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Smooth pursuit gain during eye tracking – a comparison of toddlers and preschoolers with autism spectrum disorders and typically developing controls

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For my family and friends

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Abbreviations

[⬚]	Round down to next integer
A-FFIP	ASD-specific-Frankfurt Early Intervention Program
ADI-R	Autism Diagnostic Interview-Revised
ADOS	Autism Diagnostic Observation Schedule
ASD	Autism-spectrum-disorder ≙ Autismus-Spektrum-Störung
BAYLEY	Bayley Scales of Infant and Toddler Development
CBCL 1 ½-5	Child Behavior Checklist 1 1/2 -5
CBCL 4-18	Child Behavior Checklist 4-18
CCC-2	Children's Communication Checklist-2
CCL-R	Children's Communication Checklist revised
CL	Confidence level
cm	Centimeter
CR	Corneal reflection
dpt	Diopter
DSM-PDP	Diagnostic and Statistical Manual of Mental Disorders-Pervasive Developmental Problems
DSM V	5th edition of the "Diagnostic and Statistical Manual of Mental Disorders"
EEG	Electroencephalography
e.g.	exempli gratia (English: for example)
LM	Linear model
mm	Millimeter
MRI	Magnetic resonance imaging
ms	Millisecond
px	Pixel
RBS-R	Repetitive Behaviors Scale – Revised
RSME	Root Mean Square Error
scr_x, scr_y	Screen, measure for x- and y-position, 1 = one screen width resp. height
s	Second
SPG	Smooth Pursuit Gain
SPEM	Smooth Pursuit Eye Movements

SRS T-Score	Social Responsiveness Scale T-score
SRS-16	Social Responsiveness Scale-16 item version
TD	Typically developing
VC	Visual cortex
WPPSI III	Wechsler Preschool and Primary Scale of Intelligence III
z.B.	zum Beispiel (English: for example)

Definitions regarding the eye-tracker

axis [px]	the x-/y-axis of the screen with 1920 and 1080 pixel
$gazepos_x$ [px]	x-position of gaze
$gazepos_y$ [px]	y-position of gaze
moment	Every trial consists of several moments. Each moment represents one recording of ball and gaze position at one point in time.
timestamp [ms]	time point of each moment
trial	This task consists of 6 horizontal and 6 vertical trials per participant. The duration of one trial is defined by the target movement along one screen dimension (width = horizontal, height = vertical) with an increasing velocity of the target per trial. The odd-numbered figures represent the horizontal trials, while the even-numbered represent the vertical ones.
ts.index	numeration of the moments per trial

Additional measures and definitions

accuracy [px][1]	root mean square error (RMSE) $= \sqrt{(\mathrm{x_{pos}} - gazepos_x)^2 + (\mathrm{y_{pos}} - gazepos_y)^2}$
chronological age	biological age
developmental age	result of BAYLEY-/WPPSI III-testing
gain	$\frac{gazevelocity}{targetvelocity}$ (see Lencer et al.)[2]
group.numeric	0: TD, 1: ASD
sex	0: male; 1: female

smooth pursuit velocity	gaze velocity at the time of smooth pursuit eye movement
target direction	0: horizontal, 1: vertical
time [s]	$= \frac{timestamp - (first\ timestamp\ of\ belonging\ trial)}{10^6}$
trial.index	numeration of the 12 trials per participant
trial.index.6	modified trial-counter per target direction
x_{pos} [px]	$= \left\lfloor \frac{ts.index}{5} \right\rfloor * targetvelocity + 1$, if horizontal, otherwise 960
y_{pos} [px]	$= \left\lfloor \frac{ts.index}{5} \right\rfloor * targetvelocity + 1$, if vertical, otherwise, 540

1 Zusammenfassung

Eine Störung aus dem Autismus-Spektrum (ASD) ist eine in der frühen Kindheit einsetzende neurologische Entwicklungsstörung.[3–6] Sie tritt in verschiedenen Schweregraden auf und beeinflusst die Betroffenen somit unterschiedlich stark in ihrem Leben.[7] Eine frühzeitige Diagnose von ASD ist elementar, um Kindern eine bestmögliche Förderung zu ermöglichen.[8] Eye-Tracking kann hierbei eine frühere Diagnostik von ASD unterstützen: Verschiedene Studien zeigen Unterschiede der Augenbewegung bei Menschen mit Autismus-Spektrum-Störung (ASD) gegenüber sich neurotypisch entwickelnden Kindern (TD). Unterschiedliche Augenbewegungen können zu einer veränderten visuellen Wahrnehmung führen. Diese wiederum kann abweichende Aufmerksamkeits-, Kommunikations- und soziale Interaktionsschwierigkeiten zur Folge haben.[9–12] Eye-Tracker erfassen die Augenbewegung in hoher zeitlicher Auflösung.[13] Für die Testung von jungen Kindern hat sich das Hornhautreflexions-Eye-Tracking bewährt, da hierbei keine störenden Vorrichtungen, wie beispielsweise eine spezielle Brille, nötig sind.[14] Man unterscheidet drei Typen von Augenbewegung: Fixationen, Sakkaden (schnelle und kurze Augenbewegungen)[15] und kontinuierliche Augenbewegungen, auch Smooth Pursuit Eye Movements (SPEM). Letztere sind Thema der vorliegenden Arbeit. SPEM ermöglichen das Verfolgen von sich bewegenden Objekten auf gleichmäßige Weise (engl. smooth). Sie bestehen aus zwei Phasen: Initiierungsphase (die ersten 50-100ms) sowie Erhaltungsphase (nach ca. 100ms). Zur Quantifizierung der SPEM wird meist der sogenannte *Gain-Index* berechnet. Dieser ist definiert als das Verhältnis der SPEM-Geschwindigkeit zu der Geschwindigkeit des Objekts und liegt idealerweise bei 1.[2] Bei einem Gain-Index von 1 würde sich eine perfekte Verfolgung des Objektes durch die Proband:in zeigen, da die SPEM-Geschwindigkeit die gleiche ist wie die Objektgeschwindigkeit.

Die SPEM bei jungen Kindern mit ASD sind bisher wenig untersucht worden. Einzelne vorangegangene Studien zeigten jedoch sowohl in der Initiierungsphase, als auch in der Erhaltungsphase Auffälligkeiten bei Kindern mit ASD.[11,12,16] Da im Kleinkindalter die Grundsteine für die Ausbildung von sozialen Fähigkeiten gelegt werden,[17–19] wird vermutet, dass eine abweichende SPEM zu veränderten Entwicklungsprozessen betragen könnten.

