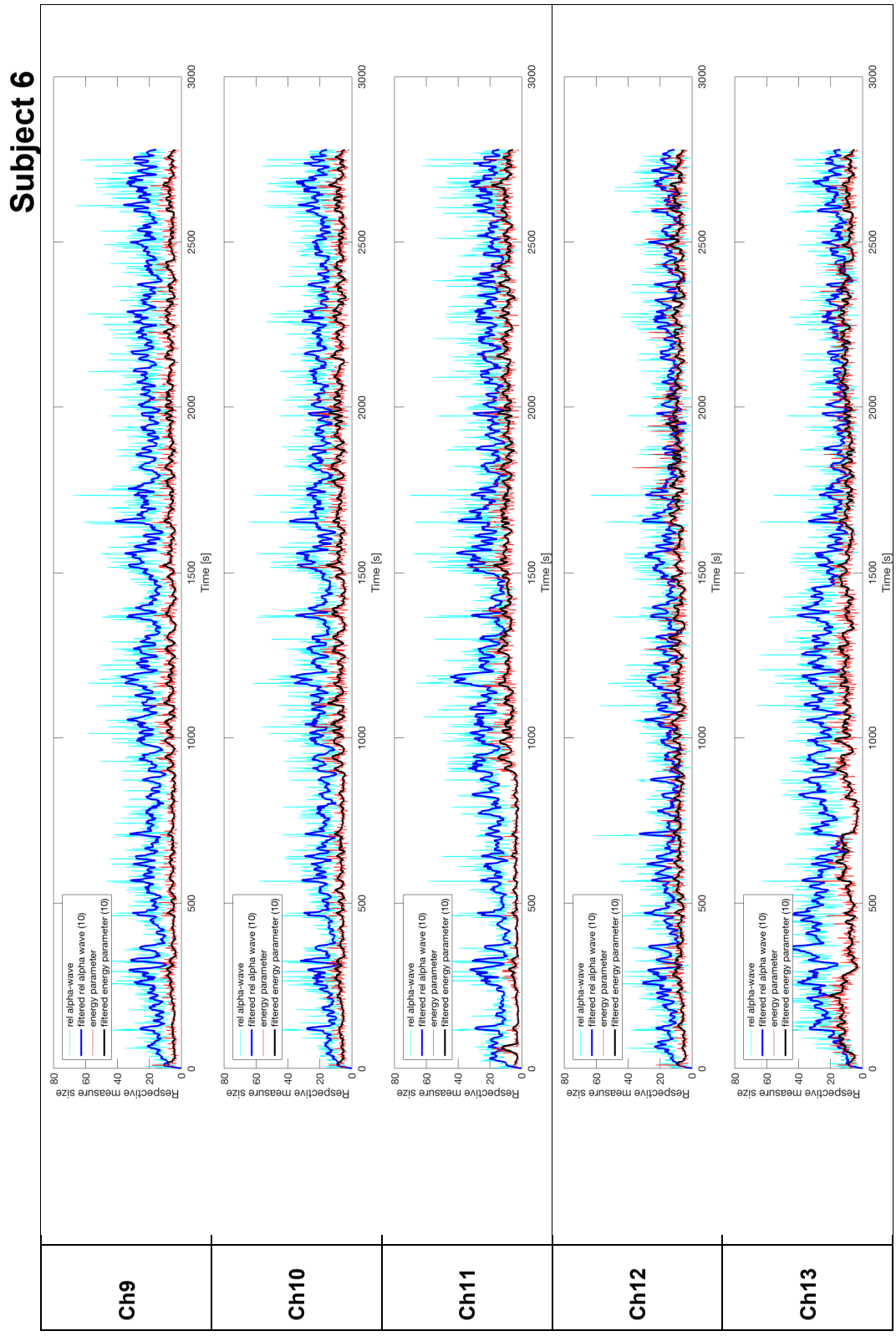
Results of EEG data evaluation for *pilot study 2* are attached on the next pages.

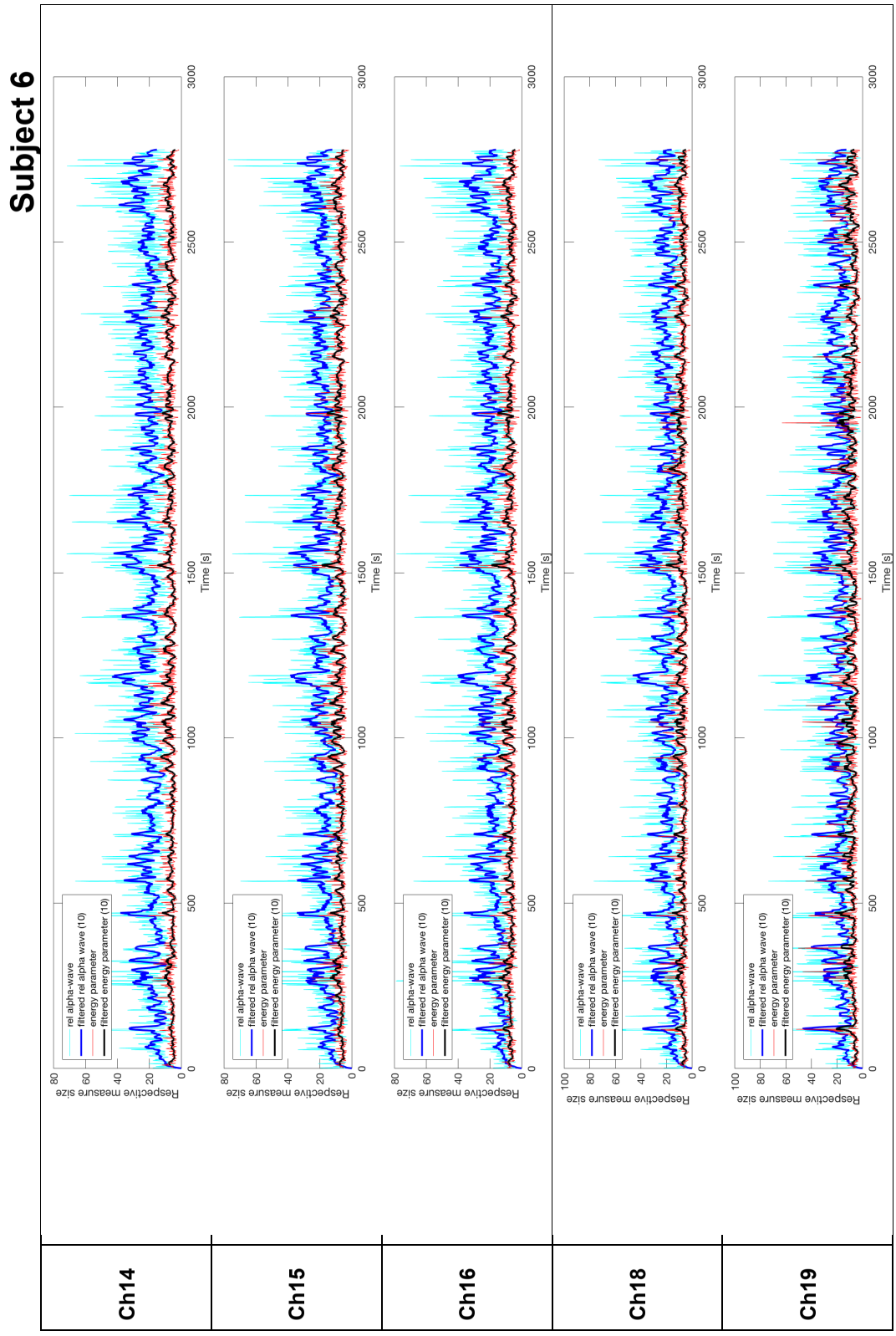
The following applies to all images:

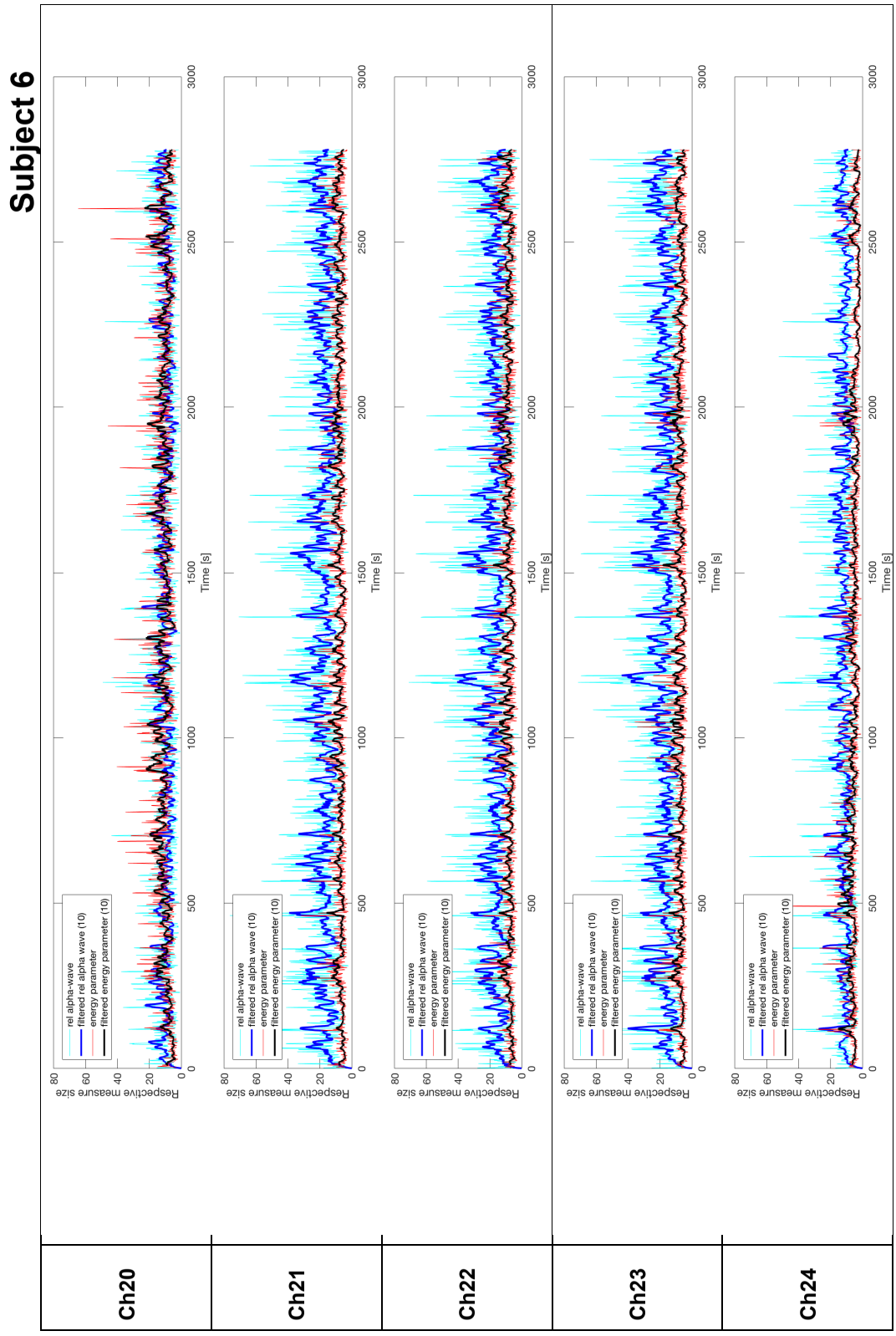
- Peri: perimetric data
- Ch: EEG channel number
- If filters were applied, data were filtered over time periods of 10 seconds, respectively

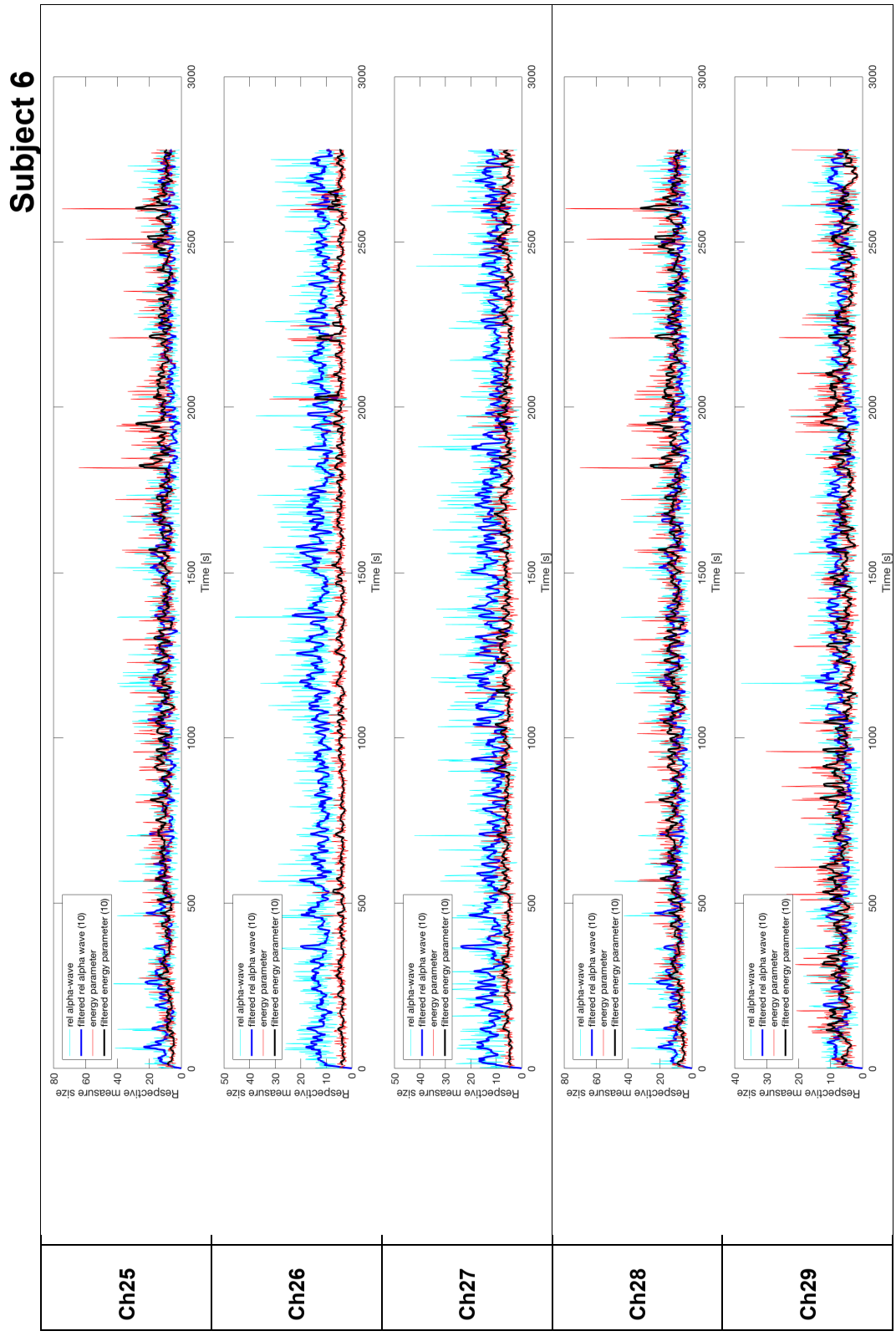

Subject 6
Peri
Ch1
Ch2
Ch3
Respective measure size
Time [min]
pupil diameter variability
false negative trial
false positive trial
false negative response
false positive response
heart rate variability
reaction time variability
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Time [s]

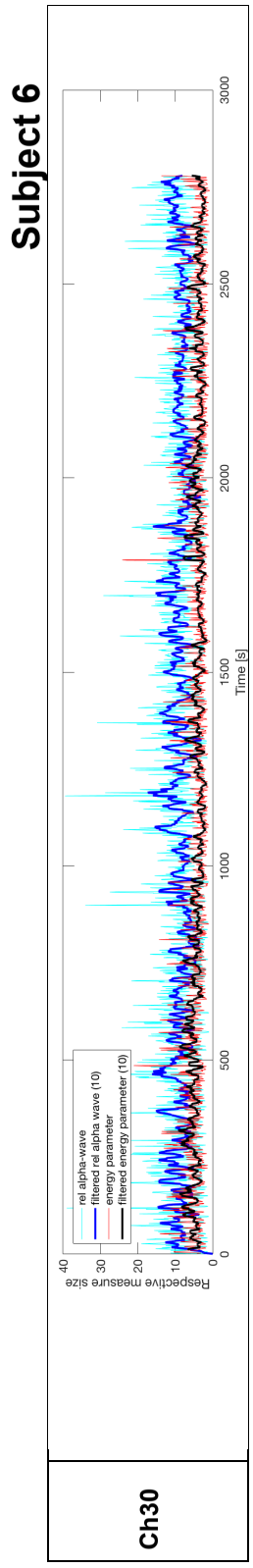

Subject 6
Ch4
Ch5
Ch6
Ch7
Ch8
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]

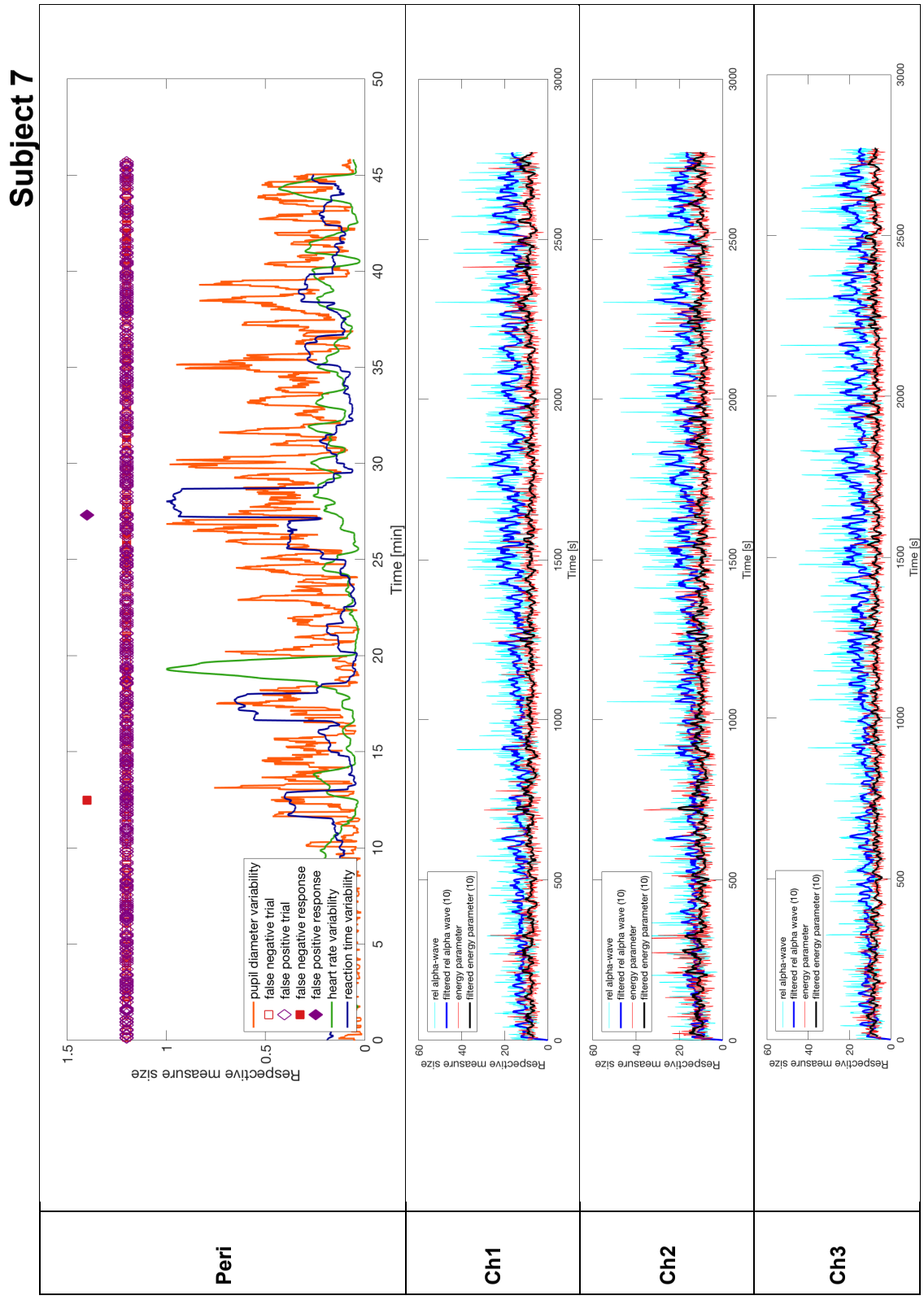

Subject 6
Ch9
Ch10
Ch11
Ch12
Ch13
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]
0
20
40
60
80
0
500
1000
1500
2000
2500
3000

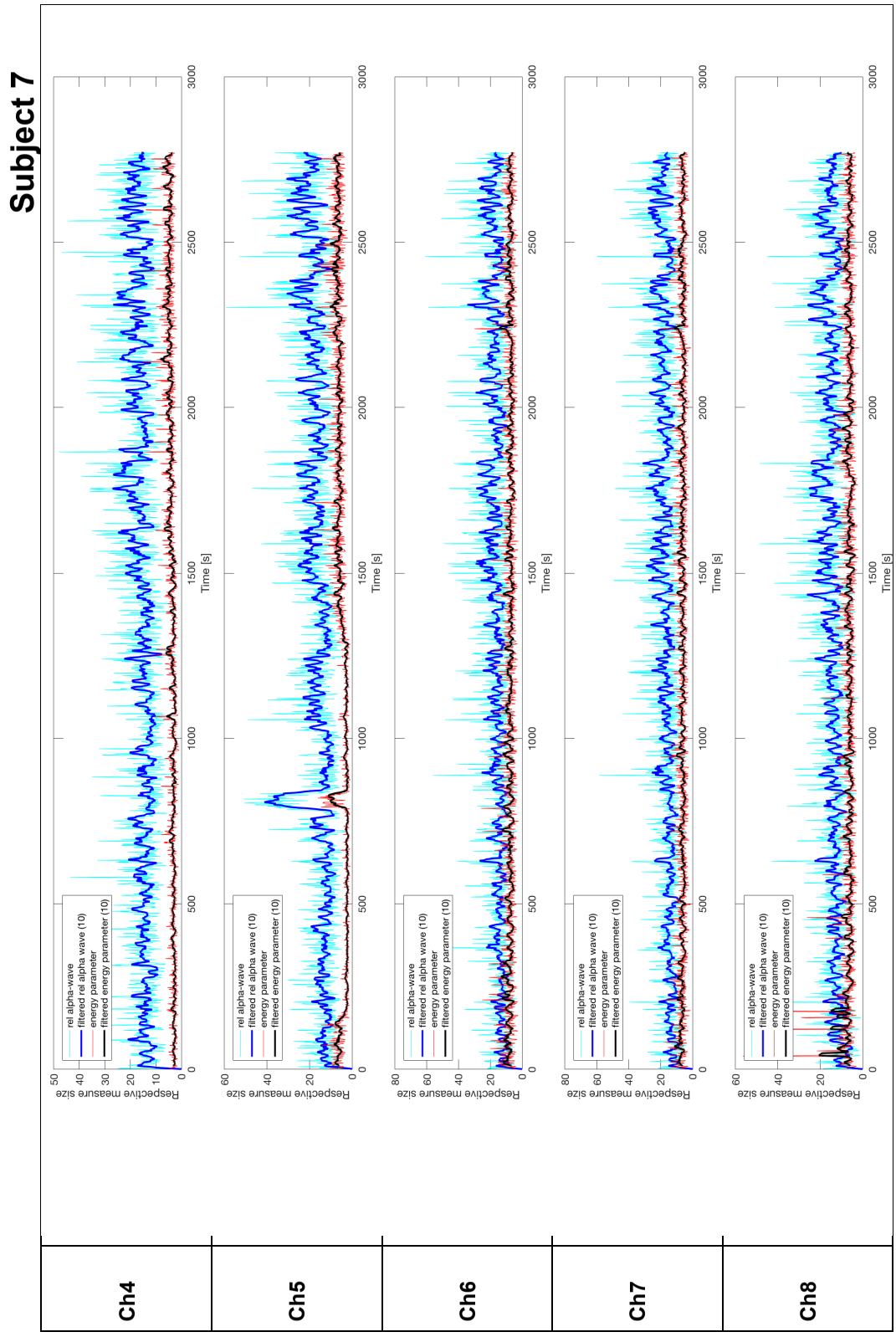

Subject 6
Ch14
Ch15
Ch16
Ch18
Ch19
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]

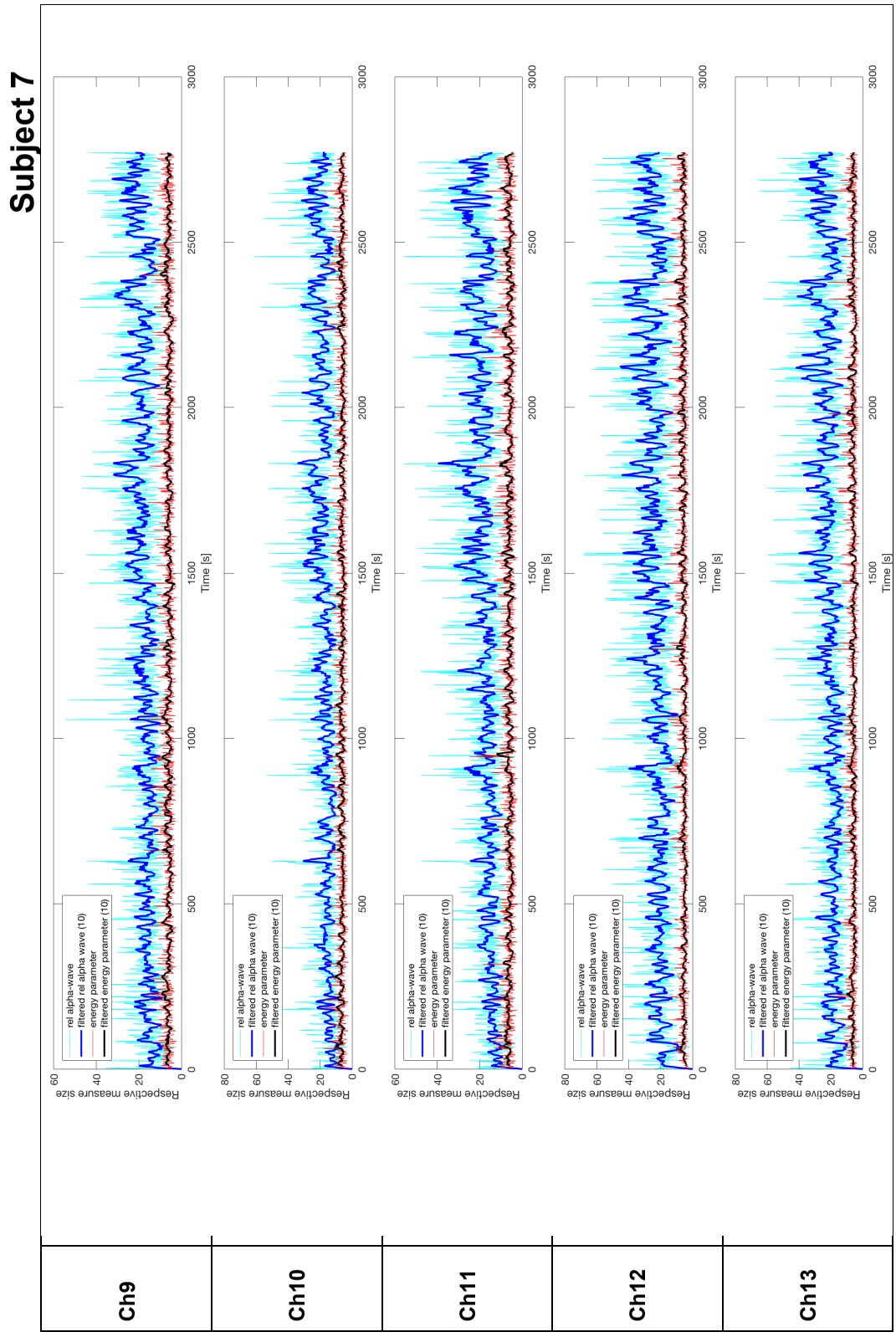

Subject 6
Ch20
Ch21
Ch22
Ch23
Ch24
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]
0
20
40
60
80
0
500
1000
1500
2000
2500
3000

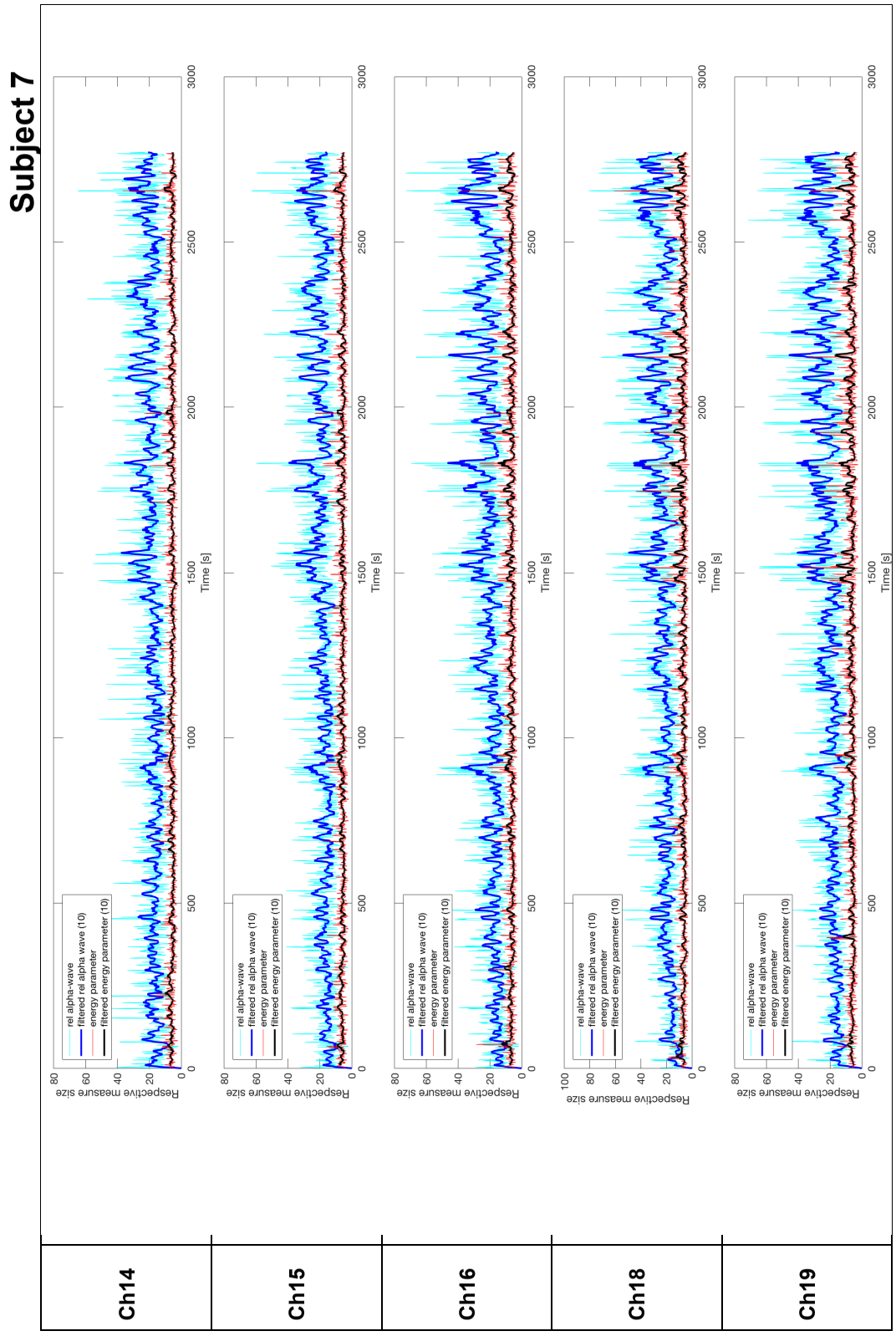

Subject 6
Ch25
Ch26
Ch27
Ch28
Ch29
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]

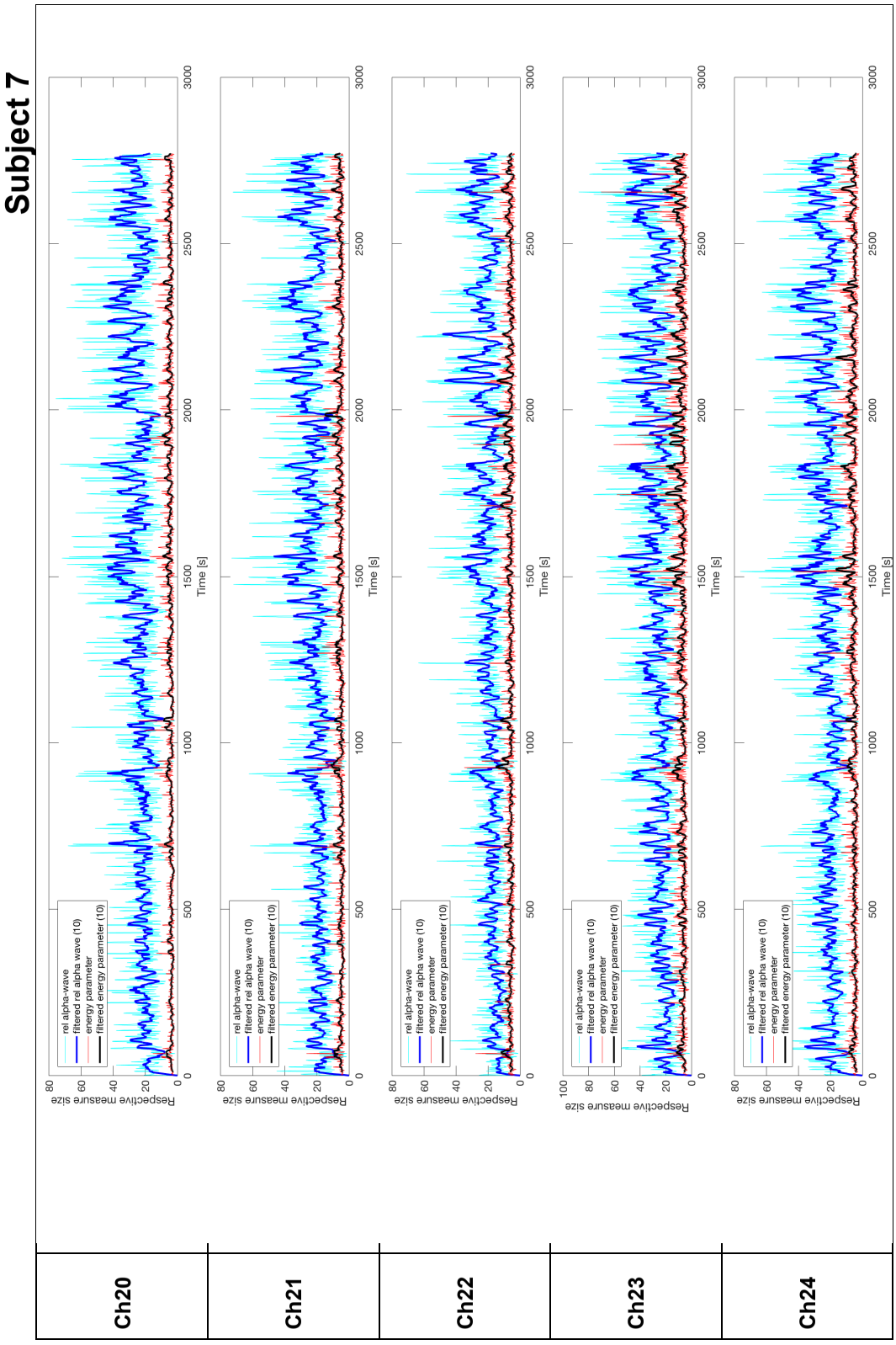

Subject 6
Ch30
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]
0
10
20
30
40
500
1000
1500
2000
2500
3000

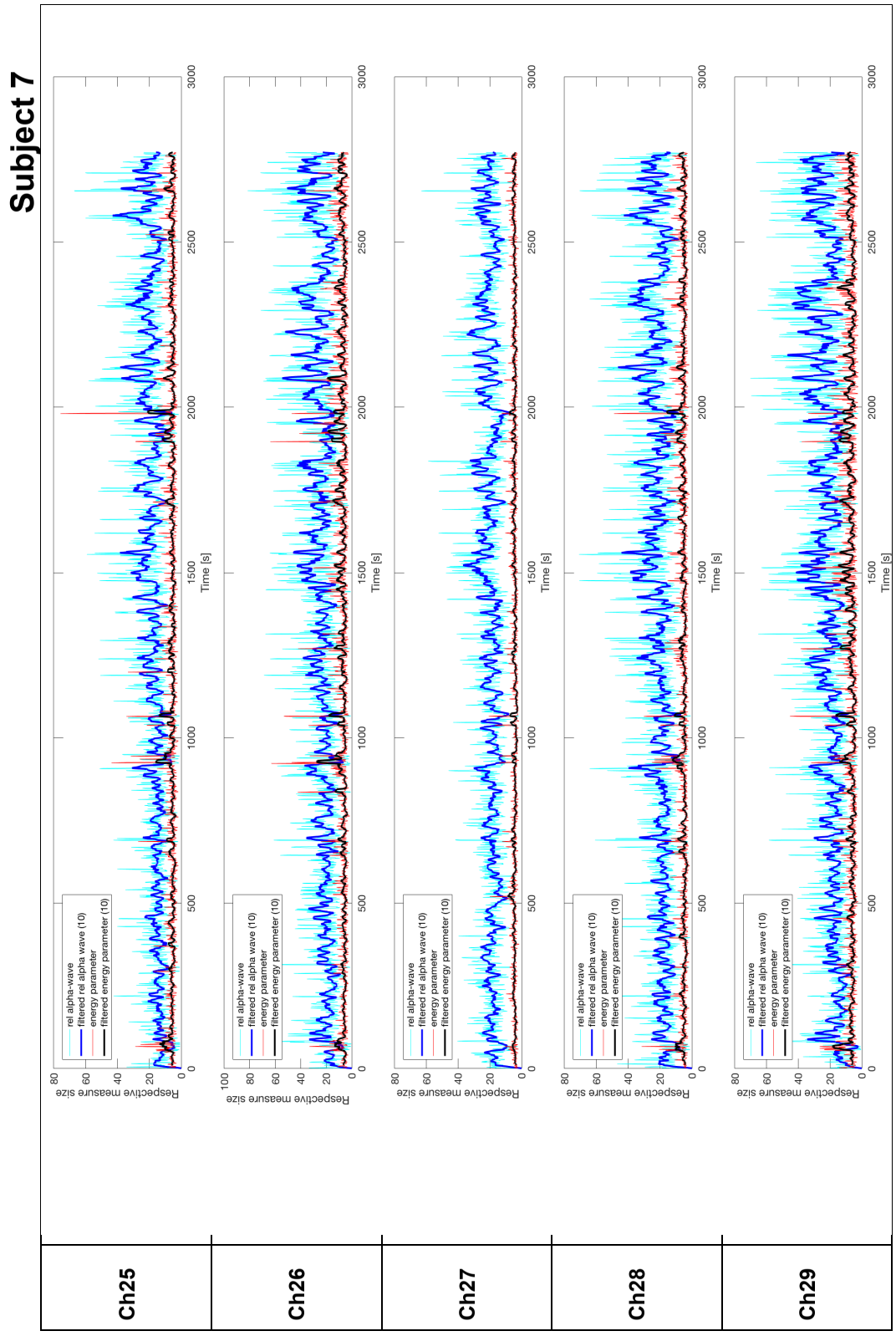

Subject 7
Peri
Ch1
Ch2
Ch3
Respective measure size
Time [min]
Time [s]
pupil diameter variability
false negative trial
false positive trial
false negative response
false positive response
heart rate variability
reaction time variability
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)

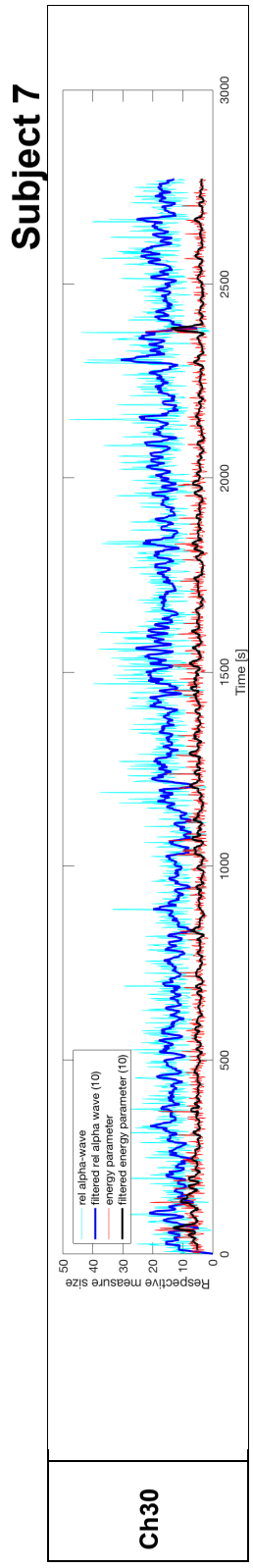

Subject 7
Ch4
Ch5
Ch6
Ch7
Ch8
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]

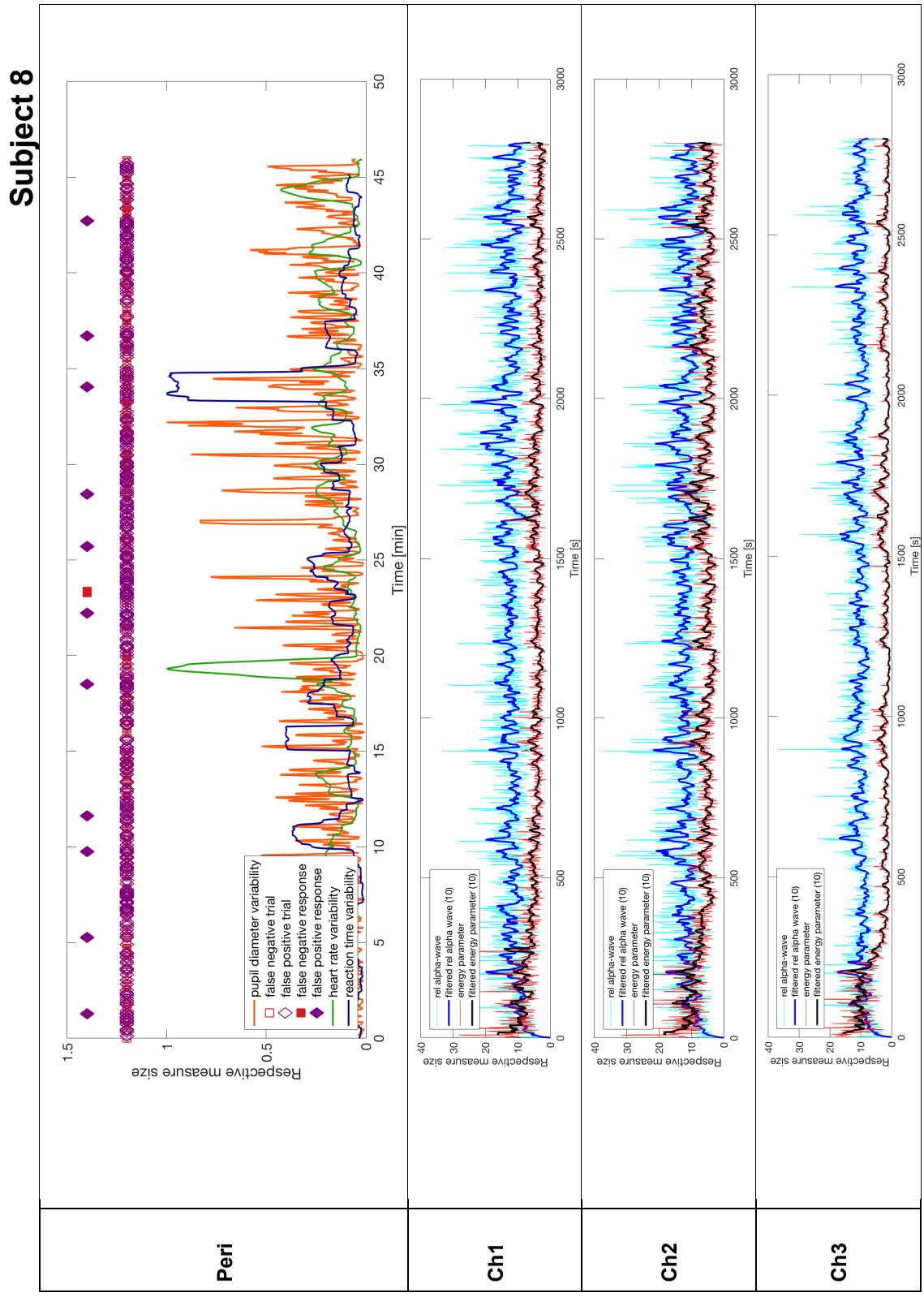

Subject 7
Ch9
Ch10
Ch11
Ch12
Ch13
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]