In der vorliegenden Studie wurden Klein- und Vorschulkinder mit ASD und sich neurotypisch entwickelnde Kinder (TD) (Alter zwischen 1,5 und 6 Jahren, ASD: n = 33, TD: n = 33) untersucht. Die Gruppen wurden nach kognitiver Fähigkeit (BAYLEY oder WPPSI-III)[20,21] und Geschlecht gematcht. Zentrales Ziel war dabei der Vergleich des *Gain-Index* (Smooth Pursuit Gain = SPG) von Teilnehmer:innen mit ASD im Vergleich zur Kontrollgruppe. Vermutet wurde ein geringerer smooth pursuit gain (SPG) bei Kindern mit ASD.[22]

In der vorliegenden Studie zeigte sich ein signifikanter Einfluss der Gruppe auf den Gain-Index bei Berücksichtigung der Interaktion zwischen Objektgeschwindigkeit und Gruppe ($p = 0.041$). Die TD-Gruppe zeigte eine stärkere Abhängigkeit von der zunehmenden Objektgeschwindigkeit als die ASD-Gruppe mit einem Trend von -0.30 ± 0.11 in der TD-Gruppe und einem Trend von -0.13 ± 0.12 in der ASD-Gruppe. Die Ergebnisse über die Gruppen hinweg zeigen, dass der SPG mit steigender Objektgeschwindigkeit abnahm und in vertikalen Sequenzen schneller abfiel als in horizontalen Sequenzen. Darüber hinaus zeigten Teilnehmer:innen in vertikalen Sequenzen einen niedrigeren SPG als in horizontalen Sequenzen.

Kinder im Vorschulalter stellen eine Gruppe dar, die bisher wenig Gegenstand von Forschung gewesen ist. Zusätzlich gibt es bis dato eine begrenzte Anzahl an Studien, die sich mit SPEM in ASD auseinandersetzen. Um einen möglichen Gruppenunterschied ohne Wechselwirkungen zu überprüfen, sollte eine Studie mit einer größeren Stichprobengröße und einheitlicher Objektgeschwindigkeit sowie Objektrichtung erfolgen.

2 Summary

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition with an onset in early development.[3–6] ASD has varying degrees of severity and thus affects people differently throughout their lives.[7] Early diagnosis of ASD is essential to provide children with individually-tailored support.[8] Eye-tracking may contribute to an earlier diagnosis: Several studies showed differences in eye movements between people with autism spectrum disorder (ASD) and typically developing controls (TD). Different eye movements may contribute to different

visual perception that perpetuates to problems in attention, communication and social interaction.[9,10,12,23]

Eye movements are divided into: (1) Fixations (2) Saccades (fast and short eye movements)[15] and (3) Smooth Pursuit Eye Movements (SPEM). SPEM follow the target in a continuous manner.[24] The latter are the subject of the present thesis. SPEM consist of two phases: the open loop phase (= phase of initiation, first 50-100ms) and the closed loop phase (= phase of maintenance, after about 100ms).[2] SPEM are usually measured by a gain index. It is defined as the ratio of smooth pursuit velocity and visual target velocity and ideally equals to 1.[2]

In young children, corneal-reflection (CR) eye-tracking is usually applied to quantify eye movement. It allows precise measurements without the use of potentially intrusive devices.[14]

Studies in ASD reported deficits in open loop and closed loop pursuit in children and adults with a mean age of 19.32 (TD) and 20.04 (ASD) years.[12,25] However, SPEM in preschoolers with ASD remain understudied, although this developmental phase is crucial to the development of non-social and social attentional abilities.[17–19]

In the present study 66 toddlers and preschoolers (18 to 72 months; ASD: n = 33, TD: n = 33) with matched cognitive abilities and sex were assessed. The main objective was to compare the gain index (Smooth Pursuit Gain = SPG). SPEM were compared between groups with gain index as a dependent measure. We hypothesized that participants with ASD show lower average gain compared to the control group.[22]

We could show a significant group influence on the gain when considering interactions between target velocity and group ($p = 0.041$). The TD group showed a greater dependence on the increasing object speed than the ASD group with a trend of -0.30 ± 0.11 in the TD group and a trend of -0.13 ± 0.12 in the ASD group. Across groups, the gain decreased with increasing target velocity and dropped faster in vertical than in horizontal trials. Additionally, participants showed a lower SPG in vertical sequences than in horizontal sequences. This supports the general validity of the measure.

Toddlers and preschoolers represent a group that has been subject of little research to date. In addition, there has been only a limited number of studies analyzing SPEM in ASD. To check for a possible group difference without

interactions a study with a larger sample size at fixed target velocity and target direction should follow.

3 Introduction

3.1 Autism-Spectrum disorder (ASD)

Autism spectrum disorder (ASD) is an early-onset and persistent neurodevelopmental condition that is characterized by difficulties in social interactions and restrictive repetitive behaviors (e.g. hand-flapping, adjusting objectives).[3–6] Patients often present delayed developmental milestone or stereotyped speech. Several studies show non-social attention deficits in ASD.[e.g. 12,26] The prevalence is at least 1% in a global population and approximately four times higher in males than in females.[5,27,28]

A diagnosis of ASD according to the DSM-V is dependent on the following symptom criteria: 1. Developmental deficits must be present in each area of social communication and interaction (social exchange, nonverbal communication skills and relationship establishment/maintenance). 2. At least two of the four types of restricted-repetitive behaviors must be reported. 3. The symptoms must affect the child significantly in everyday life and can't be explained by intellectual and/ or global development delay. The named above can present themselves at an early age, starting at about 18 months.[8,29]

Current research suggests an interaction of genetic and environmental factors in the etiology of ASD.[5,27] The first symptoms typically are observed at the age of three years.[5] ASD manifests itself in varying degrees of severity: some patients live independent lives, while others require lifelong support.[7] Various studies have shown that adults with ASD have higher rates of under-/unemployment, a lack of reciprocal relationships and even higher mortality rates.[7,30–32]

ASD is further associated with high rates in somatic and psychiatric comorbidity.[33,34]

ASD is related to high costs in the health care sector and often associated with a high burden to social systems. Knapp et al.[5] estimated the lifetime cost of individuals with ASD in the UK to be around £1 million, depending on whether the patient was affected by a cognitive disability.[6] The lifetime cost for individuals with ASD in the USA is estimated to be between $1.5 and $2.5 million.

The difficulty in finding an appropriate treatment for ASD may be due to the heterogeneity of ASD symptom phenotypes. To date, both the pathophysiology and the etiology of ASD remain elusive.[35] There are no curative treatment for the core symptoms of ASD.[36,37] However, several authors have discussed the potential of early intervention for children with ASD.[38–42] Children who received an early intervention (between 18-48 months) showed improvement in IQ and language, as well as in social interaction and daily-life functioning. Early intervention was also associated with an outcome of lower severity in ASD symptoms.[39,41,42] Eye-tracking may assist in an earlier diagnosis that enables early interventions and improves lifetime outcome.