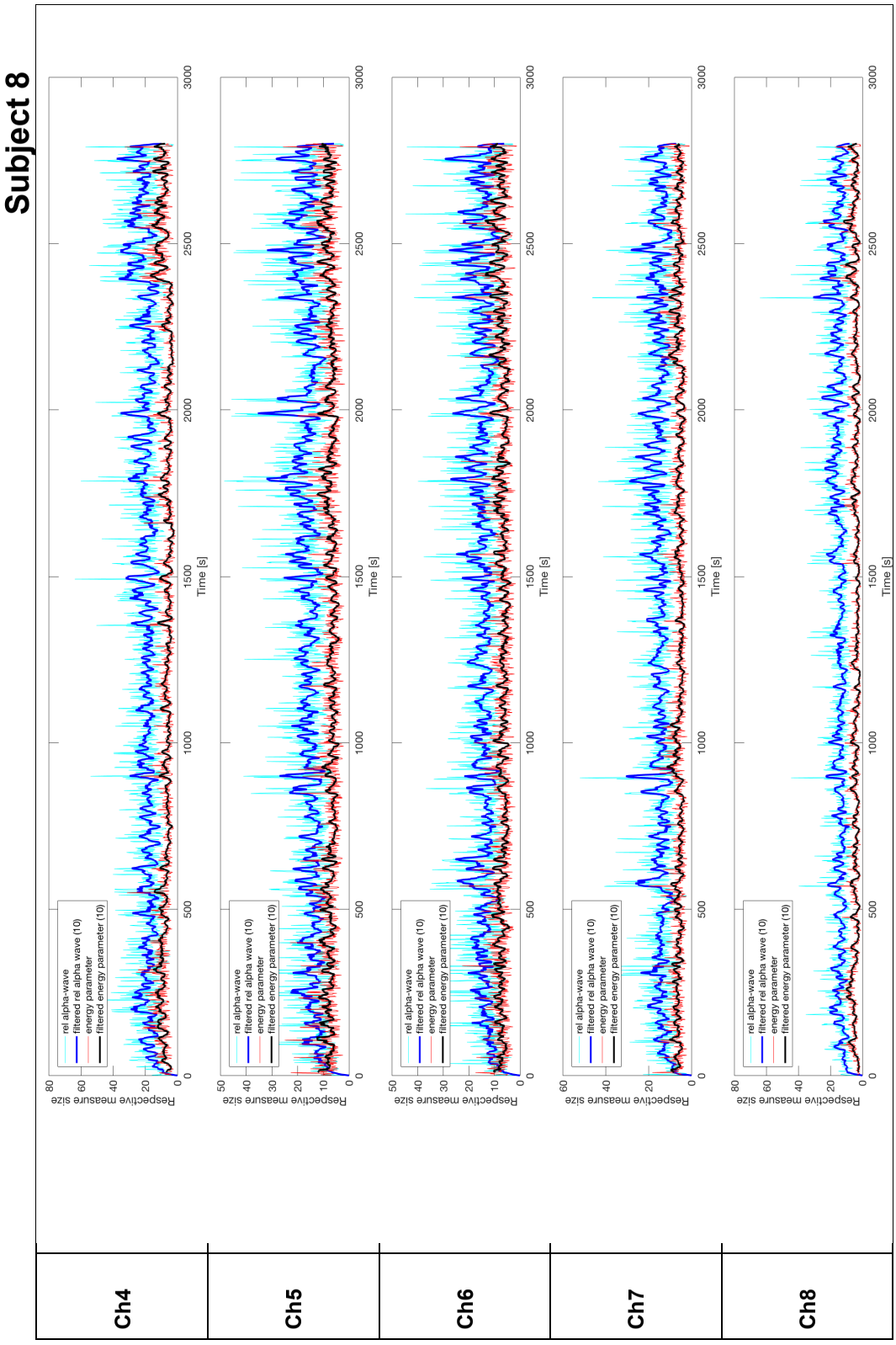

Subject 7
Ch14
Ch15
Ch16
Ch18
Ch19
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]

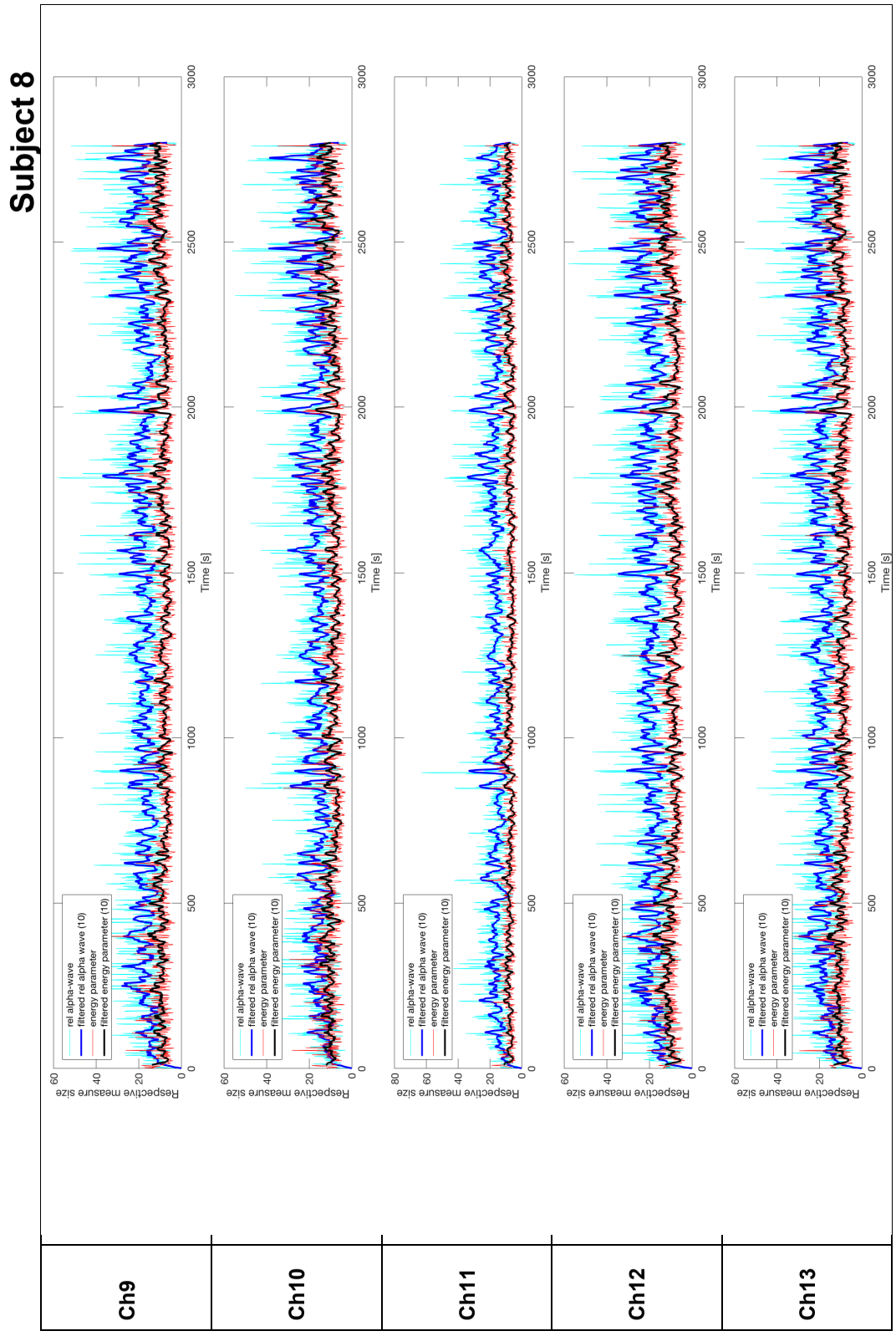

Subject 7
Ch20
Ch21
Ch22
Ch23
Ch24
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]

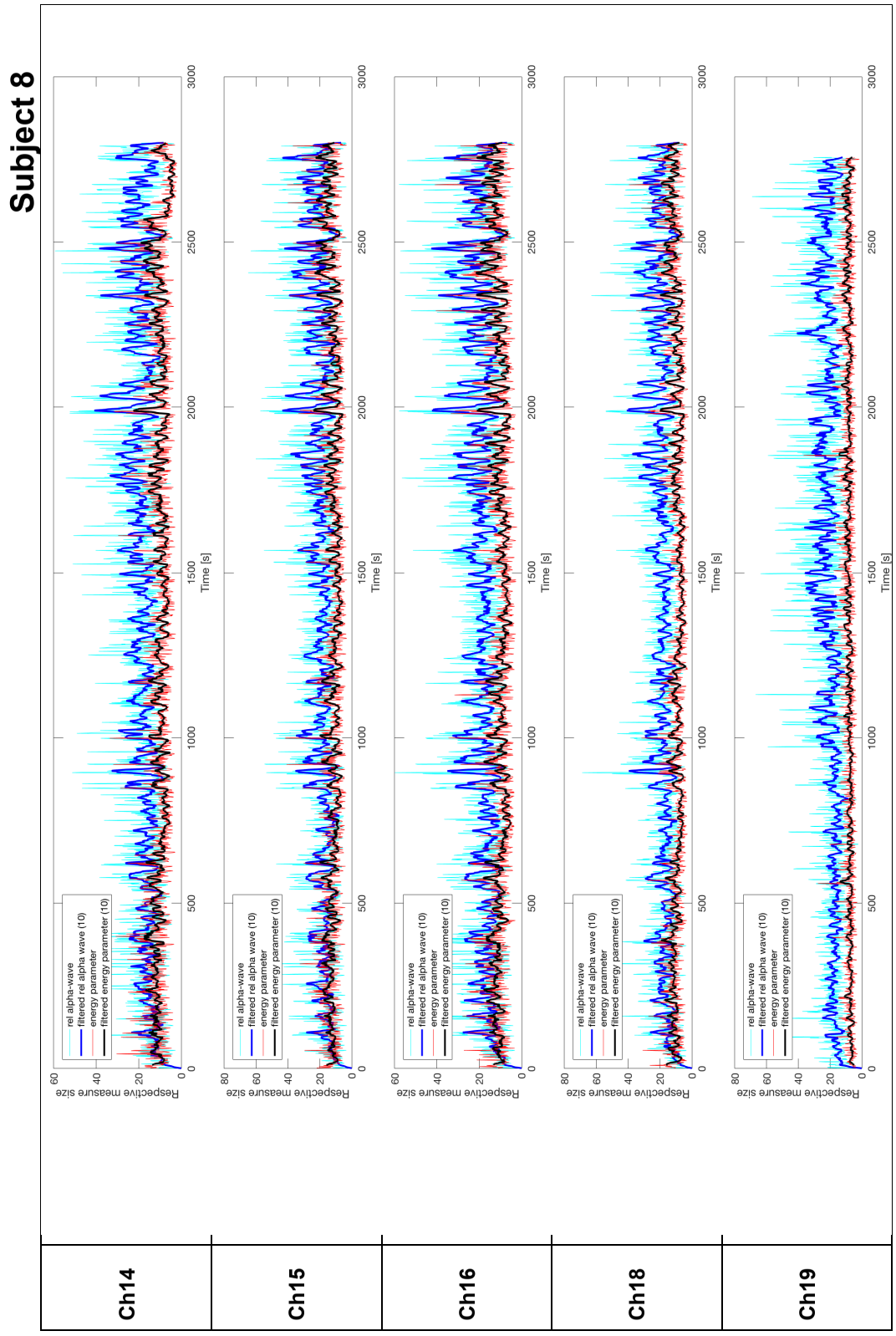

Subject 7
Ch25
Ch26
Ch27
Ch28
Ch29
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]

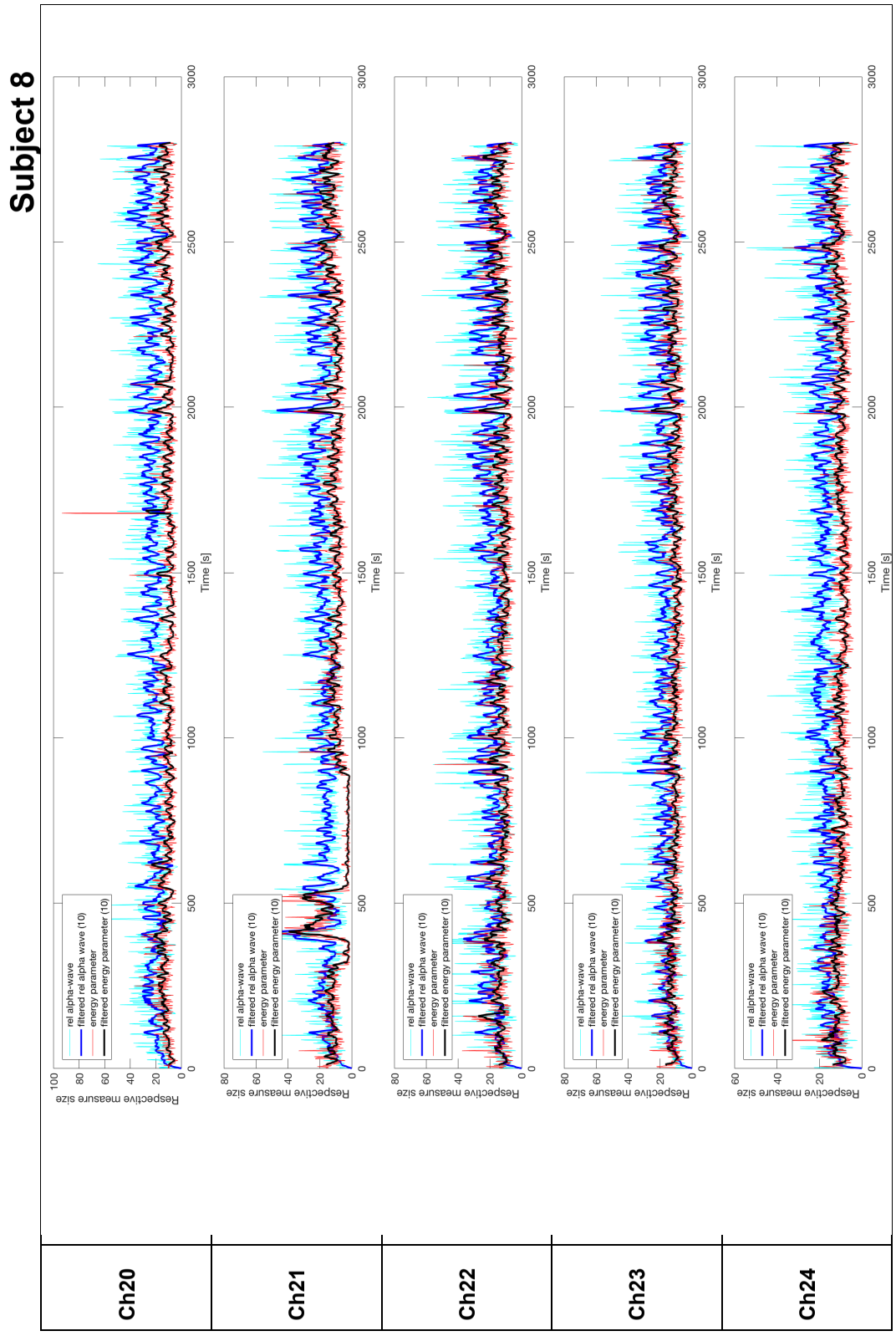

Subject 7
Ch30
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]
0
10
20
30
40
50
0
500
1000
1500
2000
2500
3000

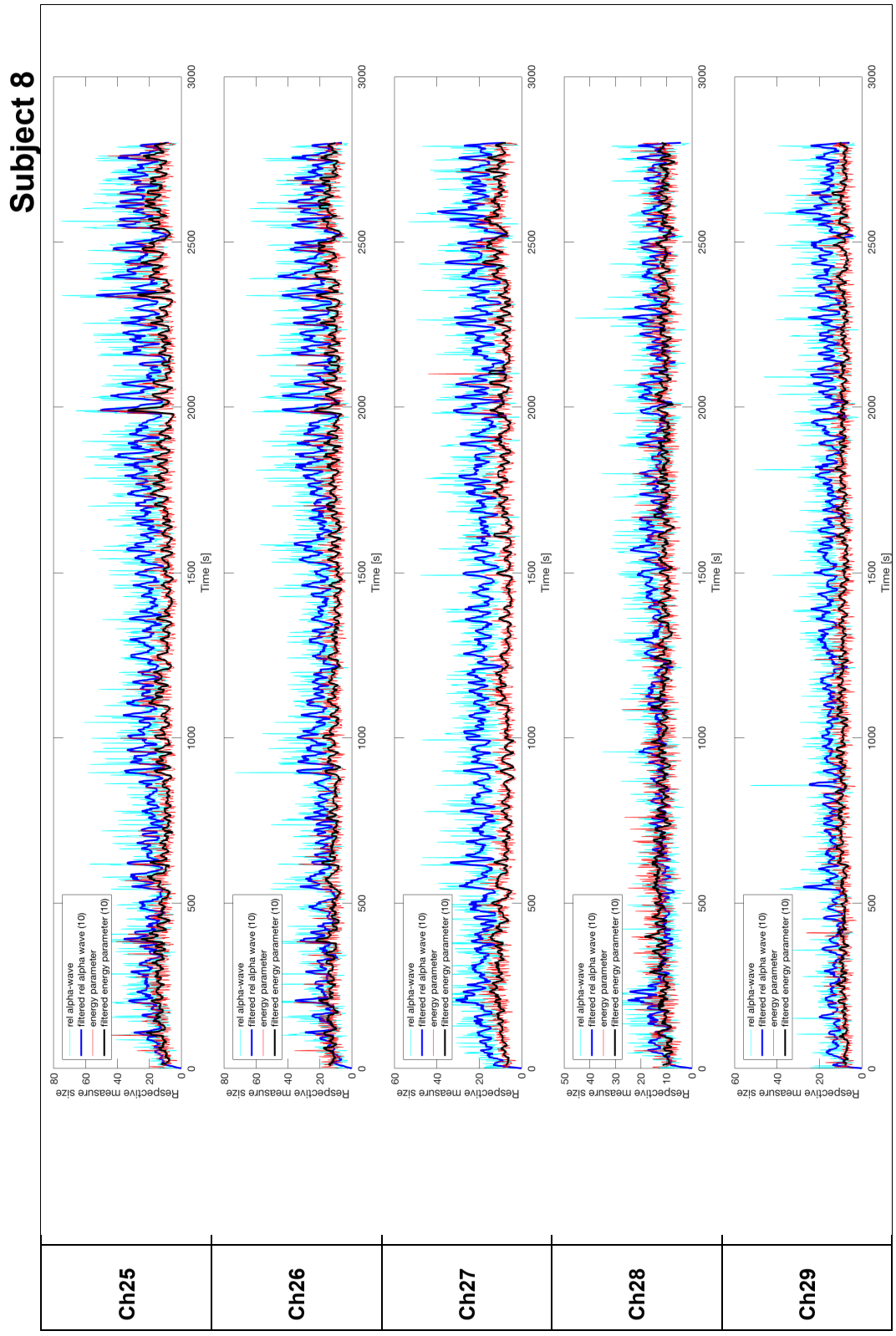

Subject 8
Peri
Ch1
Ch2
Ch3
Respective measure size
Time [min]
pupil diameter variability
false negative trial
false positive trial
false negative response
false positive response
heart rate variability
reaction time variability
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Time [s]

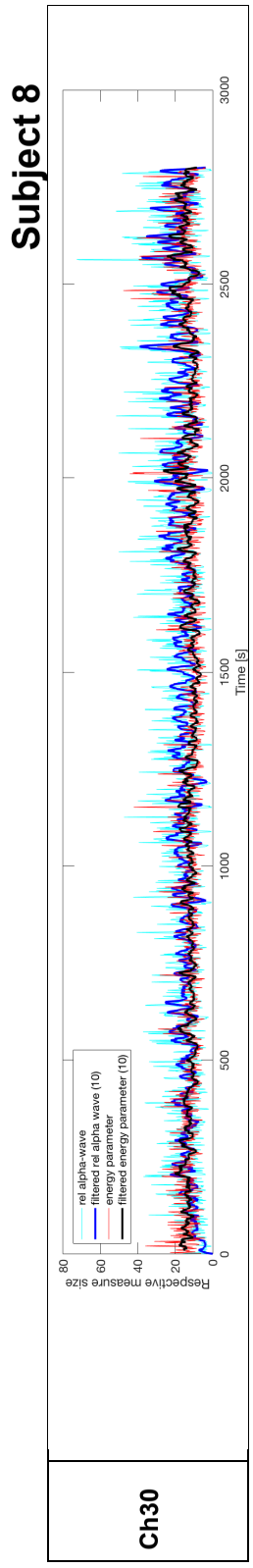

Subject 8
Ch4
Ch5
Ch6
Ch7
Ch8
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]

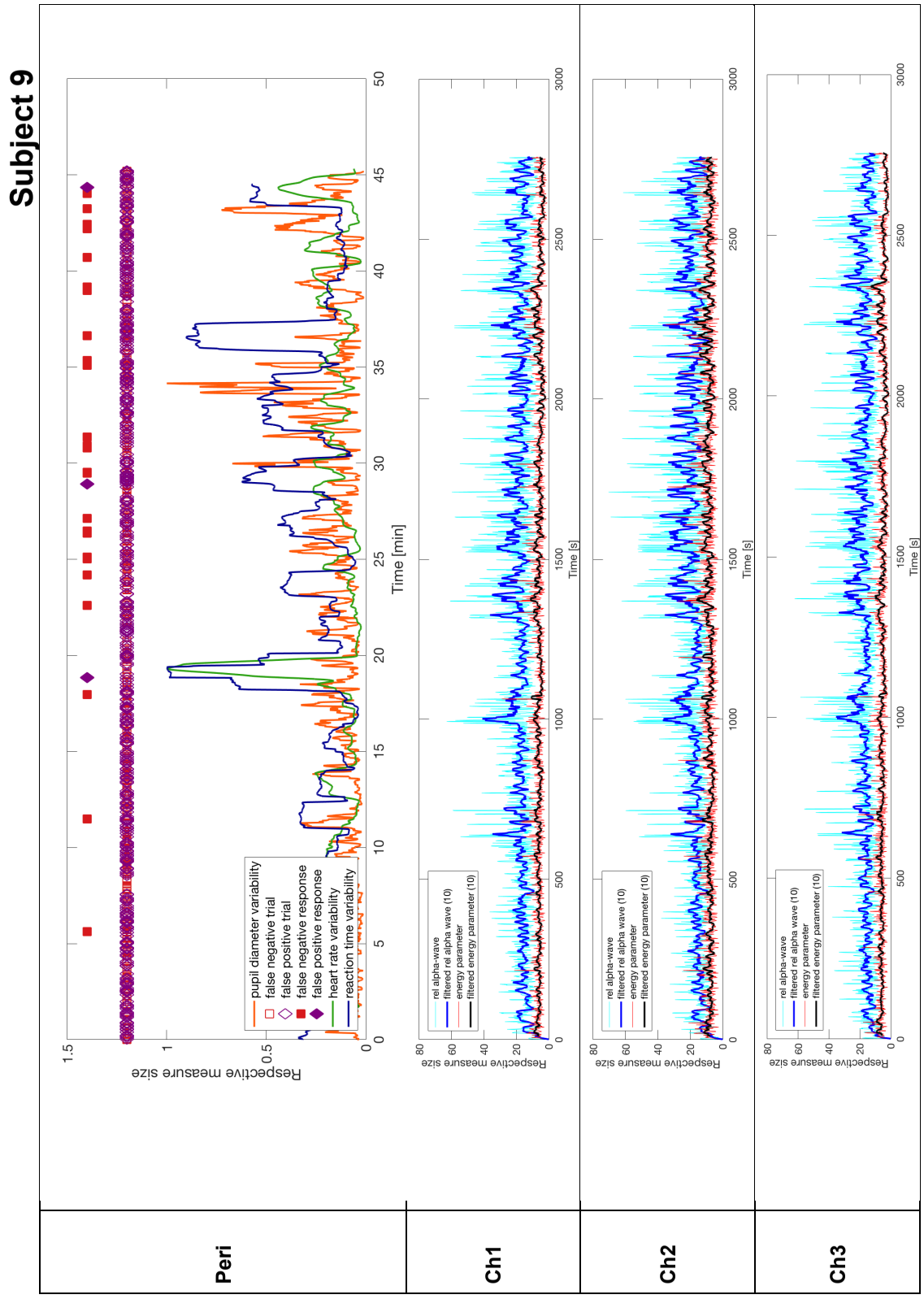

Subject 8
Ch9
Ch10
Ch11
Ch12
Ch13
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]