3.2 Anatomy of the eye

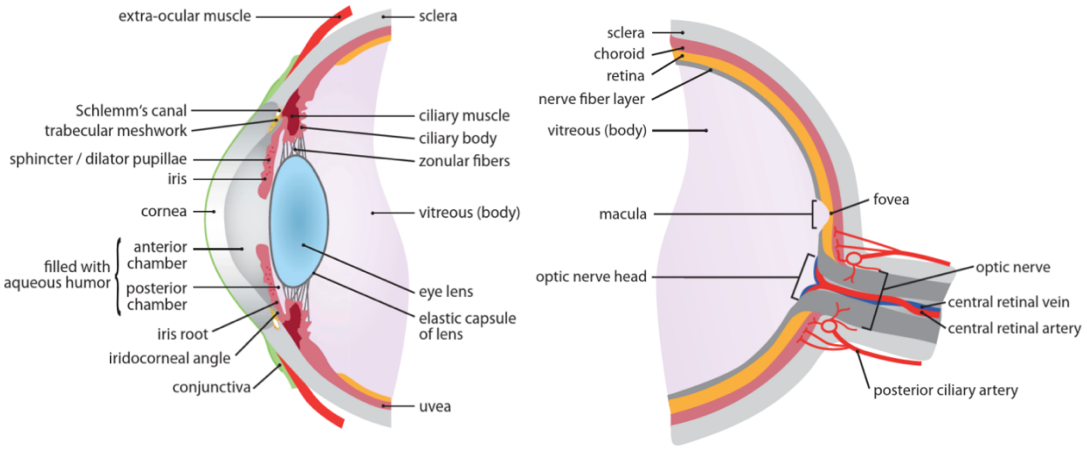

Figure 3.1 Anterior (l.) and posterior (r.) segment of the eye according to Kaschke et al. 2014, p.7. [43]

The eye consists of the eyeball, the optic nerve and several protective and supporting structures. Anatomically, the eyeball can be divided into the anterior segment and the posterior segments (s. figures above). The anterior segment contains the cornea, a transparent layer with a refractive power of 43 diopter (dpt) that reflects infrared light, which is utilized in eye-tracking.[44,45]

The retina can be found in the posterior part. The retina consists of 127 million photoreceptors. The greatest density of photoreceptors is found on the fovea that is located at a central area of the retina and allows for the sharpest vision of the visual apparatus.[45] The fovea has a diameter of 0.5-1 mm.[46] The retinal periphery has a comparatively bad resolution and is primarily used for motion detection.[47]

When the gaze is directed at an object, the visual information falls on the fovea, ensuring sharp vision.

3.3 Visual pathway and human vision

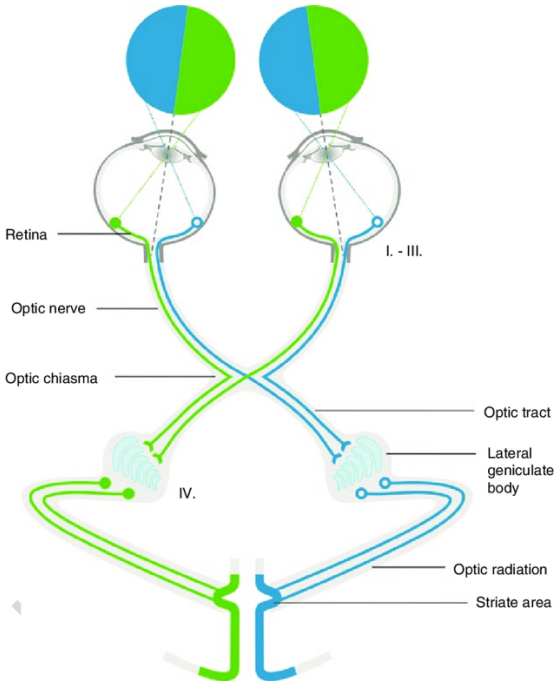

Figure 3.2 Visual pathway according to Joukal 2017, page 2.[48]

The visual pathway originates from the axons of the retinal ganglion cells, which make up the optic nerve. The optic nerve enters the skull through the foramen opticum to reach the optic chiasma. Here the fibers of the nasal parts of the retina cross to the other side and combine themselves with the lateral retinal parts of the opposite side to the optic tract. In the lateral geniculate body, the axons of the retinal ganglion cells are connected to the following cells and the visual information is transmitted to the optic radiation. The striate area then forms the first part of the visual cortex (V1), which is the basis of the binocular vision. Depending on the type of vision being used, different parts of the human brain are involved: for example, color and shape are rather processed in the inferotemporal cortex, while motion and depth perception are rather processed in the parietal posterior cortex (s. figure below).[45]

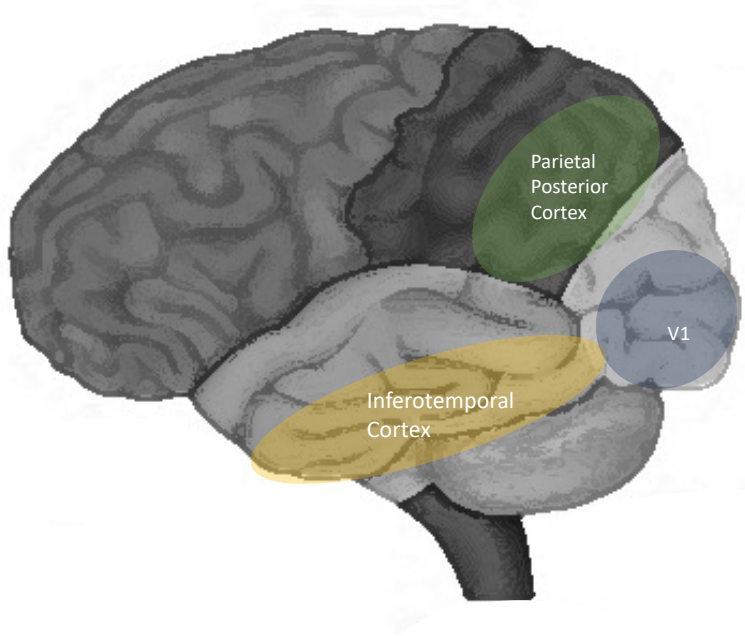

Figure 3.3 Gain structures regarding visual pathways[49]

3.4 Eye movements

There are three different types of eye-movements: Fixation, saccades and smooth pursuit.[1]

3.4.1 Fixations and fixational eye movements

Fixations are moments of relative stasis in which the gaze is kept on an object. It allows sharp vision on the focused object. However, small movements are essential to avoid neural adaptation and consequent reduction of vision: Microsaccades, drifts and oculomotor microtremor.[1]