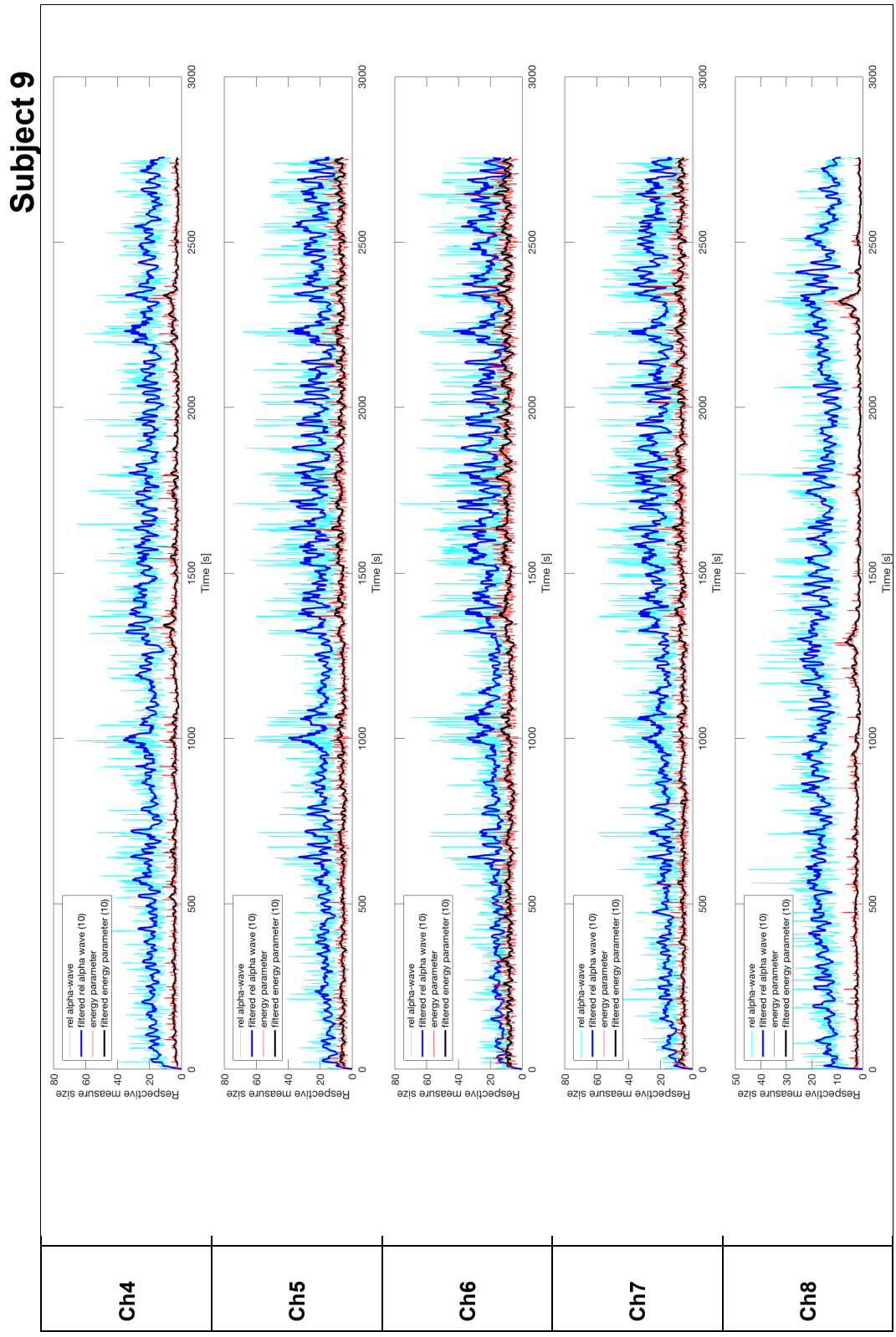

Subject 8
Ch14
Ch15
Ch16
Ch18
Ch19
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]

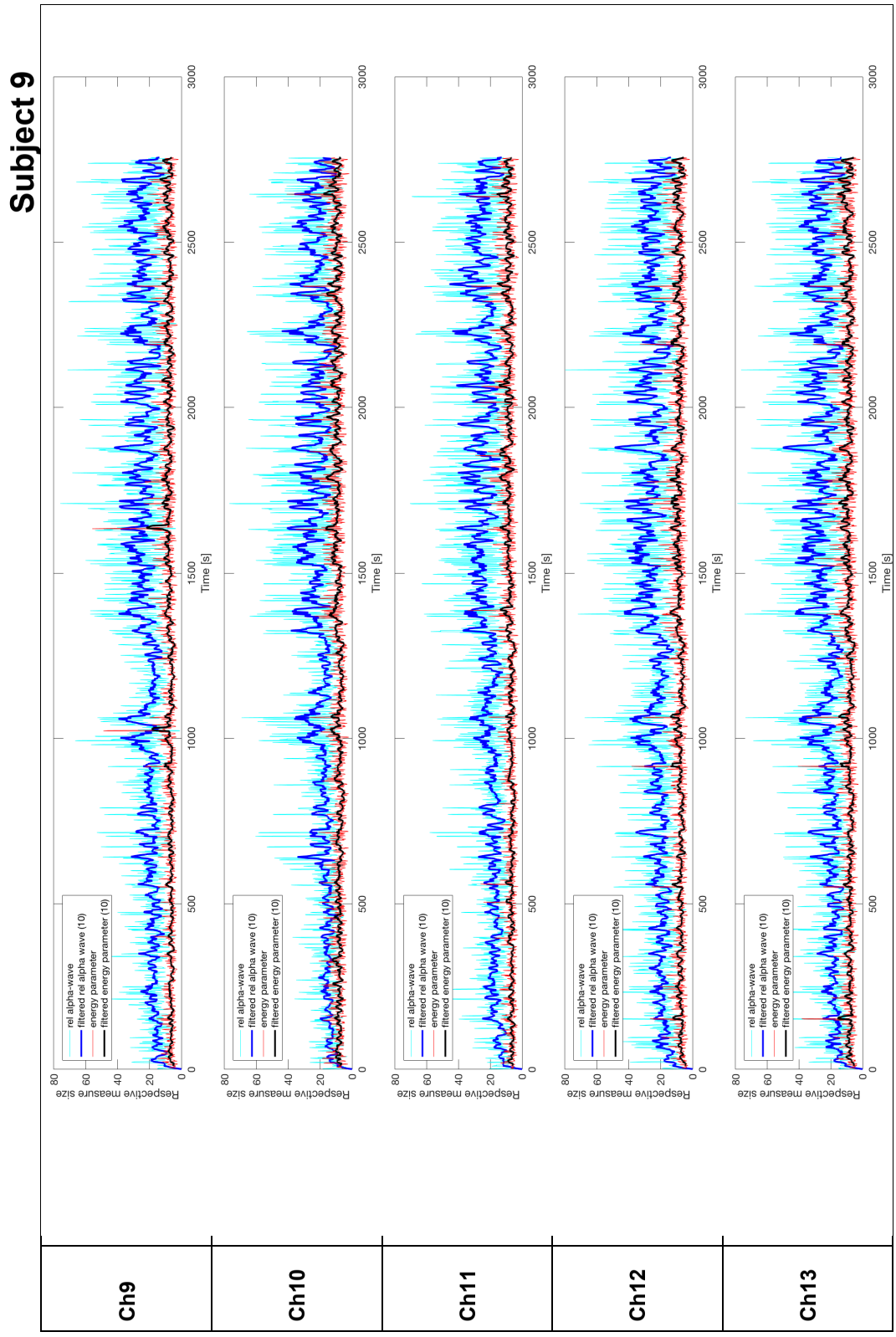

Subject 8
Ch20
Ch21
Ch22
Ch23
Ch24
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]

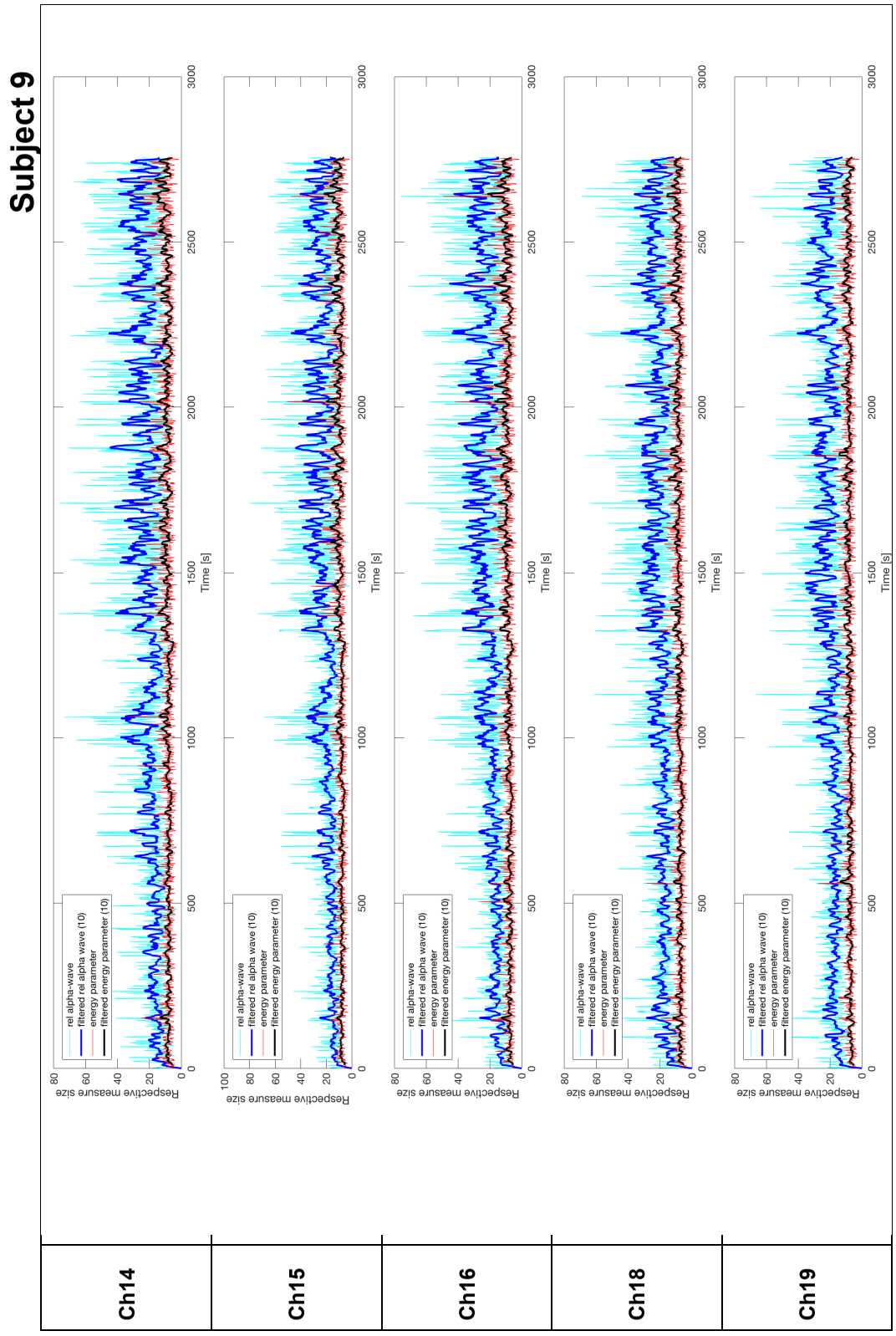

Subject 8
Ch25
Ch26
Ch27
Ch28
Ch29
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]

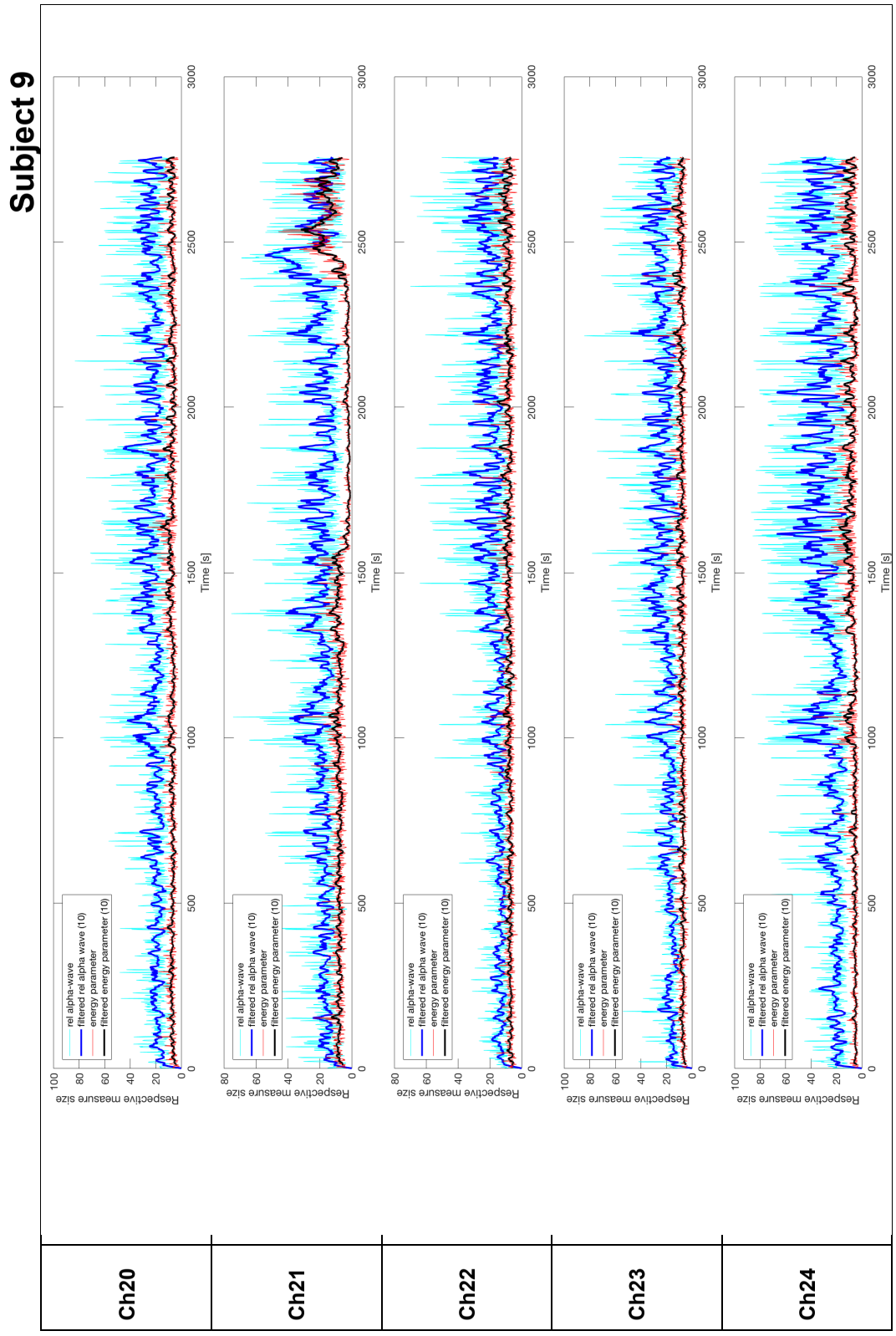

Subject 8
Ch30
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]
0
20
40
60
80
0
500
1000
1500
2000
2500
3000

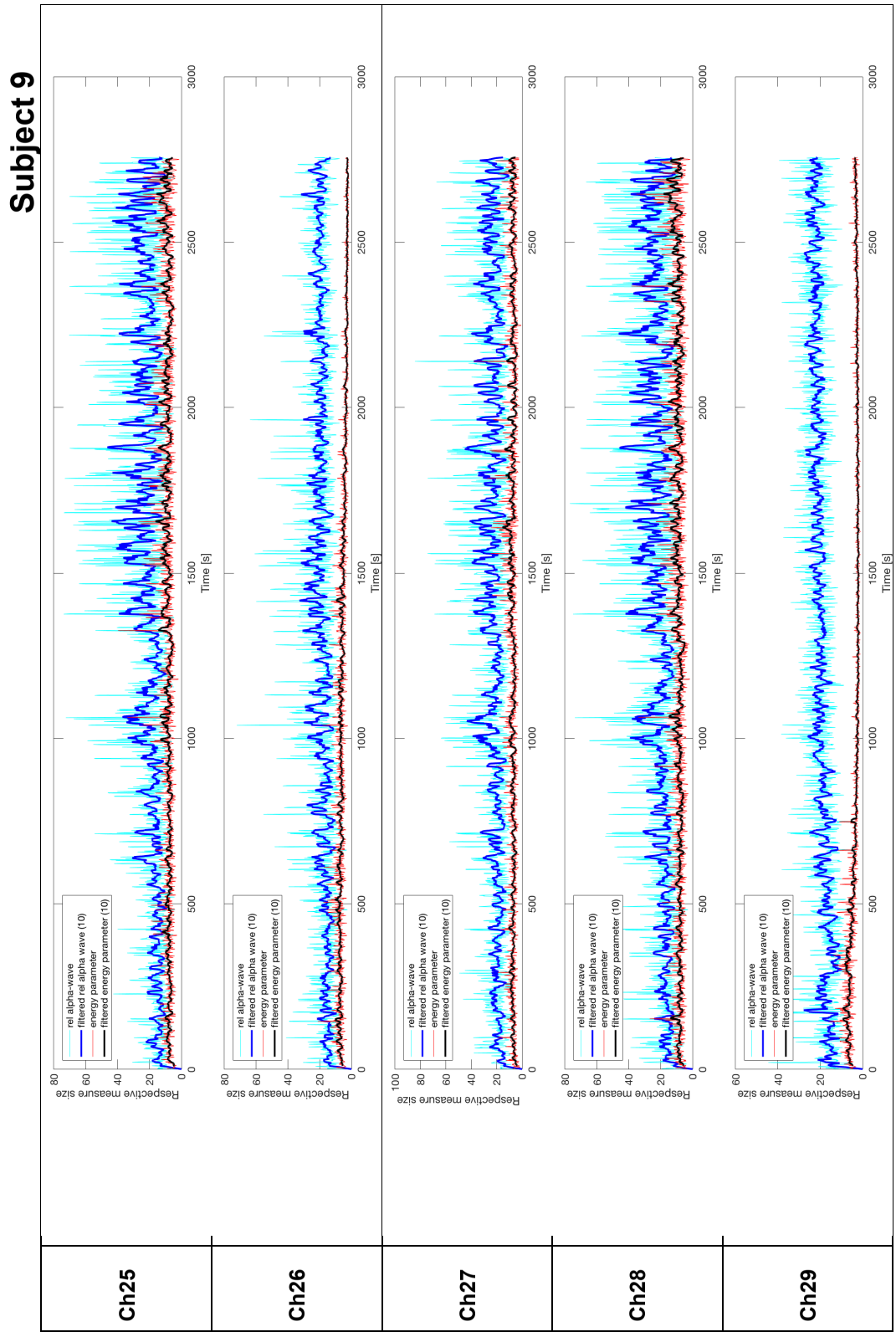

Subject 9
Peri
Ch1
Ch2
Ch3
Respective measure size
Time [min]
pupil diameter variability
false negative trial
false positive trial
false negative response
false positive response
heart rate variability
reaction time variability
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Time [s]

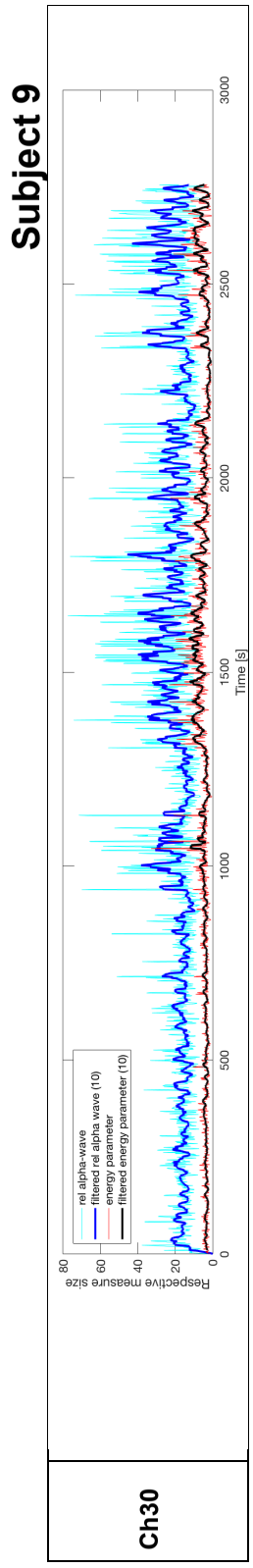

Subject 9
Ch4
Ch5
Ch6
Ch7
Ch8
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]