Microsaccades are the largest of these three eye movements, with a frequency of 1-2 jerks/second and a duration of 25 ms.[1,50] They typically occur in a conjugate manner and have an amplitude of <1 degree.[51] It can be difficult to distinguish between microsaccades and saccades. Therefore, it has been suggested that they share the same underlying circuitry. Some authors have even conjugated them as the same type of eye movement.[1,52,53]

Drifts are slow and steady eye movements that occur in between microsaccades.[1,50] They have a velocity of approximately 50 arcmin/s and with an amplitude of less than 0.1°. This is a much smaller than a microsaccade.[1,54]

Drifts are thought to play a compensatory role in ensuring precise fixation when microsaccades are of poor quality or absent.[55–58]

Oculomotor microtremors, hereafter referred to as tremors, are the tiniest fixational eye movements. They occur simultaneously with drifts. Tremors have a high frequency of about 90 Hz and small amplitude of about 4/1000 degrees.[50,59] High-resolution equipment is essential to detect them.[60] While some authors claim that tremor originates from motor neurons,[61] others claim that it originates from antagonistic muscles.[62]

3.4.2 Saccades

Saccades are rapid, brief eye movements that allow us to explore our environment. Saccades occur at a frequency of approximately two to three times per second. They can be initiated internally/voluntarily or triggered by an external source. Voluntary saccades occur in special situations and require more concentration and focus for their execution than visually guided saccades, which appear frequently in everyday situations when moving the head and body. In between saccadic movements, there are fixational movements. Thus, these two types of eye movements are closely related and intertwined.[15]

3.4.3 Smooth Pursuit Eye Movements (SPEM)

SPEM are continuous eye movements that enable the gaze to follow a moving object smoothly up until a speed of ~30 degrees of visual angle. This is crucial to keep the retinal image on the fovea, which is the site of the sharpest vision.[2]

SPEM consist of two phases: 1. The open loop phase (initiation phase) consists of the first 50-100ms, during which exogenous visual target information is encoded and translated to SPEM oculomotor movement that allows foveal fixation of the visual target. 2. The closed loop phase (maintenance phase) begins after approximately 100ms and is driven by continuous feedback such as predictive or performance-based information and extra retinal factors.[1,9,63]

SPEM can be initiated by motion perception and auditory stimuli. Besides the processing of visual motion and auditory stimuli, the control of SPEM requires a sensorimotor transformation of the motion signal into an oculomotor command and its integration into extra retinal mechanisms. It has been shown that SPEM

can be modified by working memory, visuospatial attention, visuomotor control and also the amount of experience with the stimulus.[1,64]

Visual target information consists of target speed and orientation, which is translated into an ocular command that is then transmitted to the oculomotor nuclei of the brainstem. To maintain the pursuit, a combination of retinal feedback on foveal fixation status and extra retinal mechanisms such as an efference copy of the demand, anticipation and prediction is essential. The velocity of smooth pursuit roughly equals the target velocity to follow the moving target. The goal of tracking the moving target is to keep the image on the retina.[1,65] In the analysis of SPEM, several aspects of pursuit are assessed: 1) initiation of pursuit movement 2) pursuit maintenance 3) cognitive components such as prediction and anticipation using knowledge of predictable target movement.[1]

3.4.3.1 Neural Networks of Smooth Pursuit Eye Movements

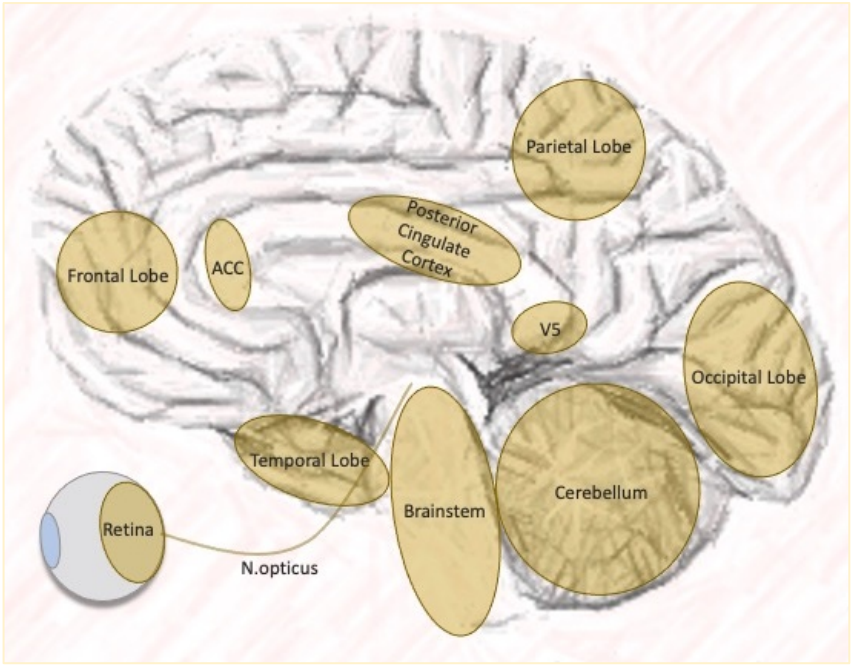

Figure 3.4 Brain schematic for the smooth pursuit network modified from Bruckner et al. p.13[66(p13)] and Schünke et al.[67] ACC = anterior cingulate cortex. V5 as a projection from the lateral view.

The visual pathway describes how and where eye movements are generated and processed. The most important areas involved in eye movements are the frontal eye fields adjacent to the frontal cortex, the posterior parietal cortex, and the occipital and temporal lobes. In addition, the cerebellum is also important for the initiation and maintenance of pursuit.[68] All of these are connected by association

pathways.[69] From the primary visual cortex, information is sent to the human visual area V5.[1] Several authors argue that this area is crucial for smooth pursuit control, also because a positive correlation between smooth pursuit velocity and neural activity in V5 has been shown.[1,70,71] The posterior parietal cortex, which follows the V5, is not only important for maintaining fixations but also for suppressing saccades during smooth pursuit.[72,73] Nagel et al.[74] and Konen et al.[75] reported that neurons in the ventral intraparietal area monitor the pursuit response. Fundamental for the initiation of pursuit are the areas in the frontal cortex, where the actual command for smooth pursuit originates.[76]

3.4.3.2 Smooth pursuit gain

Smooth pursuit gain is defined as the ratio of the smooth pursuit velocity and the velocity of the visual target. It is a commonly used parameter measuring pursuit maintenance and thus quantifies the pursuit performance. The ideal ratio is one.[2] Here, the smooth pursuit velocity is equal to the target velocity and thus shows a perfect tracking of the target. Smooth pursuit gain differs by target velocity, while best performance is achieved at target velocities between 15 and 30°/s.[77,78]

3.5 Eye-tracking

Eye-tracking is used to analyze the people's gaze behavior and can therefore be used to track smooth pursuit performance.[1]

3.5.1 Eye-tracking in children

Eye tracking in children is usually achieved by the corneal reflection (CR) method. It has a high spatial and temporal accuracy.[44] Initial CR eye-tracking was developed in the 1960's by Haith (1969), Salapatek and Kessen (1966).[79,80] Infrared light is reflected off the cornea and with the sphericity of the eyeball, the reflection remains relatively constant despite eye movement. In addition, infrared light is not visible to the human eye and therefore doesn't elicit a response. A calibration is required to assess individual eye ball features: For children older than 4 months, a 5-to-6-point calibration has been found to be appropriate. Here five to six different positions on the screen are chosen and at each of them the calibration procedure will be performed: an object moves towards the calibration

point, stays there for 0.5s and becomes smaller. This enables the eye to focus on the object. Eventually, the eye tracker stores the eye's data.[81] Screen attendance can be emphasized by the presentation of appealing stimuli.[44]

3.5.2 Eye-tracking in ASD

There has been research on eye tracking in ASD regarding adults and children. Riddiford et al.[82] showed a correlation between the gaze's focus on the head/ face of people and social ability in ASD. Additionally, they stated that the social ability was influenced by other factors, e.g., intelligence. Frazier et al.[83] and Chita-Tegmark et al.[84] also conducted meta-analyses presenting diminished social attention in ASD compared to TD. The difficulty in social attention in ASD became more striking when more than one person was displayed. This was underlined by Riddiford et al.[82]. Frazier et al.[83] stated that people with ASD struggled to differentiate between important and non-significant information for attention. Dalton et al.[85] suggested that reduced gaze fixation and subsequent hypoactivation of the fusiform gyrus is ubiquitous in ASD.

Kwon et al.[86], Jones et al.[87] and Papagiannopoulou et al.[88] presented results regarding characteristics in children with ASD. Kwon et al.[86] analyzed how toddlers' gaze changed when geometrical stimuli served as distraction from a social scene. They showed that fixation of eye-regions didn't differ between the two groups. Nevertheless, fixation of faces was diminished in toddlers with ASD. This became even more noticeable when geometrical figures were added to the scene.[86] Papagiannopoulou et al.[88] found that children with ASD had a shorter duration of gaze fixation than TD controls when looking at eye regions. Jones et al.[87] revealed that children with ASD are not born with a deficit in eye fixation but rather present a decline in the first year of age.

However, limited research on SPEM in children with ASD exists. Johnson et al.[11] and Takarae et al.[22] showed a significantly lower gain in the open-loop phase and the closed-loop phases. Aitkin et al.[89] found no significant abnormalities regarding the anticipatory SPEM in ASD.

Previous research by Lencer et al.[2] explored gaze velocity during phases of optimal gain (see figure 5.5). The group excluded saccades before further

interpretation and mean gaze velocity varied between 10 and 20°/s (degrees per visual angle).[2]

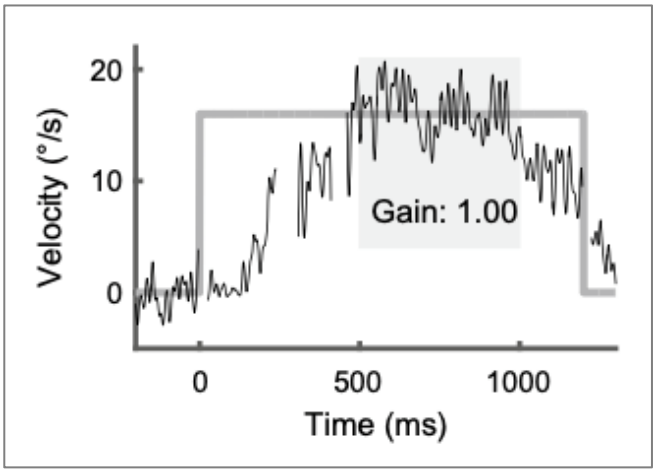

Figure 3.5 Mean maintenance gain. The grey line represents the target (at velocity 16°/s), the black line the gaze and the grey box the slot used for SPEM-analysis after exclusion of saccades from Lencer et al.[2(p138)]

3.6 Objective

SPEM in preschoolers with ASD remain largely unexplored. To date, only few studies have examined SPEM in ASD.[e.g. 2,11,22] However, this developmental period is critical for the development of non-social and social attentional difficulties that might be associated with altered smooth pursuit.[17–19] Thus, we assessed toddlers and preschoolers with ASD and typically developing controls (TD) matched for cognitive ability and sex. We compared the smooth pursuit gain for each subject and hypothesized that subjects with ASD would have lower mean gain compared to the control group.

Findings may contribute to a further characterization of different eye movements in ASD. This could inform advances in the earlier diagnosis of ASD, which would allow for potentially earlier intervention and improved support for children with ASD.

4 Materials and methods

4.1 Participants and recruitment

A total of 92 participants (ASD: 46, TD: 46) age of 1.5 to 6 years, both female and male, participated in the current study. After exclusion and matching (s. below) a

total of 66 participants (ASD: 33, TD: 33) were analyzed. Demographics are shown in the figure below.

Table 1 Demographic data with SD = standard deviation

Variable	Measure	ASD	TD
Participants	Number	33	33
Sex	Females	21%	42%
Age [months]	Mean	47.4	43.1
	SD	9.9	15.6
	Minimum	26	24
	Maximum	65	77
IQ	Mean	61.9	103.4
	SD	16.9	11.9
	Minimum	39	73
	Maximum	101	132
CBCL	Mean	63.8	44.6
	SD	9.0	7.7
	Minimum	46	31
	Maximum	93	58
SRS-16	Mean	27.8	4.8
	SD	7.6	3.0
	Minimum	12	1
	Maximum	39	12
RBS-R	Mean	38.2	10.0
	SD	26.9	11.0
	Minimum	2	0
	Maximum	126	54
ADOS	Mean	6.8	
	SD	1.5	
	Minimum	4	
	Maximum	10	
ADI-R	Mean	30.6	
	SD	13.1	
	Minimum	13	
	Maximum	57	

The control group was recruited through advertisement on social media, kindergartens, and cultural programs such as theaters, museums, and recreational activities. Participants with ASD were recruited through the A-FFIP-study. The A-FFIP study is a multicenter, randomized controlled study comparing the *Frankfurt Early Intervention Program* to common early interventions for young children with ASD.[90]

ASD was diagnosed by clinical experts according to DSM-V-criteria using the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R).