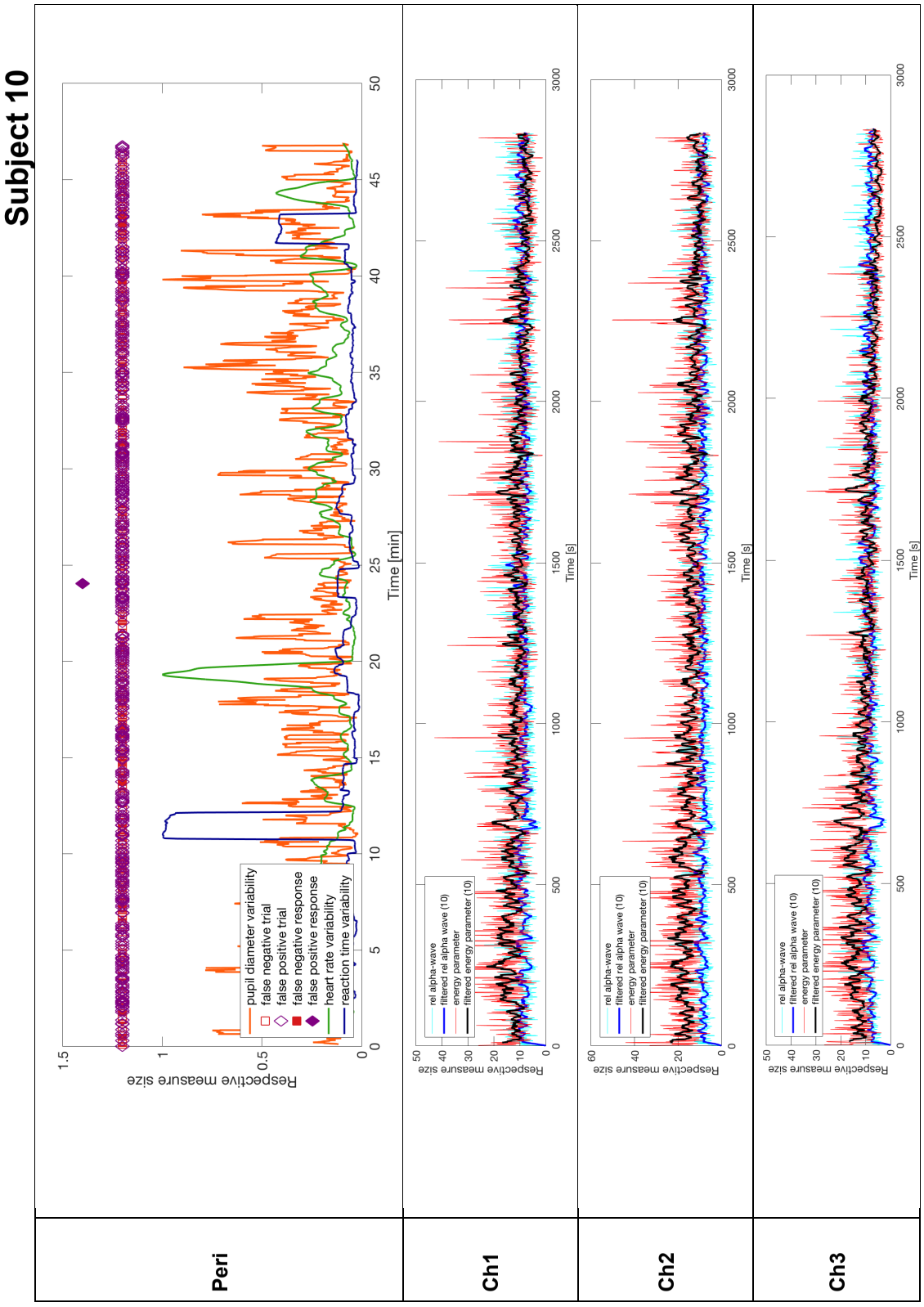

Subject 9
Ch9
Ch10
Ch11
Ch12
Ch13
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]

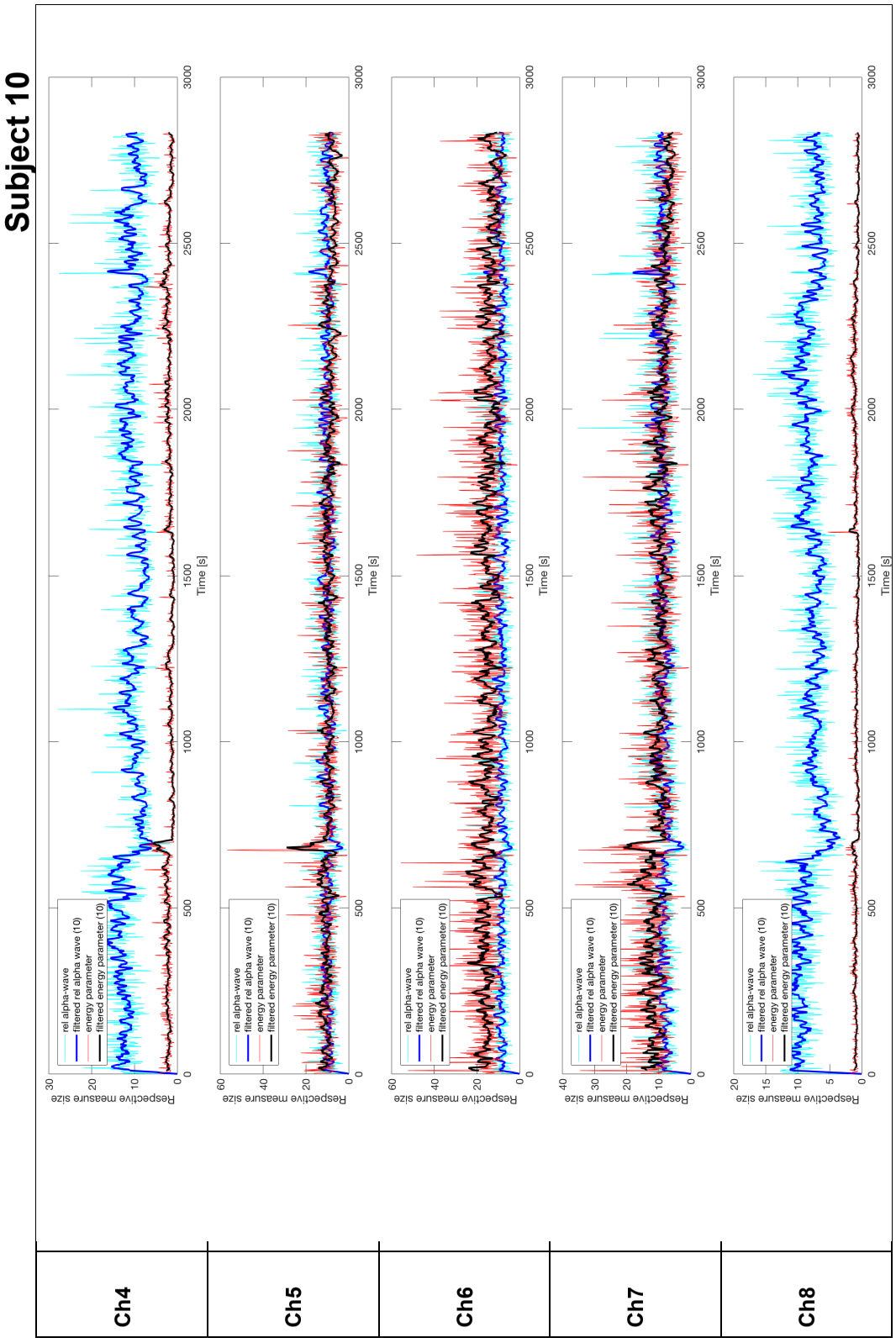

Subject 9
Ch14
Ch15
Ch16
Ch18
Ch19
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]

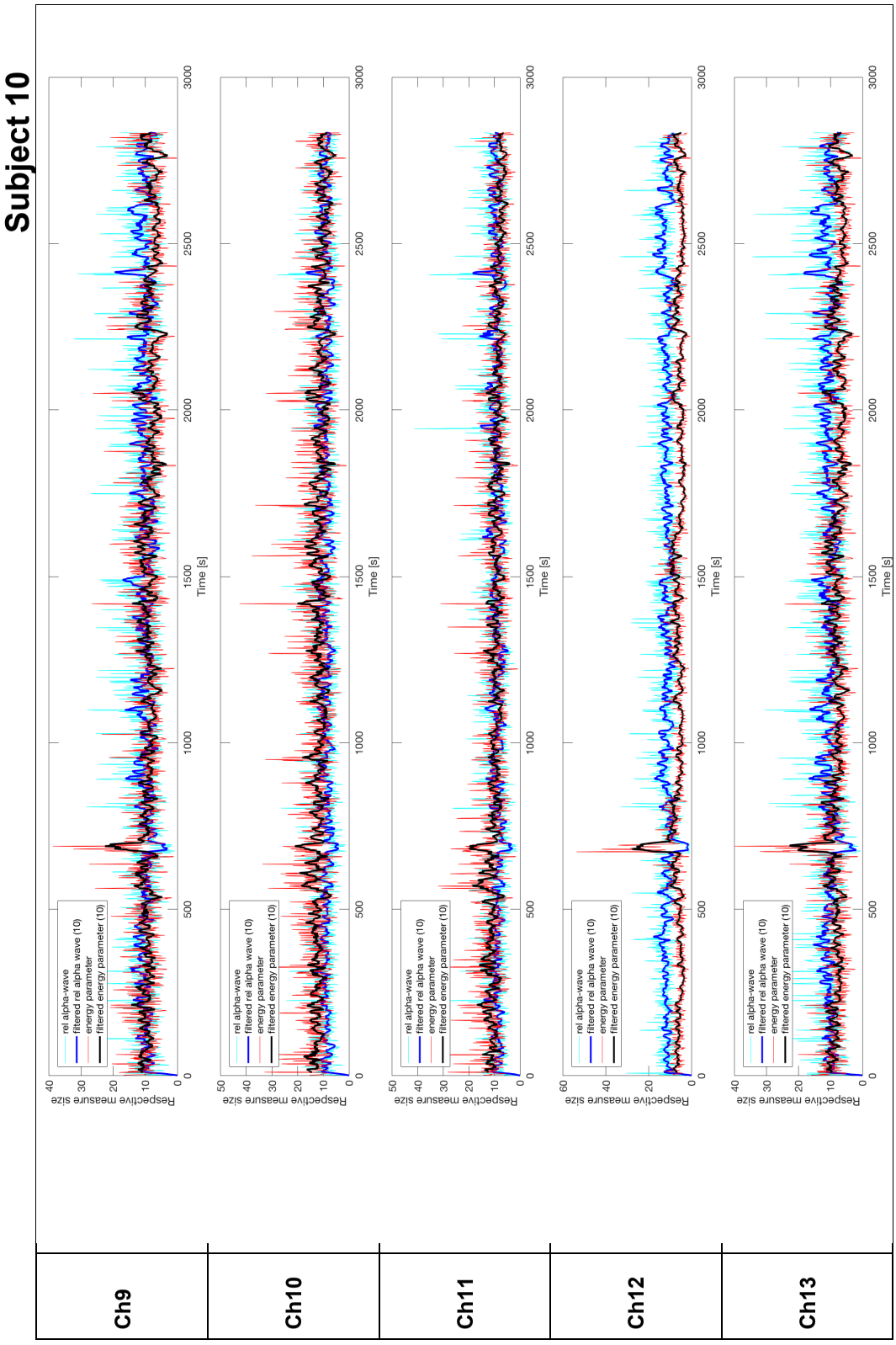

Subject 9
Ch20
Ch21
Ch22
Ch23
Ch24
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]

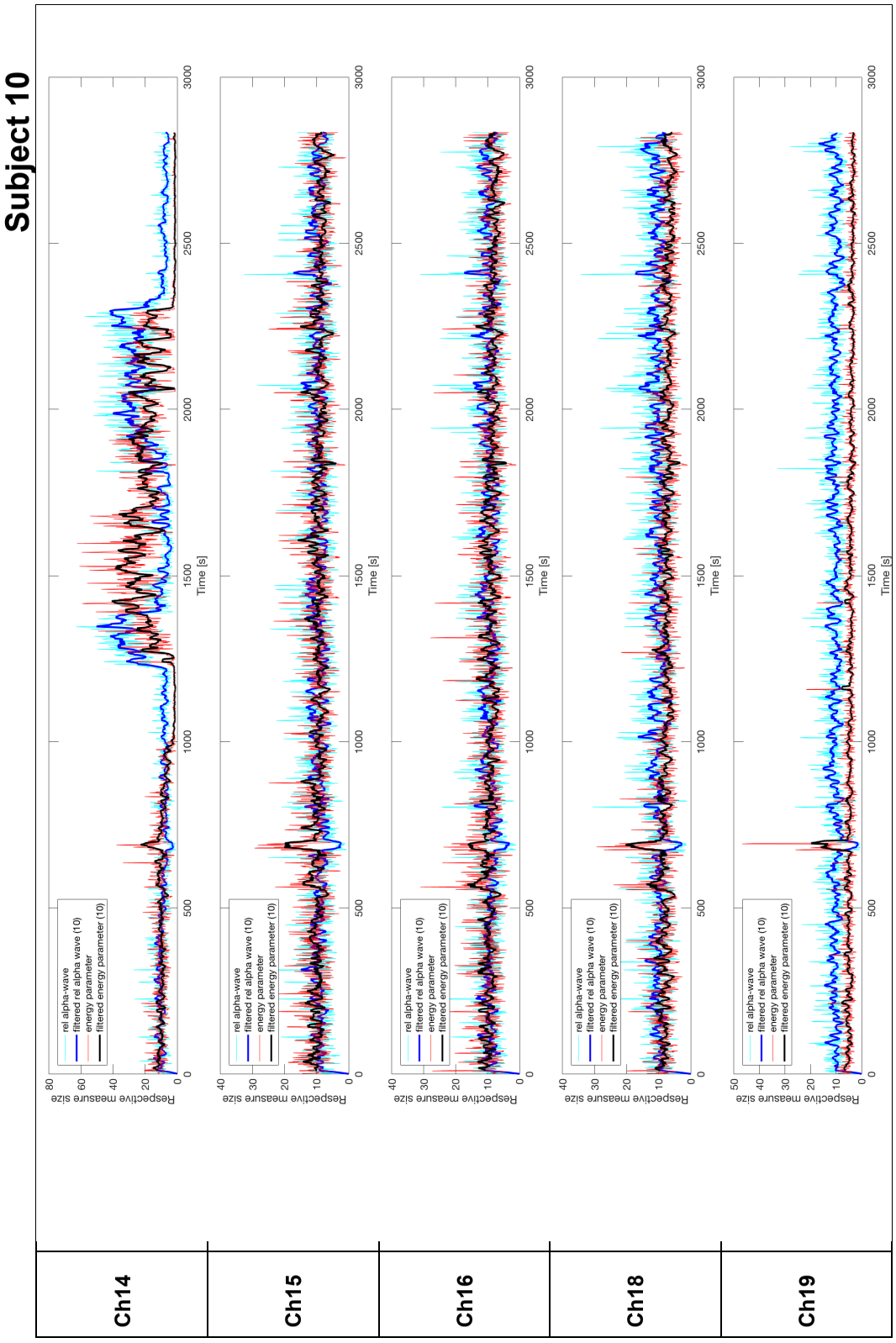

Subject 9
Ch25
Ch26
Ch27
Ch28
Ch29
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]

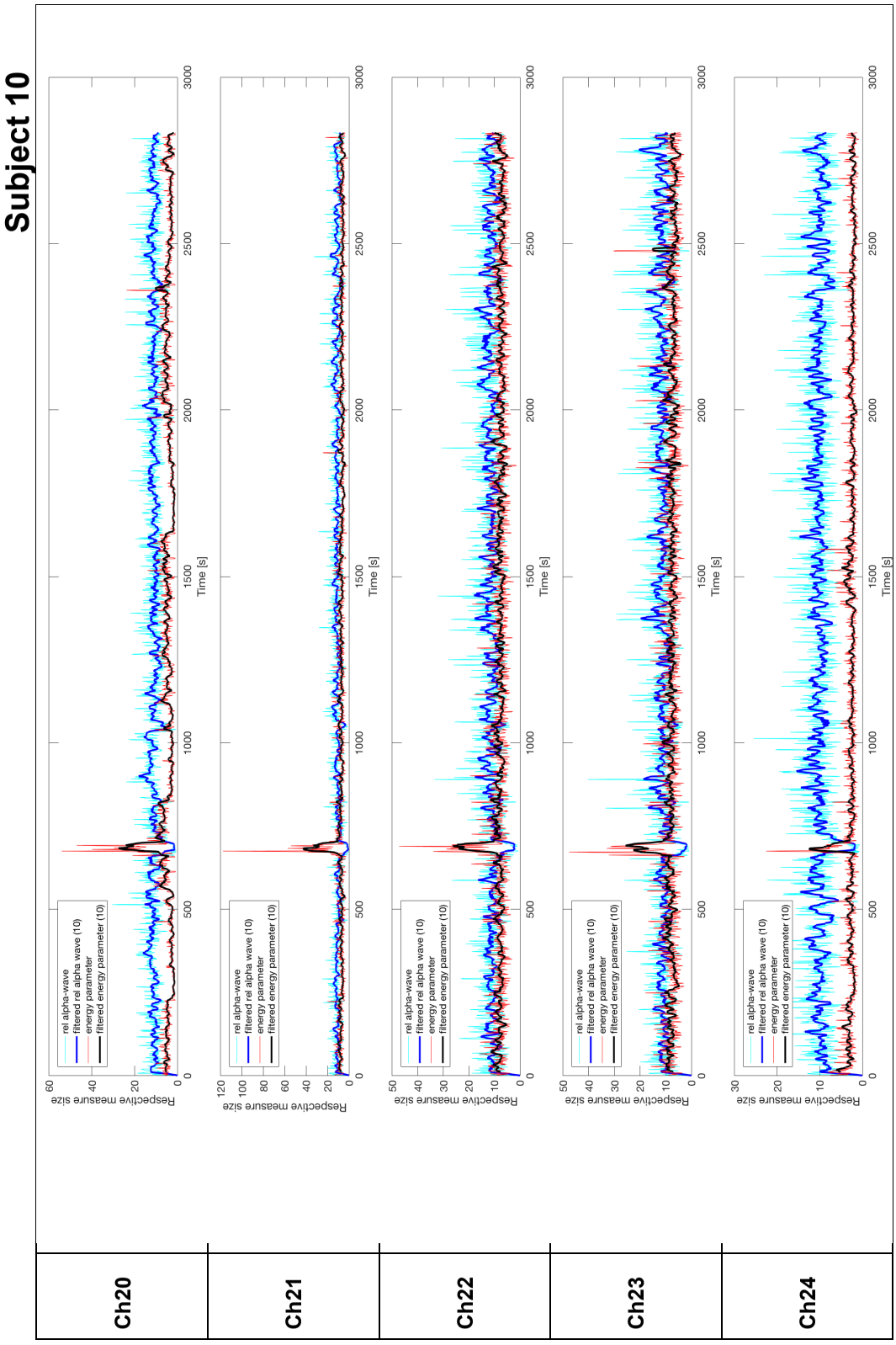

Subject 9
Ch30
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]
0
20
40
60
80
0
500
1000
1500
2000
2500
3000

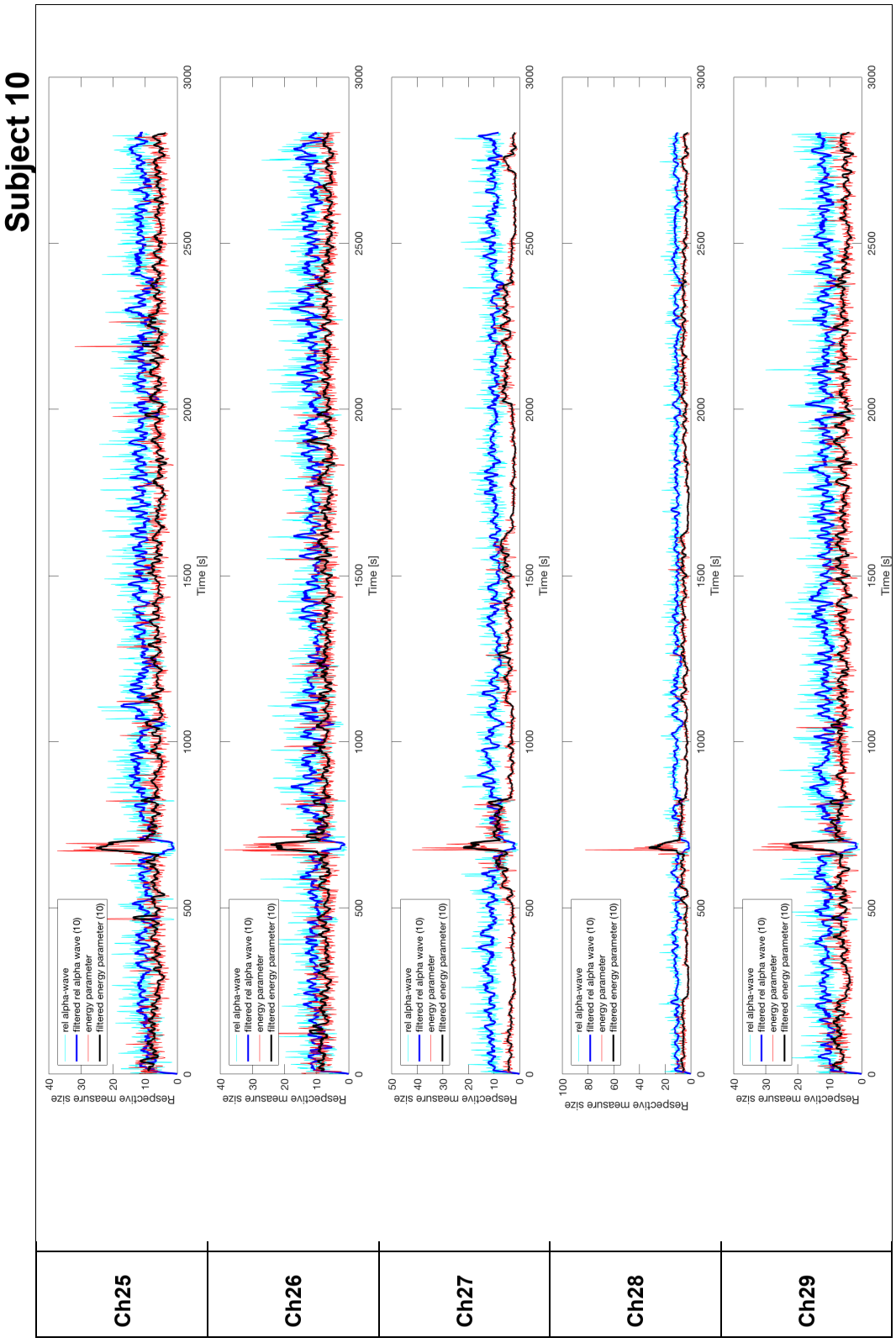

Subject 10
Peri
Ch1
Ch2
Ch3
Respective measure size
Time [min]
pupil diameter variability
false negative trial
false positive trial
false negative response
false positive response
heart rate variability
reaction time variability
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Time [s]

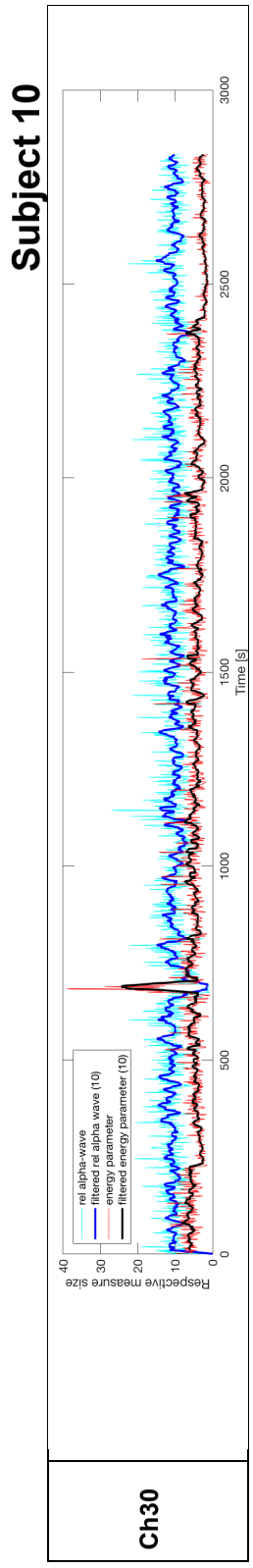

Subject 10
Ch4
Ch5
Ch6
Ch7
Ch8
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]


Subject 10
Ch9
Ch10
Ch11
Ch12
Ch13
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]


Subject 10
Ch14
Ch15
Ch16
Ch18
Ch19
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]


Subject 10
Ch20
Ch21
Ch22
Ch23
Ch24
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]


Subject 10
Ch25
Ch26
Ch27
Ch28
Ch29
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]


Subject 10
Ch30
rel alpha-wave
filtered rel alpha wave (10)
energy parameter
filtered energy parameter (10)
Respective measure size
Time [s]
0
10
20
30
40
500
1000
1500
2000
2500
3000

H Email correspondence between Prof. Dr. Yvonne Weber and the author

The email correspondence between Prof. Dr. Yvonne Weber and the author of this work is attached on the following pages.