Exclusion criteria were an intellectual/developmental quotient <30 and a developmental age <12 months, chronic neurological or neurodegenerative or attachment disorder, unstable epilepsy, severe psychosocial deprivation, severe sensory impairment, cerebral palsy, Rett/Angelman syndrome, institutional upbringing as well as non-fluent German-speaking caregivers.

TD participants were also excluded if they presented at least one scale of the Child Behavior Checklist 1½ - 5 in clinically significant ranges (T > 65) and a Social Responsiveness Scale (SRS) T-score > 75.[91,92] The SRS T-score was interpolated from the sum score of the Social Responsiveness Scale-16 item version (SRS-16), which has been shown to be highly correlated with the SRS long form (r = 0.98).[93]

Thirteen ASD- and five TD-participants were excluded for criteria named above or for assessment difficulties like insufficient screen attention, strabismus and abortion of the testing.

Next, the participants were matched for IQ and sex. This resulted in the exclusion of a further eight TD-probands.

Participants in the ASD-group showed a great discrepancy between their chronological age and the developmental age (result of the intellectual/ developmental tests described in *4.3*). Regarding sex [percentage of females], we found that 21% of the ASD group were female, while the TD group had 42% females. A female-to-male ratio of 4:1 has been reported in ASD.[5,94] This is almost exactly the same ratio as in our study population. Compared to the population distribution in Germany, where 49% of children < 10 years of age in 2020 were female (3,692,000 females, 3,896,000 males)[95], females are overrepresented in the TD group.

Informed consent of the participation was given by the caregivers/ legal guardians in written form. Ethical approval was granted by the Ethics Committee of the Medical Faculty of the *Johann Wolfgang Goethe-University, Frankfurt/M.*

4.2 Procedures

Data were collected from June 25th 2018 to October 15th 2020 via questionnaires, developmental or intellectual testing and eye tracking. Once participants and their legal guardians agreed to participate in our study, we sent them the questionnaires and asked them to complete them in advance. Prior to developmental or intellectual testing, the participants were given the opportunity to familiarize themselves with the material and the examiner. In addition, caregivers could join the assessments to comfort the participants. Participants from 18 to 35 months completed the Bayley Scale of Infant and Toddler Development (BAYLEY) scales to assess their developmental age, whereas participants from 36 to 72 months completed the Wechsler Preschool and Primary Scale of Intelligence III (WPPSI III) performance scale (s. chapter 4.3.2).[20,21] When participants in the respective age range were not able to do the WPPSI III, we applied the BAYLEY scales as an alternative measure. WPPSI III results were translated to a developmental age estimate.

In most cases, the eye-tracking was assessed on the same day as the developmental or intellectual testing. For children with a low attention span in the cognitive testing, the eye-tracking-assessment was postponed to a second appointment. Participants with ASD returned a third time for the ADOS-2-assessment.

For the eye tracking assessment, the room was dimly lit without direct sunlight. Depending on the participants preference, the participant sat either in a highchair by her-/himself or on the caregiver's lap during the assessment. If the participant sat alone, the caregiver sat next to the participant, but outside the track box of the eye-tracker. The distance between the participant and the eye-tracking battery was between 60 and 80 cm. Eye-tracking was monitored on a separate experimenter screen. The experimenter was seated next to the computer so that he/she could see the participant, the eye-tracking battery and the additional monitor at the same time. The setup is shown in the figure below.

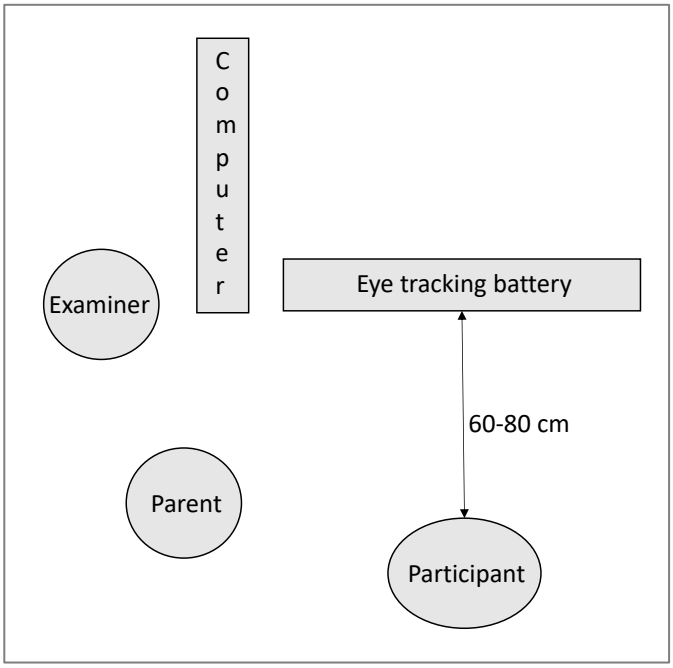

Figure 4.1 Setup for eye tracking

The participant was asked to attend at the screen. Before starting the experimental tasks, a short (approx. 2 minutes), child-friendly video chosen by the family was shown to motivate the participant. Next, a 5–point calibration was performed. There, the eye-tracker calculated gaze data by combining measurements of the participants' eyes with an internal 3D-eye-model.[81] This was followed by the actual eye-tracking assessment. The experimental tasks were interspaced by child-friendly, motivational video sequences to maintain the participants' motivation and screen attendance.

The SPEM-task was one of several tasks in a more extensive eye tracking battery, which took about 25 minutes to complete. The SPEM-task was presented at a pseudorandom position within the eye-tracking battery. The SPEM-task only took 1 minute to complete. The eye-tracking battery was coded in Matlab with Psychtoolbox-3 and is freely available online.[96]

4.3 Measures

Analysis and modeling were performed with *R version 4.1.3* with the following packages: cobalt[97], contrast[98], dplyr[99], effsize[100], emmeans[101], ggplot2[102], lme4[103], lmerTest[104], magrittr[105], Matchit[106], openxlsx[107], psych[108], readxl[109], tidyverse[110], WriteXLS[111], zoo[112].

4.3.1 Bayley Scales of Infant and Toddler Development (BAYLEY)

The BAYLEY is a standardized quantitative score for assessing child development. It is commonly used in clinical studies to assess developmental delays in children from 1 to 42 months of age. It takes approximately 0.5 to 1.5 hours to complete the entire score. The score consists of several play tasks to assess the following scales: cognitive, language, motor, social-emotional and adaptive behavior. The last two scales are assessed through interviews with caregivers, while the cognitive, language and motor scales are to be administered by health care professionals. The test kit consists of different toys such as dolls, balls, blocks and cards, and a stimulus book. The test follows a step ladder format: the child's age determines the starting point. However, if the child is unable to complete the first three tasks after the age-appropriate starting point, the next lower starting point needs to be selected. Also, if the child can't complete a certain number of subsequent items, the test is stopped, and the results can then be calculated. The result is classified by comparing the developmental age to a normative age-matched representative.[113,114]

4.3.2 Wechsler Preschool and Primary Scale of Intelligence III (WPPSI III)

The WPPSI III is an intelligence test for children aged between 36 and 86 months.[115] The scale consists of 14 subtests that can be divided into four parts: General Language Scale (only for the age group 48 to 86 months), Verbal Scale, Performance Scale and Processing Speed. The test takes between 20 and 60 minutes, depending on the age and the child's performance. It is important to pay attention to the child's behavior during the testing, as it may alter the results and should therefore be taken into account in the evaluation.[116] The WPPSI is the most wisely applied intelligence test in preschool age.[117]

4.3.3 Social Responsive Scale 16 (SRS-16)

The SRS-16 is a screening tool for autism spectrum disorders.[118] It is administered by caregivers and/ or teachers, which evaluate children's everyday behavior. It assesses 16 items in five areas, such as "social awareness, social cognition, social communication, social motivation, and autistic mannerisms"[119,93].

4.3.4 Child Behavior Checklist 1½-5 and 4-18 (CBCL 1½-5 and 4-18)

The CBCL was developed to assess a wide range of behavioral and emotional problems in children. It has been applied as a screening tool of general psychopathology in children and adolescents aged 4-18 years.[120] The CBCL consists of 11 subscales: 3 competence scales (school, social and activity) and 8 syndrome scales.[121] The syndrome scales are divided into internalizing (e.g. somatic problems, anxiety/depression, withdrawn) and externalizing (attention problems, aggressive behavior).[122] There are different versions of the CBCL depending on the child's age: The CBCL 1½-5 covers the preschool age.[123]

4.3.5 Children's Communication Checklist-2 (CCC-2) and Children's Communication Checklist revised (CCC-R)

The CCC-2 was developed by Bishop in 2003 and focuses on assessing children's communication strengths and weaknesses in everyday life.[124] While the CCC-2 consists of 70 items, a study by Wellnitz et al.[126] presented a revised CCC that is a shorter and a clinically relevant alternative to the CCC-2. The CCC-R consists of 39 items and only 2 subscales, being pragmatic language and grammatical-semantic language. Both questionnaires are completed by caregivers.[124–126]

4.3.6 Repetitive Behaviors Scale - Revised (RBS-R)

The RBS-R is a screening instrument for the assessment of restrictive and repetitive behavior (RRB).[127] The RBS-R consists of 6 subscales with 43 items that are rated on a scale of 0-3 ("0=behavior does not occur", "3=behavior occurs and is a severe problem") referring to the past month. This allows the examiner the possibility to assess the diversity of RRBs in ASD.[127] A study by Kästel et al.[128] found a four-factor-analysis as reliable and valid approach, not only in children with ASD but also in TD, children with mental disorder and intellectual disability. The following scales were found to be fitting to measure repetitive behavior: persistent behavior subscale, stereotyped behavior subscale, self-injurious behavior subscale and compulsive behavior subscale.[128]

4.3.7 SPEM-task

The SPEM-task consisted of 12 trials. Each trial consisted of a target sliding across the display at a constant speed. The target was presented as a blue dot. In horizontal trials, it started at the left and ended at the right end of the display, whereas in vertical tasks, it started at the top and ended at the bottom of the display. Horizontal and vertical target trials were shown in a mixed order with ascending target speeds per trial condition. Target velocities were constant per trial. On each horizontal /vertical trial, the velocity of the target was increased by 20% compared to the last horizontal/vertical trial. The trial duration became shorter as the target became faster. The first trial lasted 4.3 s while the last trial lasted 1.1 s. Vertical trials were shorter than horizontal trials due to the dimensions of the display (16:10 aspect ratio, 24-inch screen, 1920 x 1080 resolution). The velocities and trial durations are shown below (see table 2). Trial.index is a counting method over all trials, while Trial.index.6 represents the counting method per target direction.

Table 2 Overview target velocities and trial duration, *with px = pixel*

Trial index	Trial.index.6	Target direction	Target velocity [px/s]	Trial duration [s]
1	1	Horizontal	416.93	4.30
2	1	Vertical	397.47	2.42
3	2	Horizontal	500.31	3.54
4	2	Vertical	476.96	1.96
5	3	Horizontal	583.70	2.99
6	3	Vertical	556.46	1.64
7	4	Horizontal	667.09	2.58
8	4	Vertical	635.95	1.40
9	5	Horizontal	750.47	2.26
10	5	Vertical	715.44	1.21
11	6	Horizontal	833.86	2.00
12	6	Vertical	794.94	1.06

4.4 Data preprocessing

The assessment was performed using the Tobii® TX300 eye-tracker. The eye-tracker has an optimal gaze accuracy of 0.4°/s and a sampling rate of 300 Hz (=300 measurements/ seconds). The Tobii Analytics Software Development Kit (SDK) has been applied to record raw data within Matlab.[129]

The eye-tracker used the corneal-reflection method with near-infrared light to detect the participant's eyes. The display resolution was 1920x1080 pixels. The recorded gaze data were preprocessed and analyzed using R version 4.2.0.

4.4.1 Velocity and Distance to screen

We used a single ramp task, in which the target started with a velocity of 416.929 px/s in the first horizontal trial and 397.469 px/s in the first vertical trial. During each trial the target velocity was constant, but increased by 20% with every trial:

$$\text{target velocity}_{\text{horizontal}} = (416.929) * (1 + 0.2 * (\text{trial.index.} 6 - 1))$$
$$\text{target velocity}_{\text{vertical}} = (397.469) * (1 + 0.2 * (\text{trial.index.} 6 - 1))$$

The eye-tracking battery provided the values of x-position and y-position of gaze in relative positions (range 0-1). We converted them into a parameter in pixels by multiplying them with the frame dimensions in pixel:

$$\text{gaze position}_{\text{x}}\,[\text{px}] = \text{gaze position}_{\text{x}}\,[\text{frames}] * 1920$$
$$\text{gaze position}_{\text{y}}[\text{px}] = \text{gaze position}_{\text{y}}\,[\text{frames}] * 1080$$

The eye-tracker also provided time stamps that allow assessing relative durations. We calculated the gaze velocity as the delta of gaze position over time:

$$\text{gaze velocity} = \frac{\Delta\,\text{gaze position}}{\Delta\,\text{time}}\,[\frac{\text{px}}{\text{s}}]$$