Von: **Yvonne Weber** yvonne.weber@uni-tuebingen.de
Betreff: Re: Befundung EEG
Datum: 21. Dezember 2017 um 11:39
An: Ungewiß, Judith Judith.Ungewiss@hs-aalen.de

YW

Liebe Frau Ungewiss,
es findet sich lediglich in der Zeit von 10:41 bis 10:42 eine Phase von weniger gespannter Aufmerksamkeit, die man bei gutem Willen als Ansätze von Schläfrigkeit definieren kann. Das geht aber nicht über den geänderten occipitalen Grundrhythmus, sondern über dort auftretende horizontale Augenbewegungen, die ein solches Stadium andeuten.
Ich wünsche Ihnen schöne Feiertage und einen guten Rutsch.
MfG
Y. Weber

Zitat von "Ungewiß, Judith" <Judith.Ungewiss@hs-aalen.de>:

> Liebe Frau Weber,
>
> mittlerweile habe ich die Perimetrie-Daten auswerten können - diese Daten zeigen uns, dass in bestimmten Zeitfenstern der Proband aufgrund von fehlender Aufmerksamkeit Fehler in seinen Angaben gemacht hat.
>
> Darf ich Sie vor diesem Hintergrund nochmals fragen, ob es Ihnen prinzipiell möglich wäre, in den EEG-Aufzeichnungen (interessant ist für uns in diesem Fall die Aufzeichnung von 10:39:55 bis 11:23:33) „Ansätze von Schläfrigkeit“ erkennen zu können?
>
> Mit den besten Grüßen
> Judith Ungewiß
>
> – – – – – – – – – – – – – – – – – –
>
> Judith Ungewiß
> M. Sc. Augenoptik und Psychophysik
>
> Hochschule Aalen - Technik und Wirtschaft
> Kompetenzzentrum Vision Research
> Anton-Huber-Str. 23
> 73430 Aalen
>
> Tel.: +49 - 7361 576-4625
> Fax: +49 - 7361 576-4685
> E-Mail: judith.ungewiss@hs-aalen.de<mailto:judith.ungewiss@hs-aalen.de>
>
> www.hs-aalen.de<http://www.hs-aalen.de>
> www.vision-research.de
>
> Am 15.12.2017 um 22:24 schrieb Judith Ungewiß <judith.ungewiss@hs-aalen.de<mailto:judith.ungewiss@hs-aalen.de>>:
>
> Liebe Frau Weber,
>
> ganz herzlichen Dank auch auf diesem Wege für Ihre Unterstützung und Ihre Hilfe am heutigen Vormittag, sowie für Ihre hier übermittelte Befundung.
> Sobald ich meine Gerätschaften wieder in Aalen habe und auf die Perimeter-Daten zugreifen kann, werde ich eine Auswertung auch dieser Daten vornehmen - der Vergleich beider Befunde (EEG und Perimetrie) wird für mich spannend.
>
> Mit den besten Grüßen aus Aalen
> Judith Ungewiß
>
> – – – – – – – – – – – – – – – – – –
>
> Judith Ungewiß
> M. Sc. Augenoptik und Psychophysik
>
> Hochschule Aalen - Technik und Wirtschaft
> Kompetenzzentrum Vision Research
> Anton-Huber-Str. 23
> 73430 Aalen
>
> Tel.: +49 - 7361 576-4625
> Fax: +49 - 7361 576-4685
> E-Mail: judith.ungewiss@hs-aalen.de<mailto:judith.ungewiss@hs-aalen.de>
>
> www.hs-aalen.de<http://www.hs-aalen.de/>
> www.vision-research.de<http://www.vision-research.de>
>
> Am 15.12.2017 um 14:24 schrieb Yvonne Weber <yvonne.weber@uni-tuebingen.de<mailto:yvonne.weber@uni-tuebingen.de>>:

Liebe Frau Ungewiss,
hier nun die Befundung des EEGs. Die erste Ableitung wurde 10:23:53 gestartet und lief bis 10:35:32. Darin fand sich kein relevanter Schlafanteil. Die zweite Ableitung wurde 10:39:55 gestartet und lief bis 11:23:33. Darin fand sich ebenfalls kein relevanter Schlafanteil.
MfG
Y. Weber

Prof. Dr. Y. Weber
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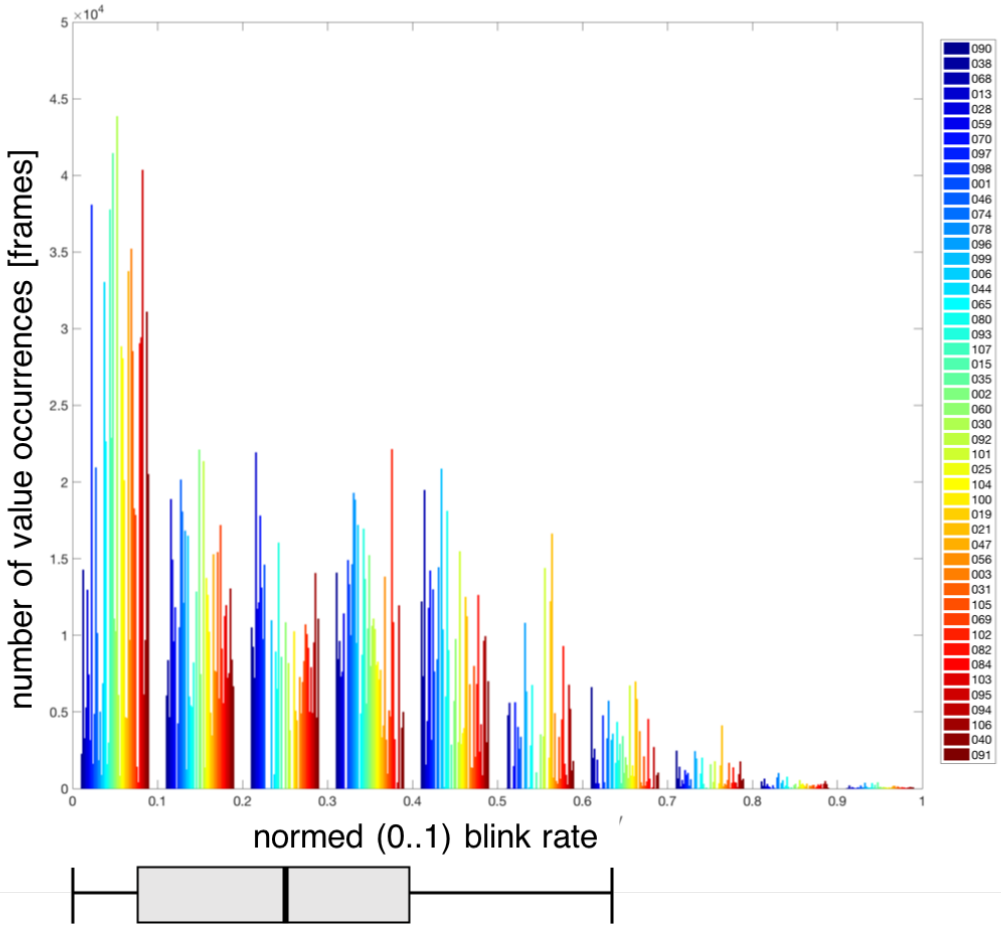
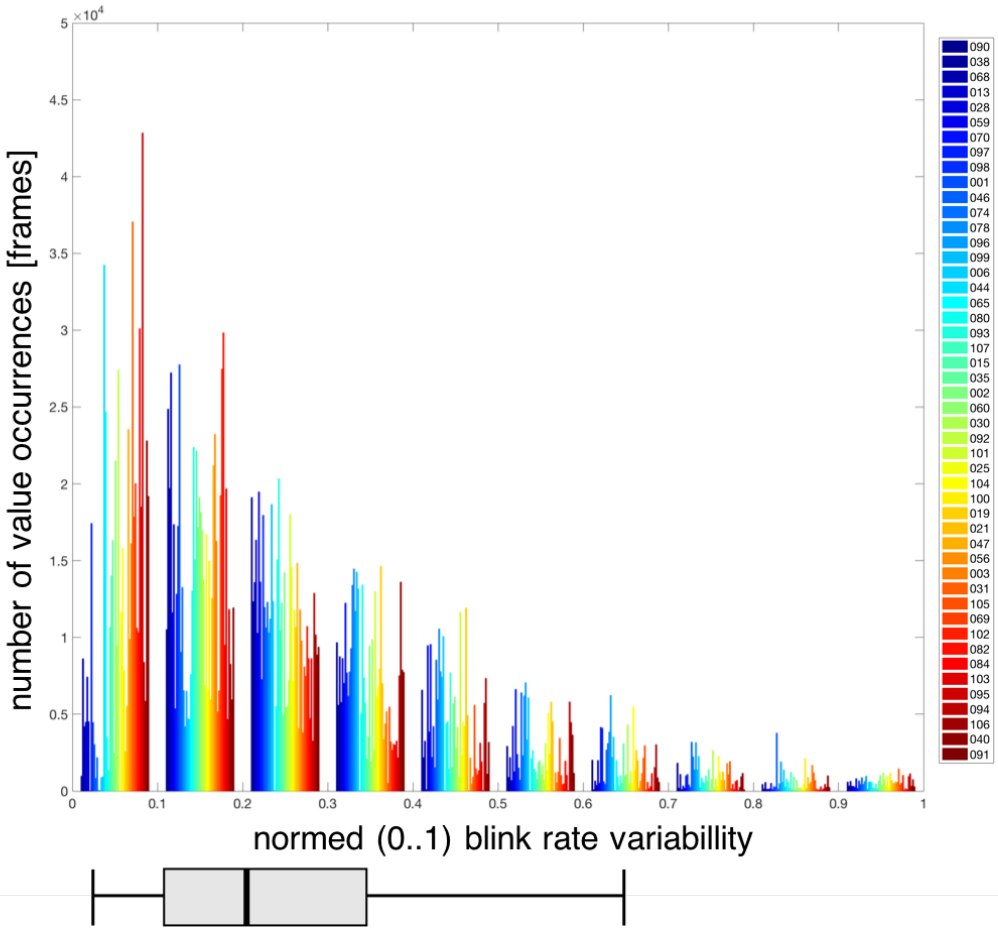
I Distribution plots for all parameters included in the study

Distribution plots for all parameters included are displayed on the following pages. Test subjects are sorted by the total number of false responses to catch trials.

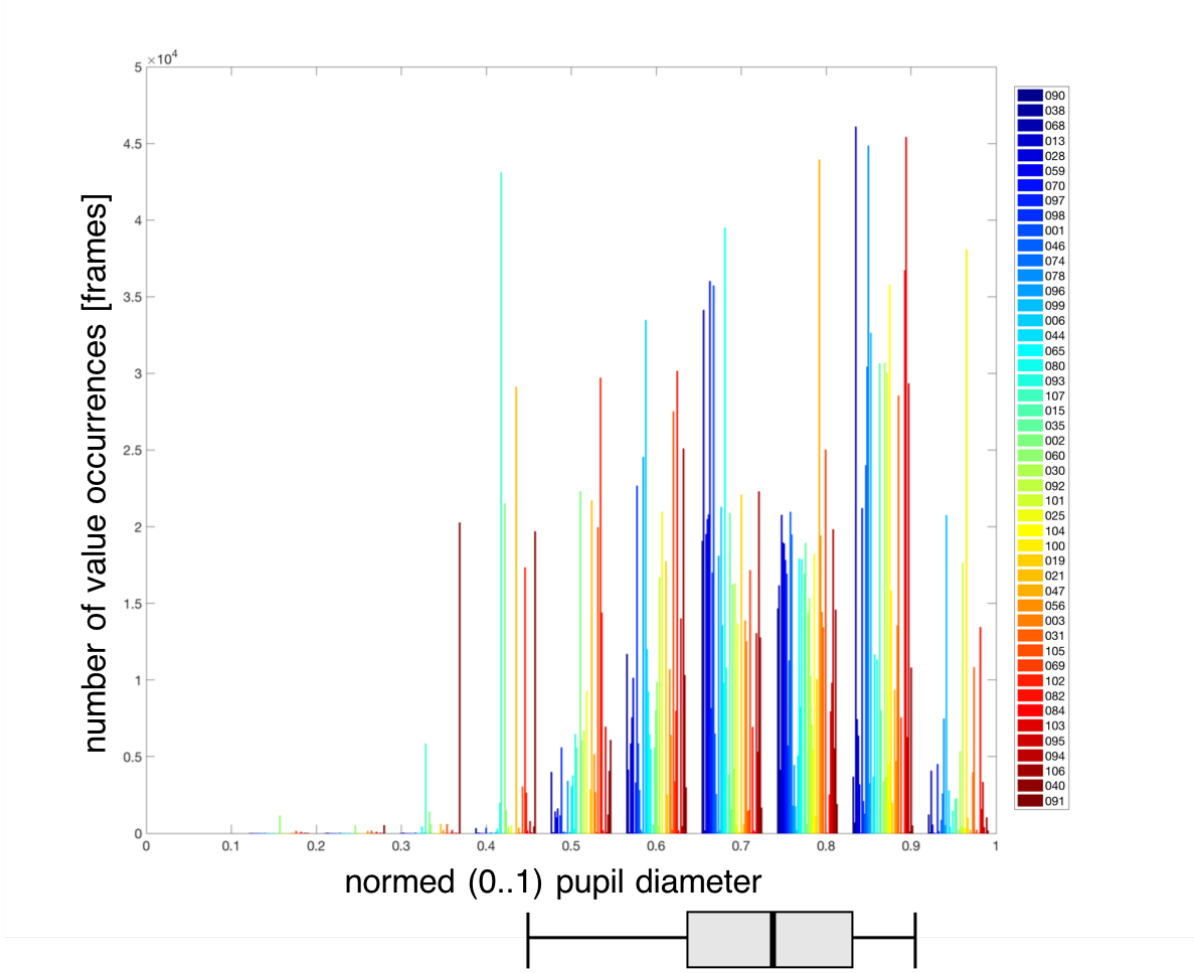
I.1 Blink rate (BR)



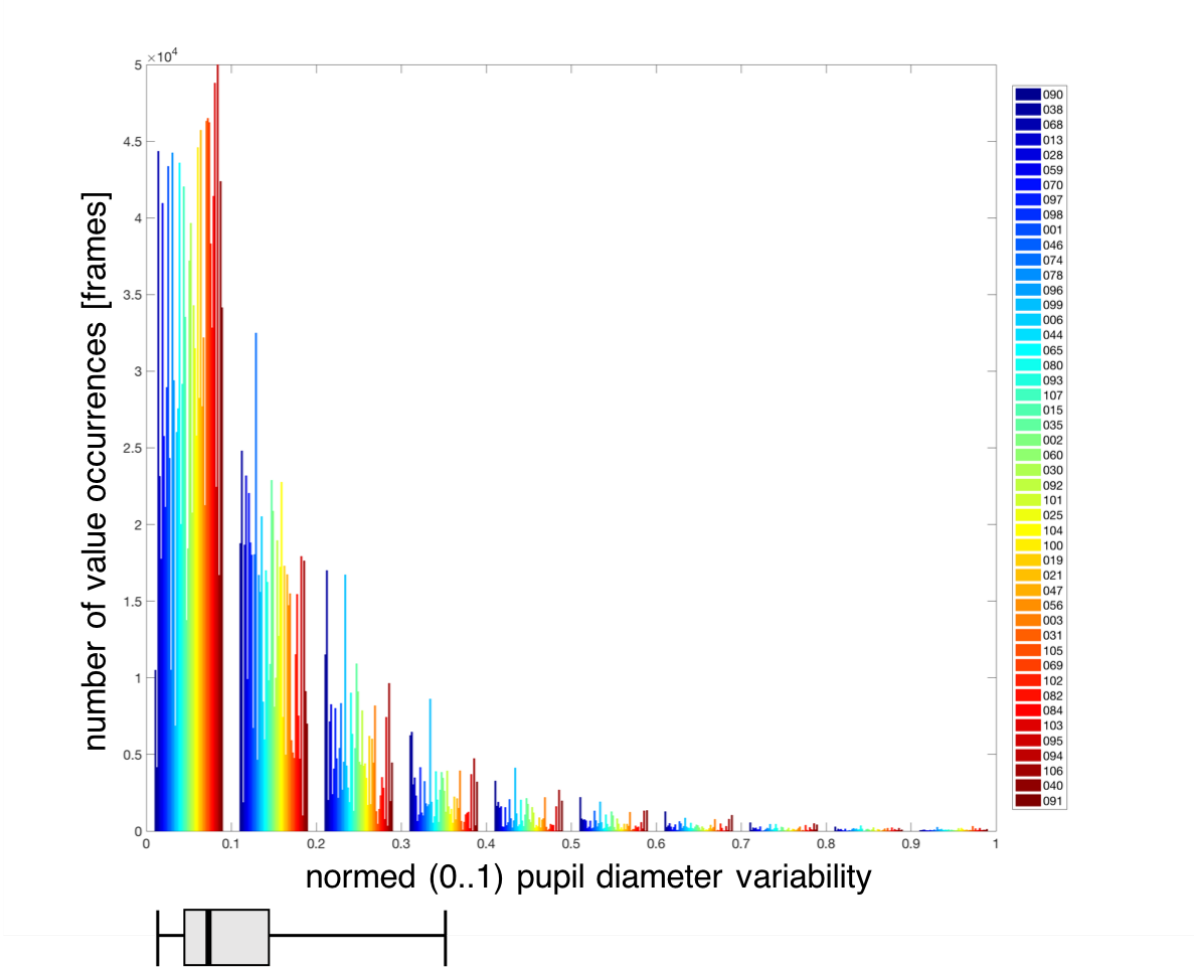
I.2 Blink rate variability (BRV)



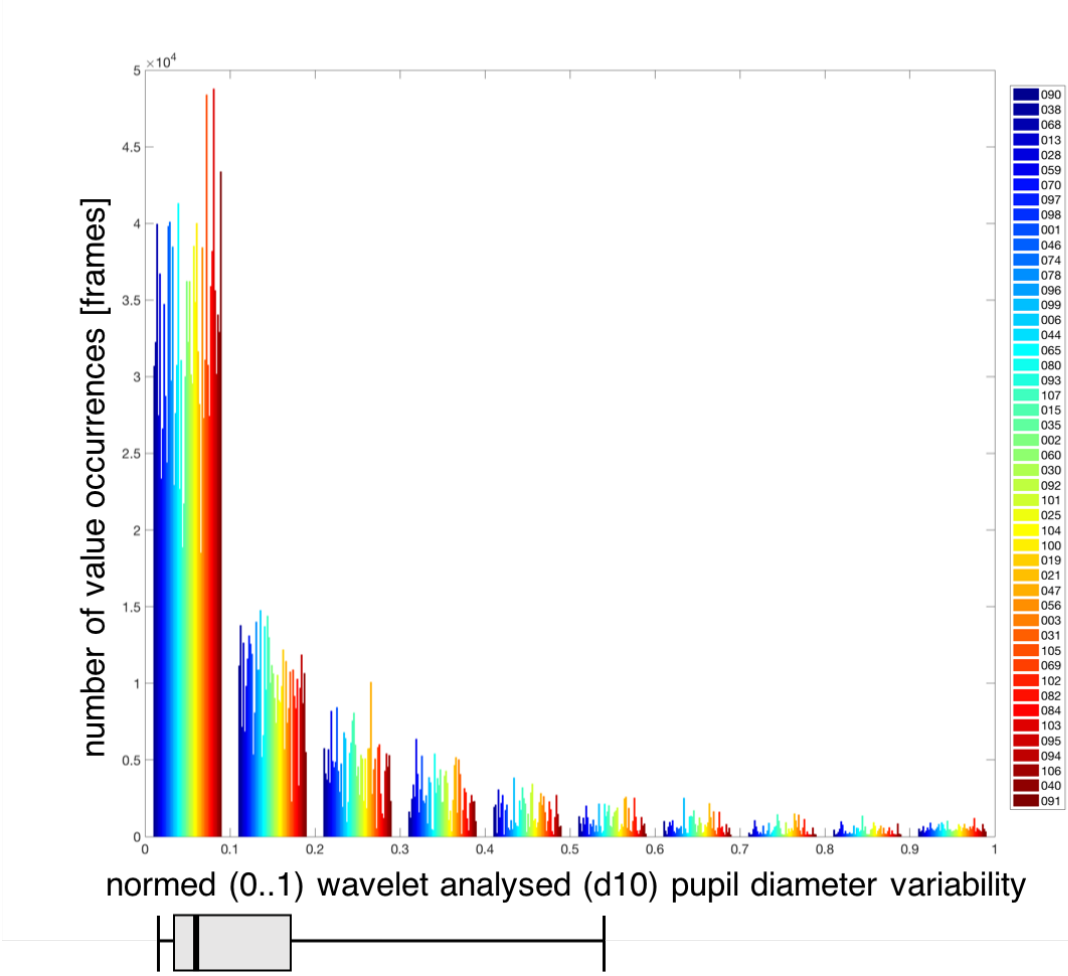
I.3 Pupil diameter (PD)



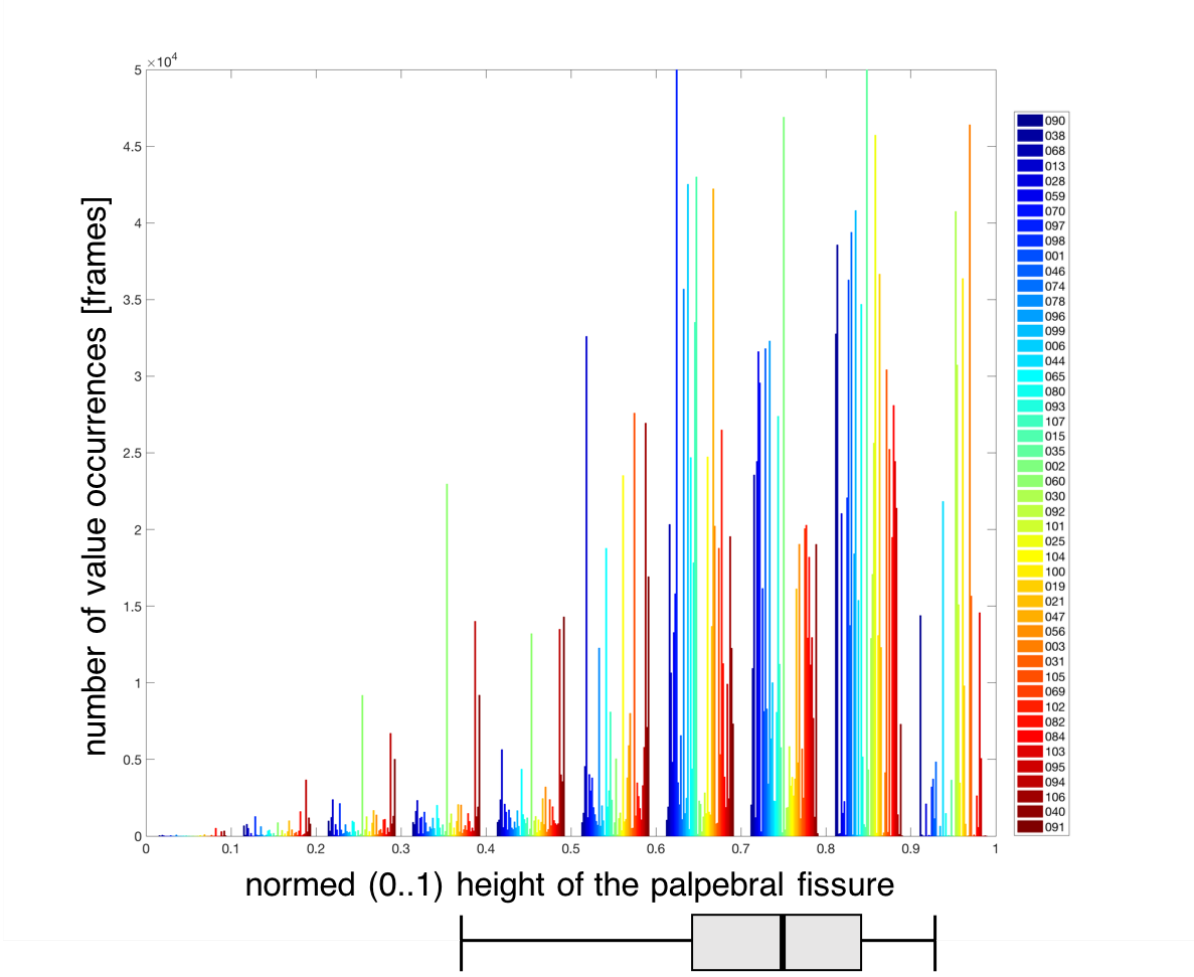
I.4 Pupil diameter variability (PDV)



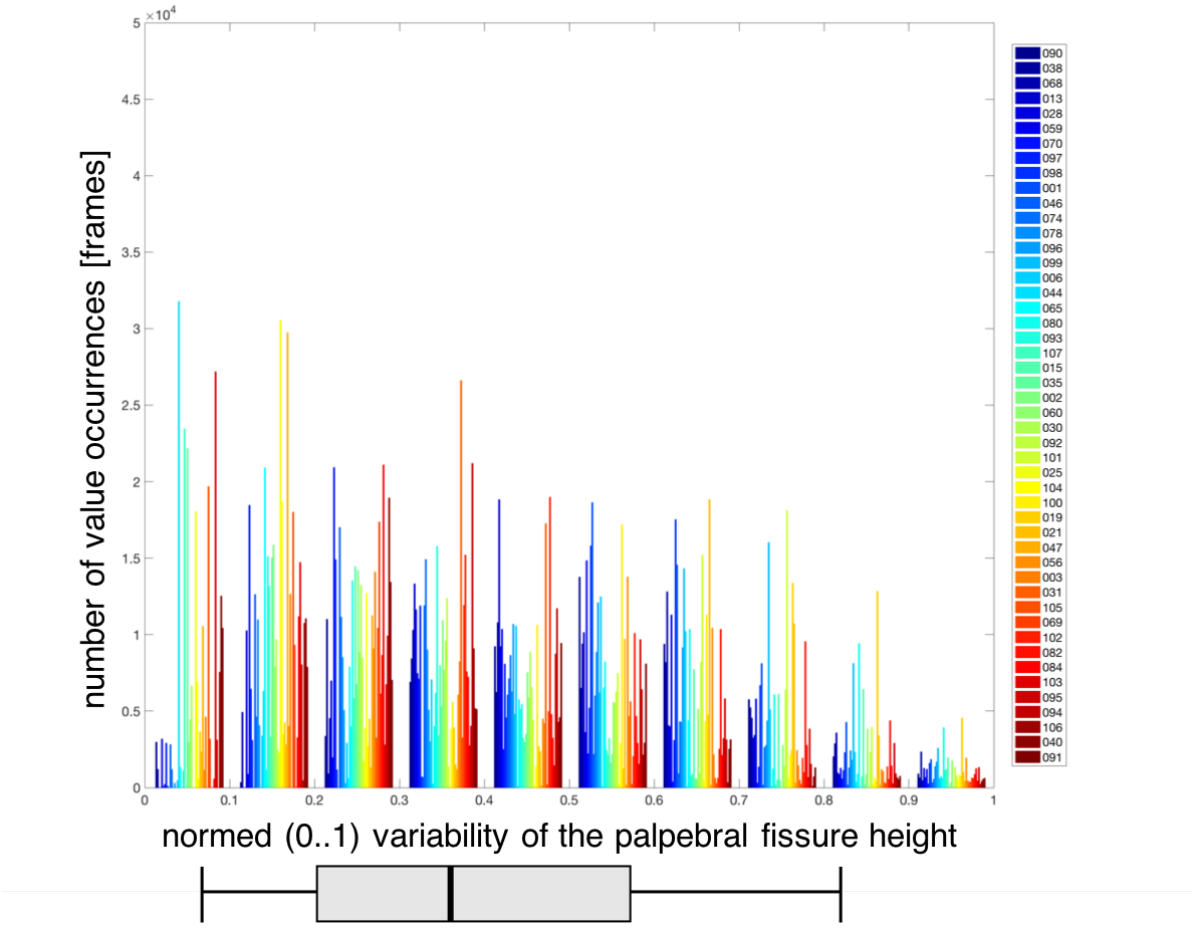
I.5 Pupil diameter wavelet analyzed parameter d10 (PDVd10)



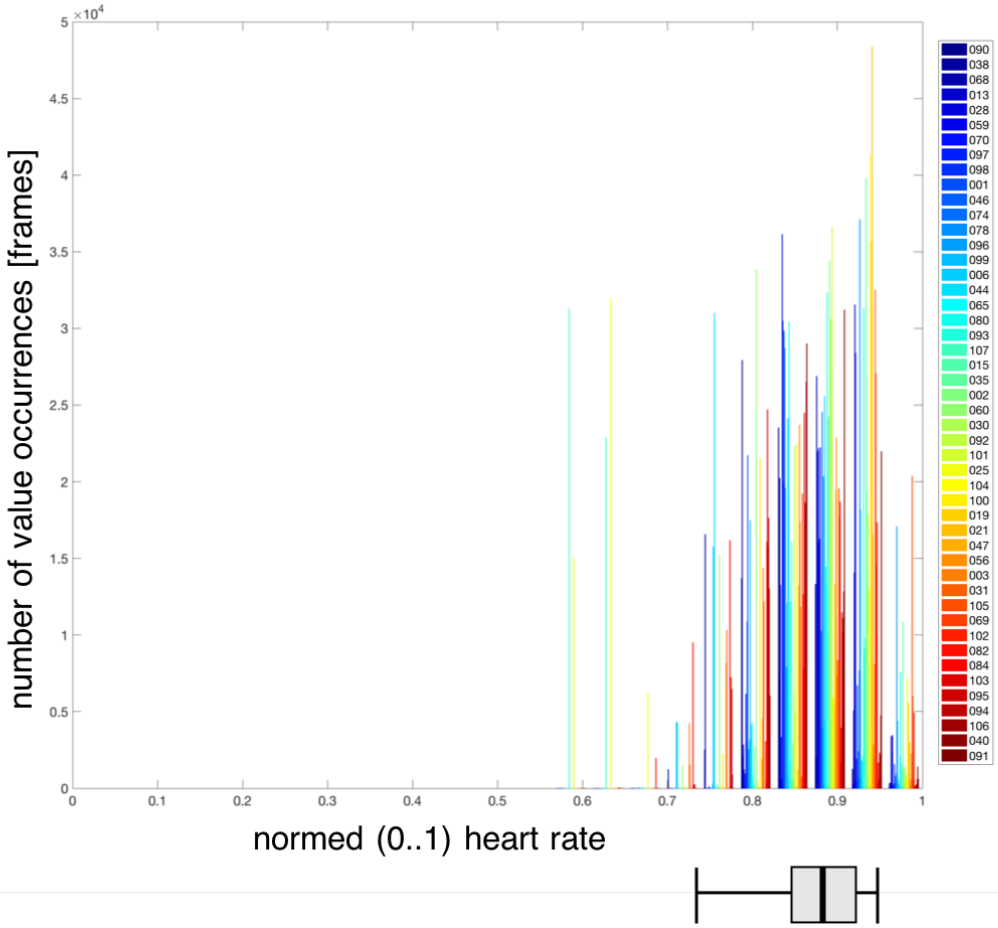
I.6 Height of the palpebral fissure (PF)



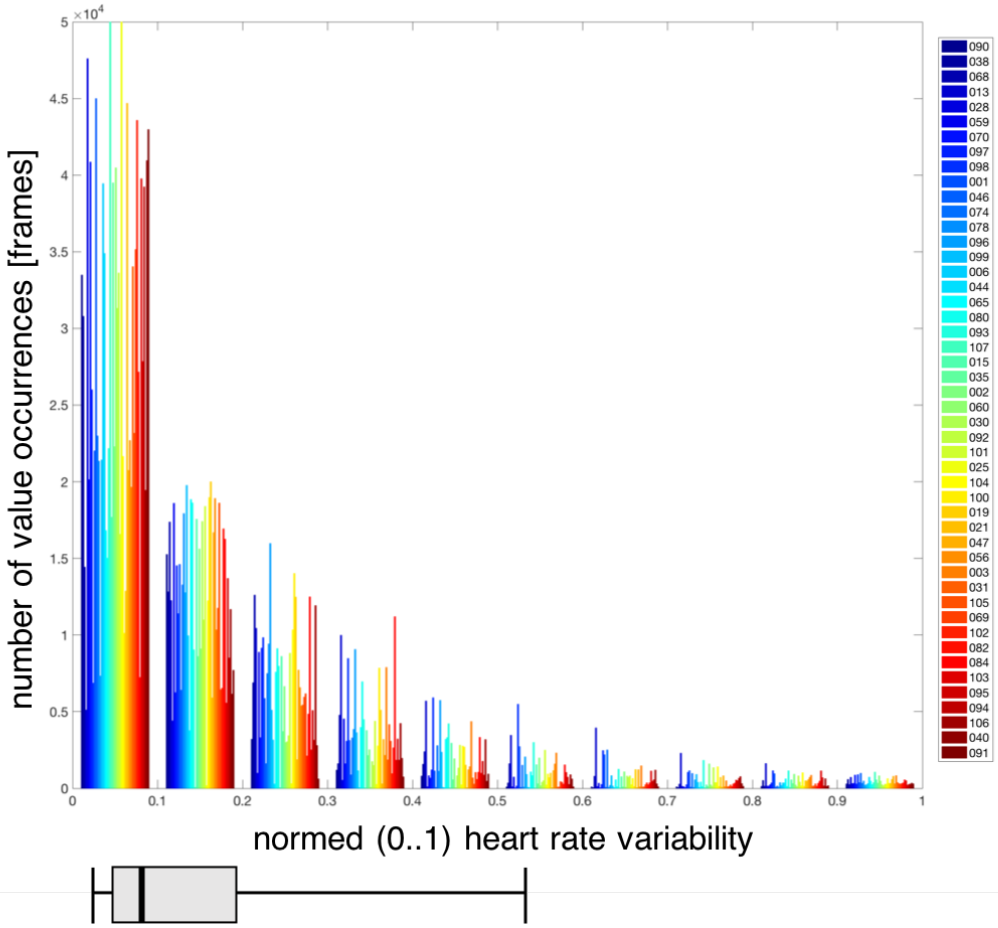
I.7 Variability of the height of the palpebral fissure (PFV)



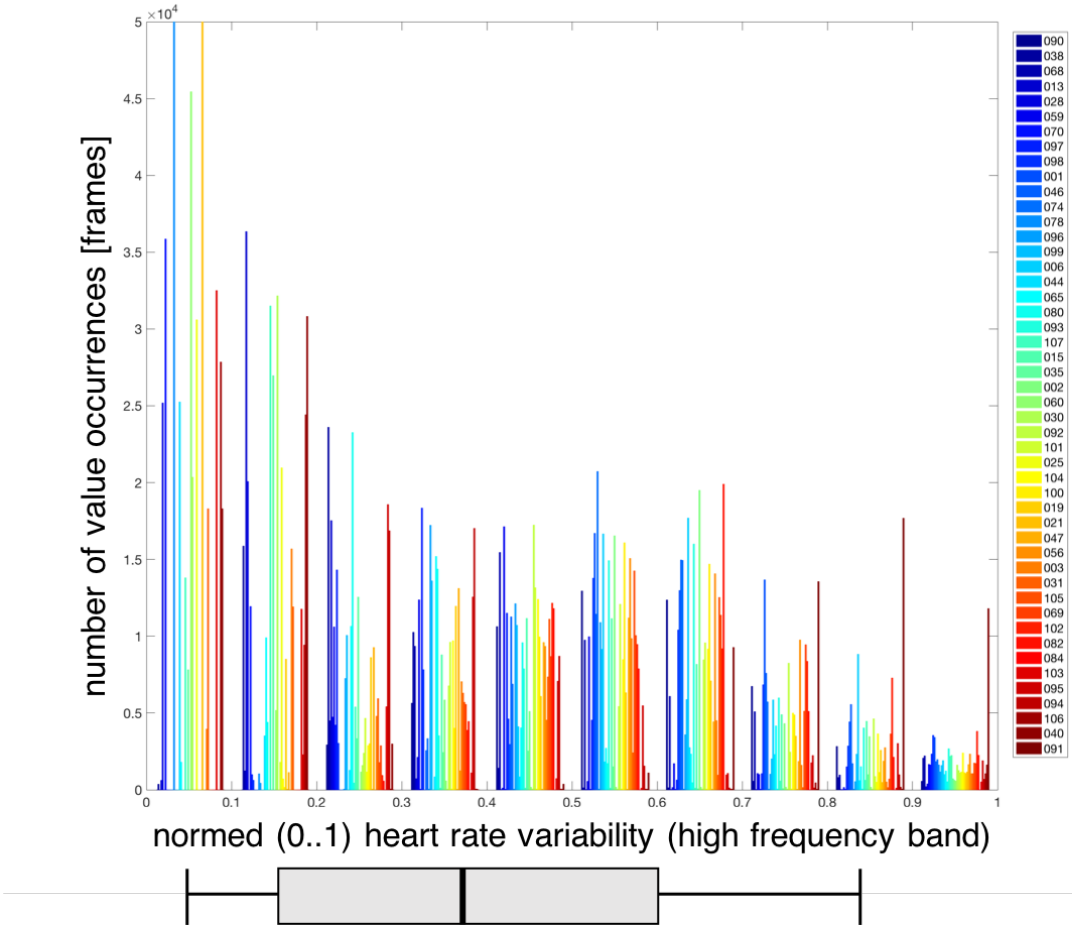
I.8 Heart rate (HR)



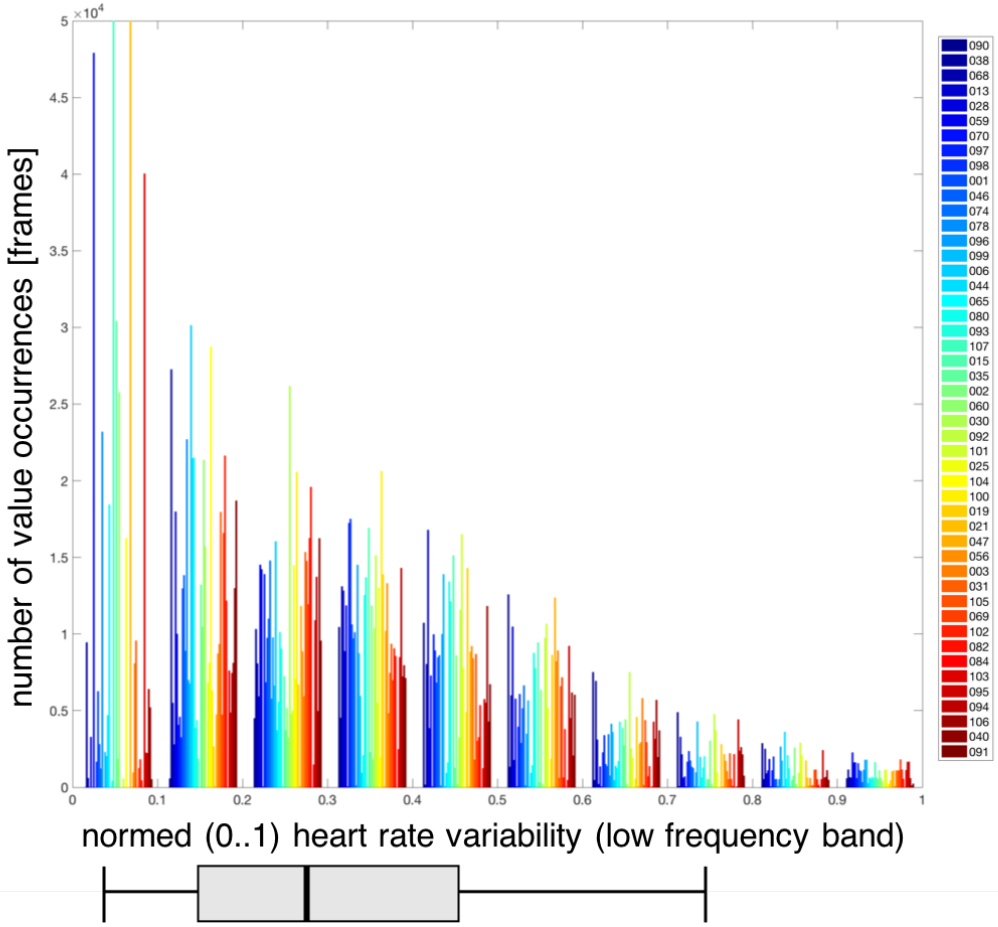
I.9 Heart rate variability (HRV)



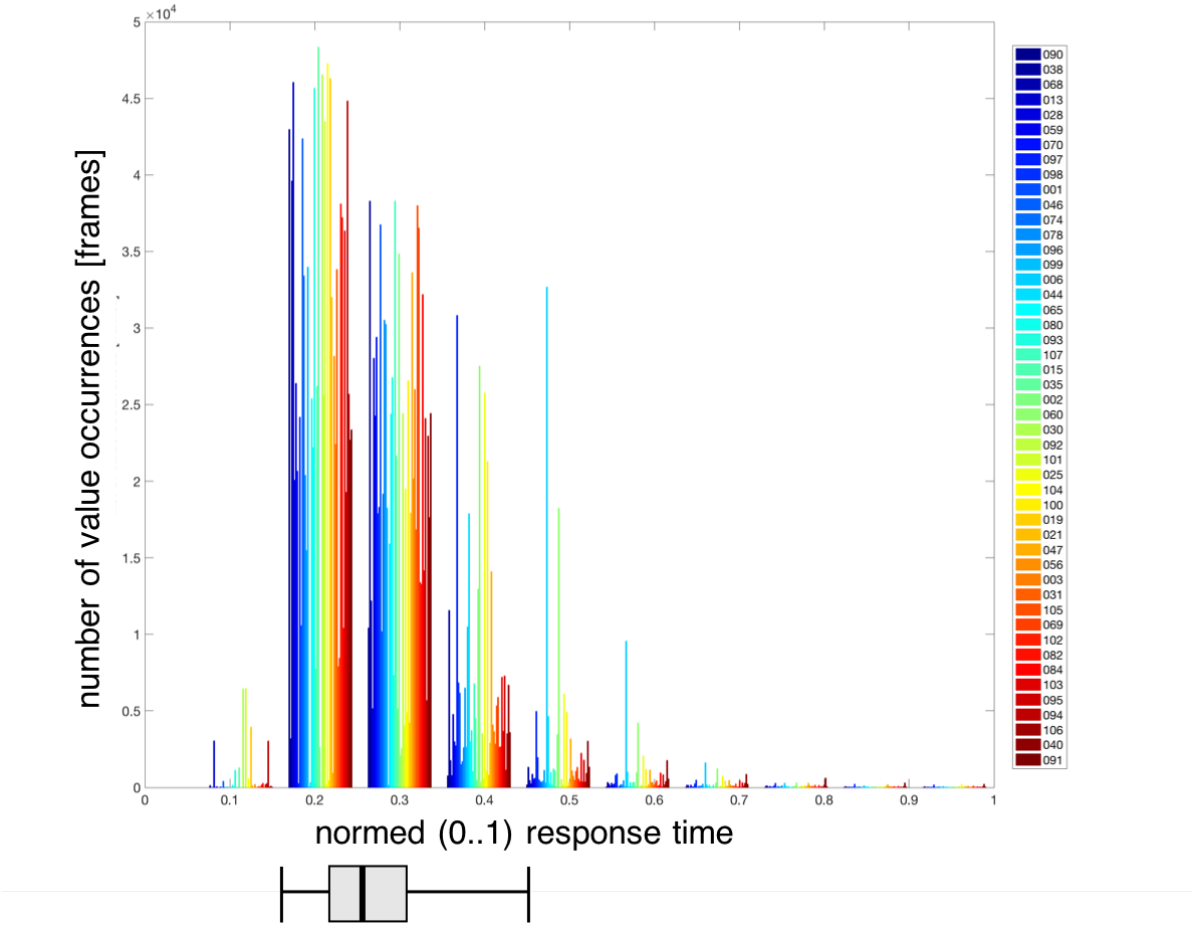
I.10 High frequency band of the heart rate variability (HRVHF)



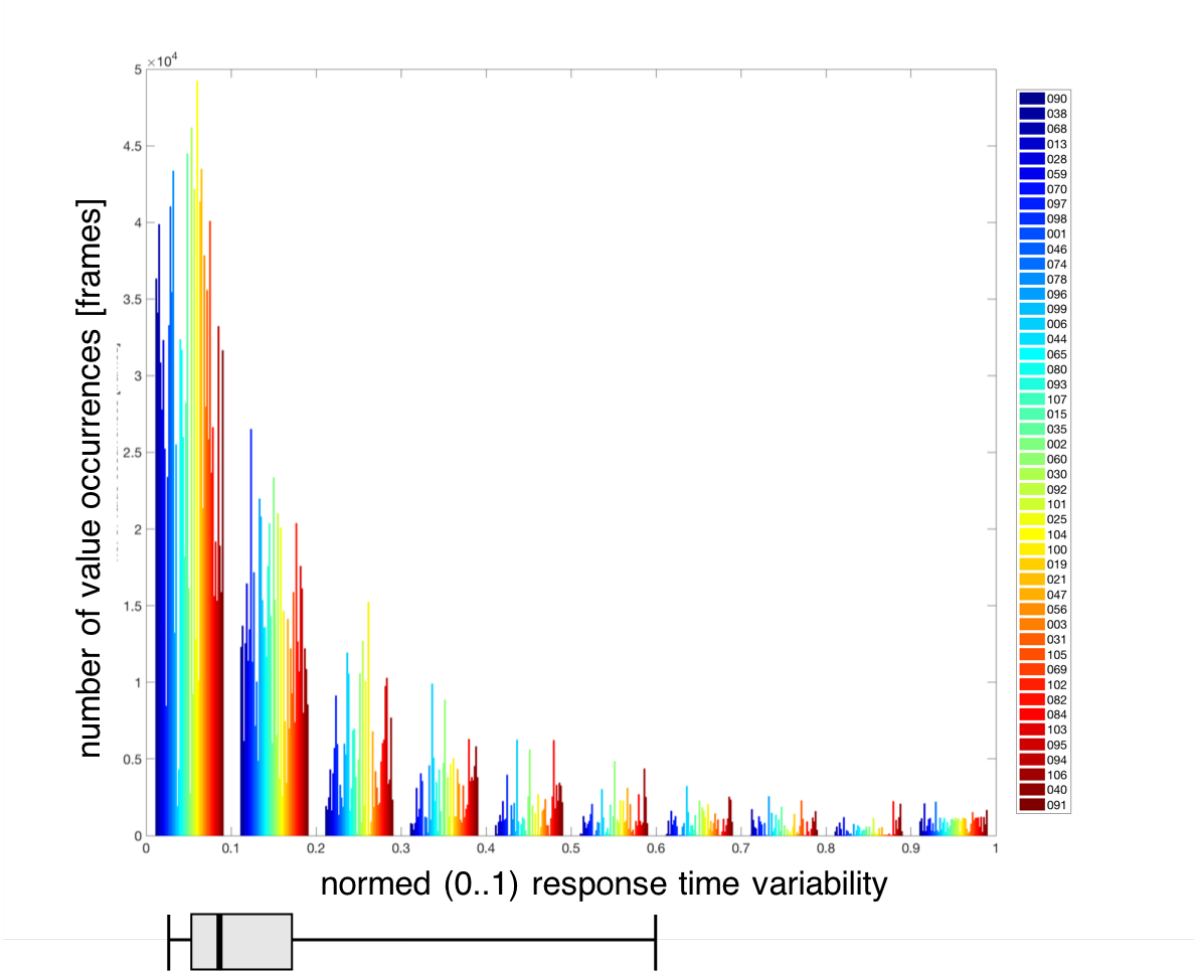
I.11 Low frequency band of the heart rate variability (HRVLF)



I.12 Response time (RT)



I.13 Response time variability (RTV)



J Correlation coefficients for all parameters included in the study

Spearman correlation coefficients and affiliated p values for all parameters and all subjects are shown on the following page. Parameters are abbreviated as follows:

- Blink rate (BR)
- Blink rate variability (BRV)
- Pupil diameter (PD)
- Pupil diameter variability (PDV)
- Peaks in pupil diameter variability (PDVpeaks)
- Pupil diameter wavelet analyzed parameter d10 (PDVd10)
- Height of the palpebral fissure (PF)
- Variability of the height of the palpebral fissure (PFV)
- Heart rate (HR)
- Heart rate variability (HRV)
- High frequency band of the heart rate variability (HRVHF)
- Low frequency band of the heart rate variability (HRVLF)
- Response time (RT)
- Response time variability (RTV)

ID	age	ESS	onset	gender	total no. of errors	rho (BR x ER)	p (BR x ER)	rho (BRV x ER)	p (BRV x ER)	rho (PDVd10 x ER)	p (PDVd10 x ER)	rho (PDV x ER)	p (PDV x ER)	rho (PD x ER)	p (PD x ER)	rho (PDVpeaks x ER)	p (PDVpeaks x ER)	rho (PFV x ER)	p (PFV x ER)	rho (PF x ER)	p (PF x ER)	rho (HRV x ER)	p (HRV x ER)	rho (HR x ER)	p (HR x ER)	rho (HRVHF x ER)	p (HRVHF x ER)	rho (HRVLF x ER)	p (HRVLF x ER)	rho (RTV x ER)	p (RTV x ER)	rho (RT x ER)	p (RT x ER)
090	27	1	NaN	m	0	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN	NaN
038	55	6	NaN	f	1	-0,0990	0,0000	-0,1073	0,0000	0,0403	0,0000	-0,0093	0,0288	0,0791	0,0000	0,0131	0,0020	-0,1065	0,0000	NaN	0,0000	-0,0246	0,0000	-0,0323	0,0000	0,0854	0,0000	0,0624	0,0000	0,0572	0,0000	-0,0523	0,0000
068	67	6	NaN	f	1	-0,1587	0,0000	0,0106	0,0129	-0,0638	0,0000	-0,1632	0,0000	0,0692	0,0000	-0,1131	0,0000	-0,1807	0,0000	0,2414	0,0000	0,0343	0,0000	0,1748	0,0000	-0,1008	0,0000	0,0472	0,0000	0,1195	0,0000	-0,0103	0,0161
013	43	11	NaN	f	2	-0,0362	0,0000	0,1304	0,0000	-0,2580	0,0000	0,0289	0,0000	0,1503	0,0000	0,0324	0,0000	-0,0959	0,0000	0,0421	0,0000	-0,0961	0,0000	-0,1476	0,0000	-0,2153	0,0000	0,1361	0,0000	0,2752	0,0000	0,0153	0,0003
028	45	10	NaN	f	2	0,0402	0,0000	0,0063	0,1433	0,1343	0,0000	-0,0058	0,1738	0,0874	0,0000	0,1837	0,0000	0,1215	0,0000	0,0344	0,0000	0,0499	0,0000	0,0908	0,0000	-0,2267	0,0000	-0,1506	0,0000	0,2582	0,0000	0,0467	0,0000
059	40	8	NaN	f	2	0,0728	0,0000	0,1426	0,0000	0,1104	0,0000	0,0015	0,7213	0,0420	0,0000	0,1404	0,0000	0,1615	0,0000	-0,2593	0,0000	0,0872	0,0000	-0,0374	0,0000	0,2426	0,0000	0,2557	0,0000	0,2972	0,0000	0,0440	0,0000
070	70	4	NaN	f	2	-0,0179	0,0000	0,0449	0,0000	-0,0334	0,0000	0,0726	0,0000	0,1051	0,0000	0,2489	0,0000	-0,1195	0,0000	-0,2057	0,0000	0,0496	0,0000	-0,2183	0,0000	-0,0917	0,0000	-0,0320	0,0000	0,0963	0,0000	0,0235	0,0000
097	23	9	NaN	f	2	0,0060	0,1573	-0,0260	0,0000	-0,0152	0,0003	0,0325	0,0000	0,0151	0,0004	0,2444	0,0000	-0,1109	0,0000	-0,0104	0,0151	0,2038	0,0000	0,1110	0,0000	-0,1586	0,0000	0,0587	0,0000	0,3152	0,0000	0,0331	0,0000
098	26	10	NaN	f	2	0,2375	0,0000	0,1791	0,0000	-0,0475	0,0000	0,0786	0,0000	0,2751	0,0000	-0,0069	0,1124	0,3049	0,0000	-0,0735	0,0000	0,0087	0,0431	0,0232	0,0000	0,2084	0,0000	0,1072	0,0000	0,2205	0,0000	0,0791	0,0000
001	46	7	NaN	f	3	0,1002	0,0000	-0,0519	0,0000	-0,0226	0,0000	0,0300	0,0000	0,0781	0,0000	-0,0867	0,0000	0,0322	0,0000	-0,0426	0,0000	-0,2301	0,0000	-0,1815	0,0000	0,1753	0,0000	-0,1702	0,0000	0,2739	0,0000	0,0153	0,0004
046	50	10	NaN	m	3	0,0693	0,0000	0,1518	0,0000	-0,0345	0,0000	-0,1457	0,0000	-0,0093	0,0281	-0,0065	0,1255	-0,0129	0,0024	-0,1538	0,0000	0,0433	0,0000	0,1184	0,0000	0,0235	0,0000	-0,0114	0,0074	0,1559	0,0000	0,0494	0,0000
074	50	3	14,7983	f	3	0,1166	0,0000	0,3183	0,0000	0,0376	0,0000	-0,0662	0,0000	0,1753	0,0000	-0,0803	0,0000	0,3055	0,0000	0,0105	0,0149	0,2000	0,0000	0,0060	0,1602	0,2160	0,0000	0,1351	0,0000	0,1887	0,0000	0,0296	0,0000
078	67	5	0,5008	f	3	-0,0990	0,0000	-0,0248	0,0000	0,2001	0,0000	-0,0417	0,0000	-0,0517	0,0000	0,1006	0,0000	-0,0346	0,0000	-0,0418	0,0000	0,2794	0,0000	-0,0601	0,0000	0,2203	0,0000	0,1224	0,0000	0,0712	0,0000	-0,0528	0,0000
096	47	3	NaN	m	3	0,1371	0,0000	-0,0080	0,0625	-0,0664	0,0000	0,1038	0,0000	0,0685	0,0000	0,0553	0,0000	0,2286	0,0000	-0,0071	0,1036	-0,0696	0,0000	0,2647	0,0000	-0,2588	0,0000	0,0355	0,0000	0,2679	0,0000	0,0057	0,1851
099	23	10	NaN	m	3	-0,1331	0,0000	-0,1287	0,0000	0,0424	0,0000	-0,0492	0,0000	0,0779	0,0000	-0,0870	0,0000	-0,1755	0,0000	0,0224	0,0000	0,0135	0,0015	0,1120	0,0000	-0,0242	0,0000	-0,0903	0,0000	0,1621	0,0000	0,0455	0,0000
006	45	3	NaN	f	4	0,1022	0,0000	0,2034	0,0000	0,1242	0,0000	0,1386	0,0000	0,1581	0,0000	0,2611	0,0000	0,2141	0,0000	0,1805	0,0000	0,1653	0,0000	0,0679	0,0000	-0,0730	0,0000	0,0645	0,0000	0,3978	0,0000	0,0739	0,0000
044	63	11	NaN	m	4	0,0580	0,0000	-0,0867	0,0000	-0,0642	0,0000	0,0289	0,0000	-0,1155	0,0000	-0,0044	0,3788	-0,0394	0,0000	-0,1729	0,0000	-0,0366	0,0000	-0,0912	0,0000	0,0143	0,0041	-0,1437	0,0000	0,1495	0,0000	-0,0222	0,0000
065	69	6	NaN	f	4	-0,0364	0,0000	0,0457	0,0000	-0,0728	0,0000	-0,1037	0,0000	0,0063	0,1431	-0,1396	0,0000	0,0156	0,0003	0,0276	0,0000	0,0985	0,0000	-0,0531	0,0000	0,0393	0,0000	0,1246	0,0000	0,1793	0,0000	0,0709	0,0000
080	62	9	NaN	f	4	0,0727	0,0000	-0,1375	0,0000	-0,0797	0,0000	0,1361	0,0000	0,0423	0,0000	0,1216	0,0000	0,0291	0,0000	0,1326	0,0000	-0,0202	0,0000	-0,0043	0,3107	0,0961	0,0000	-0,0350	0,0000	0,2096	0,0000	0,0603	0,0000
093	26	12	NaN	m	4	0,1679	0,0000	0,1657	0,0000	0,0900	0,0000	0,0548	0,0000	0,1834	0,0000	0,1502	0,0000	0,3869	0,0000	-0,0039	0,3663	0,1424	0,0000	0,0592	0,0000	0,0020	0,6346	0,2896	0,0000	0,3046	0,0000	0,0028	0,5141
107	78	6	NaN	m	4	0,0339	0,0000	0,1649	0,0000	0,1372	0,0000	0,1185	0,0000	0,2009	0,0000	0,2638	0,0000	-0,1160	0,0000	-0,3045	0,0000	0,0796	0,0000	-0,1186	0,0000	0,1132	0,0000	0,2187	0,0000	0,1594	0,0000	0,0379	0,0000
015	25	12	NaN	f	5	0,0214	0,0000	0,1109	0,0000	0,0598	0,0000	0,0110	0,0107	-0,0278	0,0000	0,0102	0,0179	0,2642	0,0000	0,0684	0,0000	0,2051	0,0000	-0,2453	0,0000	0,2470	0,0000	-0,0708	0,0000	0,1377	0,0000	0,0459	0,0000
035	43	7	18,4217	m	5	0,0406	0,0000	-0,0171	0,0001	-0,0454	0,0000	-0,0387	0,0000	-0,0151	0,0004	-0,0507	0,0000	-0,0228	0,0000	-0,1620	0,0000	-0,0480	0,0000	-0,0090	0,0345	-0,0664	0,0000	-0,2224	0,0000	0,2913	0,0000	-0,0082	0,0524
002	43	7	NaN	m	6	-0,0285	0,0000	-0,1332	0,0000	-0,0497	0,0000	0,0164	0,0001	-0,0499	0,0000	-0,0904	0,0000	-0,1472	0,0000	0,1783	0,0000	-0,1038	0,0000	-0,1539	0,0000	-0,1452	0,0000	-0,0313	0,0000	0,2853	0,0000	0,0157	0,0002
060	67	10	36,8400	m	6	-0,0264	0,0000	-0,0859	0,0000	0,1381	0,0000	0,1629	0,0000	-0,1108	0,0000	0,1176	0,0000	-0,1356	0,0000	-0,0877	0,0000	0,0112	0,0096	0,0632	0,0000	-0,0509	0,0000	0,1033	0,0000	0,1946	0,0000	0,1295	0,0000
030	22	3	5,9217	f	7	-0,0449	0,0000	-0,0031	0,4660	0,1395	0,0000	0,1496	0,0000	-0,1438	0,0000	0,0625	0,0000	0,0913	0,0000	-0,1057	0,0000	-0,0765	0,0000	-0,2332	0,0000	0,0423	0,0000	0,0541	0,0000	0,4778	0,0000	0,1516	0,0000
092	27	7	NaN	f	7	-0,0058	0,1784	-0,1048	0,0000	0,0018	0,6761	-0,1162	0,0000	-0,1615	0,0000	-0,1325	0,0000	0,0780	0,0000	-0,0352	0,0000	-0,0611	0,0000	-0,0317	0,0000	-0,0011	0,7893	0,0575	0,0000	0,4039	0,0000	0,0032	0,4504
101	28	6	29,8617	m	9	-0,0640	0,0000	-0,0378	0,0000	-0,1874	0,0000	0,0040	0,3479	-0,0252	0,0000	-0,0002	0,9615	-0,2075	0,0000	0,0436	0,0000	-0,0509	0,0000	-0,1398	0,0000	-0,1602	0,0000	-0,2150	0,0000	0,5394	0,0000	0,0182	0,0000
025	22	6	19,3650	f	10	0,0127	0,0030	0,1907	0,0000	0,1051	0,0000	-0,1594	0,0000	0,0934	0,0000	0,1016	0,0000	0,3298	0,0000	-0,0896	0,0000	0,3202	0,0000	0,2252	0,0000	0,1036	0,0000	0,1220	0,0000	0,1326	0,0000	0,1375	0,0000
104	52	7	0,5008	f	11	-0,1268	0,0000	-0,2499	0,0000	-0,1932	0,0000	-0,2054	0,0000	0,3536	0,0000	0,0222	0,0000	-0,3713	0,0000	0,4338	0,0000	0,0991	0,0000	0,2815	0,0000	-0,0809	0,0000	-0,1258	0,0000	0,5634	0,0000	0,0960	0,0000
100	26	3	3,9267	f	12	-0,1644	0,0000	-0,0715	0,0000	0,3386	0,0000	0,1467	0,0000	-0,2120	0,0000	0,2392	0,0000	-0,2584	0,0000	0,1312	0,0000	-0,2800	0,0000	0,0609	0,0000	-0,0993	0,0000	0,0492	0,0000	0,0704	0,0000	-0,0243	0,0000
019	29	14	16,4900	m	14	-0,1027	0,0000	0,1787	0,0000	0,1897	0,0000	-0,1929	0,0000	0,1691	0,0000	-0,2625	0,0000	-0,1793	0,0000	0,1132	0,0000	-0,0156	0,0002	0,0898	0,0000	-0,2913	0,0000	-0,2702	0,0000	0,3894	0,0000	-0,0102	0,0157
021	62	5	13,8792	m	14	0,1436	0,0000	0,0106	0,0139	-0,0155	0,0003	0,0521	0,0000	-0,1766	0,0000	-0,0194	0,0000	0,0763	0,0000	-0,0795	0,0000	0,1023	0,0000	0,0030	0,4905	-0,0977	0,0000	-0,1004	0,0000	0,0927	0,0000	0,1099	0,0000
047	63	5	8,3192	f	18	0,0754	0,0000	0,2462	0,0000	-0,0064	0,1351	0,1275	0,0000	-0,0494	0,0000	0,0600	0,0000	0,0774	0,0000	-0,1494	0,0000	0,0710	0,0000	-0,0818	0,0000	0,0747	0,0000	0,0069	0,1104	0,4014	0,0000	0,1481	0,0000
056	45	10	22,8467	f	18	0,3936	0,0000	0,1534	0,0000	-0,0048	0,2603	0,2171	0,0000	-0,4025	0,0000	0,2627	0,0000	0,4082	0,0000	-0,5039	0,0000	-0,0917	0,0000	-0,1428	0,0000	0,3737	0,0000	0,2041	0,0000	0,4448	0,0000	0,3158	0,0000
003	24	7	0,5008	m	19	-0,0313	0,0000	0,0965	0,0000	-0,1556	0,0000	-0,0136	0,0017	0,1687	0,0000	-0,0736	0,0000	0,1172	0,0000	-0,1714	0,0000	-0,0951	0,0000	-0,0998	0,0000	-0,0040	0,3583	-0,0529	0,0000	0,0445	0,0000	0,0479	0,0000
031	22	4	4,9950	f	20	-0,0278	0,0000	0,0200	0,0000	-0,0311	0,0000	-0,0826	0,0000	0,0936	0,0000	-0,1615	0,0000	-0,1178	0,0000	-0,0194	0,0000	0,0313	0,0000	0,1833	0,0000	-0,0431	0,0000	0,0606	0,0000	0,2762	0,0000	0,1353	0,0000
105	73	1	4,9583	f	22	0,1776	0,0000	0,0680	0,0000	-0,0152	0,0005	0,1786	0,0000	-0,1320	0,0000	0,3319	0,0000	0,1537	0,0000	-0,2926	0,0000	0,0928	0,0000	0,1240	0,0000	0,0163	0,0002	0,3446	0,0000	0,3355	0,0000	0,1744	0,0000
069	69	5	5,4100	m	24	-0,1219	0,0000	-0,1606	0,0000	-0,0573	0,0000	-0,0301	0,0000	-0,0199	0,0000	0,0282	0,0000	-0,0755	0,0000	0,0734	0,0000	0,0173	0,0001	-0,1321	0,0000	0,2263	0,0000	-0,0947	0,0000	0,1584	0,0000	0,0656	0,0000
102	74	5	0,5008	f	24	-0,0842	0,0000	0,0247	0,0000	-0,0182	0,0000	-0,0738	0,0000	-0,0678	0,0000	0,2810	0,0000	-0,2909	0,0000	-0,0231	0,0000	-0,0037	0,3890	-0,1464	0,0000	0,1882	0,0000	0,0661	0,0000	0,3397	0,0000	-0,0290	0,0000
082	47	10	0,7917	f	25	0,1918	0,0000	0,1533	0,0000	0,2110	0,0000	0,0346	0,0000	0,0433	0,0000	-0,0149	0,0005	0,2924	0,0000	-0,3354	0,0000	0,0486	0,0000	0,2617	0,0000	-0,1501	0,0000	0,1098	0,0000	0,2001	0,0000	0,0670	0,0000
084	64	5	0,5008	f	26	-0,0182	0,0000	0,1148	0,0000	0,3058	0,0000	0,0402	0,0000	-0,0695	0,0000	0,0113	0,0090	0,0737	0,0000	-0,0536	0,0000	-0,1102	0,0000	0,0350	0,0000	NaN	NaN	NaN	NaN	0,3142	0,0000	0,0606	0,0000
103	76	6	0,6458	m	27	0,2487	0,0000	0,3095	0,0000	-0,1342	0,0000	0,1915	0,0000	0,1672	0,0000	0,1922	0,0000	0,1282	0,0000	-0,3202	0,0000	0,1189	0,0000	-0,0285	0,0000	0,0594	0,0000	0,1396	0,0000	0,6099	0,0000	0,0923	0,0000
095	23	12	17,9458	f	39	0,2189	0,0000	0,4474	0,0000	-0,0110	0,0107	0,1588	0,0000	-0,2065	0,0000	0,0545	0,0000	0,5068	0,0000	-0,5994	0,0000	0,2121	0,0000	-0,3589	0,0000	0,4341	0,0000	0,5881	0,0000	0,4766	0,0000	0,3549	0,0000
094	31	8	21,0425	m	43	0,0773	0,0000	0,3285	0,0000	0,4526	0,0000	0,2947	0,0000	-0,3240	0,0000	0,1476	0,0000	-0,0479	0,0000	-0,7053	0,0000	0,1018	0,0000	-0,5364	0,0000	0,5033	0,0000	0,6133	0,0000	0,4263	0,0000	0,2186	0,0000
106	58	11	5,9692	m	44	0,3417	0,0000	0,2591	0,0000	0,1804	0,0000	0,1891	0,0000	-0,2391	0,0000	0,2054	0,0000	0,4619	0,0000	-0,1067	0,0000	0,1528	0,0000	0,2165	0,0000	0,0279	0,0000	0,3743	0,0000	0,2736	0,0000	0,1084	0,0000
040	56	6	0,8108	f	79	0,4184	0,0000	0,3546	0,0000	-0,0258	0,0000	0,4414	0,0000	0,0555	0,0000	0,2141	0,0000	0,4904	0,0000	-0,5932	0,0000	-0,2446	0,0000	-0,5698	0,0000	0,4609	0,0000	0,1742	0,0000	0,5040	0,0000	0,3293	0,0000
091	61	15	14,9608	f	82	0,6311	0,0000	0,4957	0,0000	-0,0437	0,0000	0,5302	0,0000	0,0117	0,0068	0,6147	0,0000	0,7357	0,0000	-0,8219	0,0000	0,3580	0,0000	-0,2162	0,0000	0,6706	0,0000	0,4606	0,0000	0,7387	0,0000	0,1381	0,0000
median	**46,5**	**7**	**5,94545**		**6**	**0,0371**		**0,0457**		**-0,011**		**0,0313**		**0,0286**		**0,0549**		**0,0322**		**-0,048**		**0,0433**		**-0,009**		**0,0153**		**0,0606**		**0,2739**		**0,0479**	

As correlations were carried out individually for 48 subjects and for 14 parameters, respectively, the requirement for significance is set to p < 0,0000744.

For overview and clarity reasons, only four decimal places (after rounding) are given. p values less than 0,0000744 are therefore given as 0,0000. If a p value of 0,0000744 or above occurs, a p value of at least 0,0001 is stated (the discrepancy between the rounding limit 0,00005 and the significance value p = 0,0000744 was checked before and taken into account in individual cases).

P values that do not show significance are marked in gray. As non-significant values do only occur for few, individual subjects per parameter, an "overall significance" is assumed for all parameters tested.