In addition, the eye-tracker reported the distance to the screen in mm. To obtain values given in degrees for a better comparison with literature, we first converted the measurements to *rad* using the atan-function, where 0.265 is the factor to

convert pixels to millimeters (screen resolution was 96 px/inch, resulting in 0.265 mm/px.)

$$\text{measure[rad]} = \text{atan}\frac{\left(\text{gaze position [px]} - \frac{1}{2}axis[px]\right) * 0.265}{\text{distance to screen [mm]}}$$

We then calculated the values in *degree*:

$$\text{measure[degree]} = \text{measure[rad]} * 180°/\pi$$

The smooth pursuit gain is the ratio of target and gaze velocity:

$$\text{smooth pursuit gain} = \frac{\text{target velocity}}{\text{gaze velocity}}$$

4.4.2 Exclusion of data

We had to exclude data for different reasons. First, we cleaned data due to duplicate data from one participant (076, 073). Second, data with a validity code >2 in both eyes were excluded according to the Tobii user manual: the lower the validity code (possible values 0-4), the more reliable the identification of a particular eye.[81] If the gaze position was located outside of the screen area (x-position or y-position <0 or > 1 screen-unit), either an interpolation from the other eye was performed if one eye provided data, or the data were excluded. In addition, data were excluded if participants did not look at the screen or if both x- and y-gaze positions were missing.

Data were smoothed using the “rollapply”-function to raise the signal to noise ratio according to Takarae et al.[12] and Ettinger et al.[78].

To ensure smooth pursuit analysis according to Lencer et al.[2], we only considered data after the first 300ms and up to the last 300ms of the trial. This excludes the initiation phase of SPEM and also the deceleration of gaze velocity due to anticipation of the task’s end.[2]

For the smooth pursuit maintenance analysis accuracy and gain were estimated. The parameter used to quantify accuracy was the root mean square error (RMSE).[2] Low RMSE-values represent a better accuracy.[130] We excluded

extreme values that differed by more than 3 standard deviations within participants.

Linear interpolation was used to obtain a complete data set after data cleaning. Linear interpolation has been shown to be an effective method to fill the gaps in SPEM without leading to inappropriate averaging.[131]

Saccades characterized by their velocity in degrees per second were excluded. We followed the recommended threshold-values of 40°/s.[2] This is equal to the median of the thresholds of the available publications listed in the table below.

Table 3 Overview saccade thresholds in literature

Author	Year of publication	Threshold [°/s] for saccade detection
Ettinger et al.	2003	30
Salman et al.	2006	30
Bynke et al.	2000	40
Erkelens et al.	2006	40
Lencer et al.	**2019**	**40**
Komogortsev et al.	2013	90
Larsson et al.	2015	100

Trial data were also excluded if the number of observations was lower than 50% of the average number of observations.

4.5 Nearest-neighbor-matching

In the understudied population of preschoolers, we matched the ASD and TD groups by nearest neighbor matching for *developmental age* and *sex*. Thereby we were able to compare participants with equivalent cognitive abilities and sex.[22] This led to a matching of 33 TD to the existing 33 participants with ASD. We confirmed this matching method with t-tests: $p_{before} = 0.0007$ and $p_{after} = 0.0449$ for developmental age, $p_{before} = 0.003$ and $p_{after} = 0.066$ for sex. The gain values did not significantly change ($p_{before} = 0.28$, $p_{after} = 0.21$). The figure below displays the matching results. "test_age" represents the developmental age and "sex.numeric" the sex. The red dots show the data before matching and the blue dots show the data afterwards. A standardized mean difference of 0 would be the optimal value. Thus, our data was of higher quality after matching.

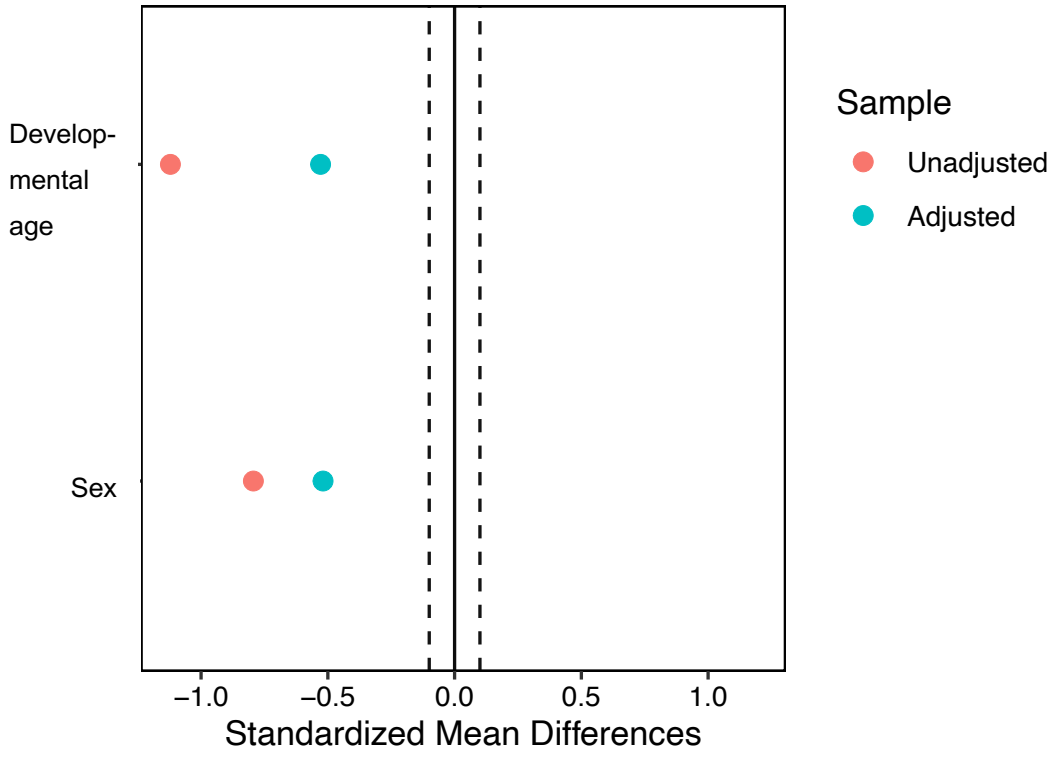

Figure 4.2 Nearest neighbor matching with Unadjusted = before matching, Adjusted = after matching.

4.6 Final data

We assessed a total of 92 participants, 46 were participants with ASD and 46 participants with TD. After cleaning the data for the reasons mentioned in chapter 4.1 and matching (see chapter 4.5), we compared 66 participants, with 33 in the ASD group and 33 in the TD group. This reduced the initially recorded 820,000 samples of raw smooth pursuit data to 242,000 (30%) samples as presented in the figure below. This dataset (dataset 1) was used for the descriptive analysis.

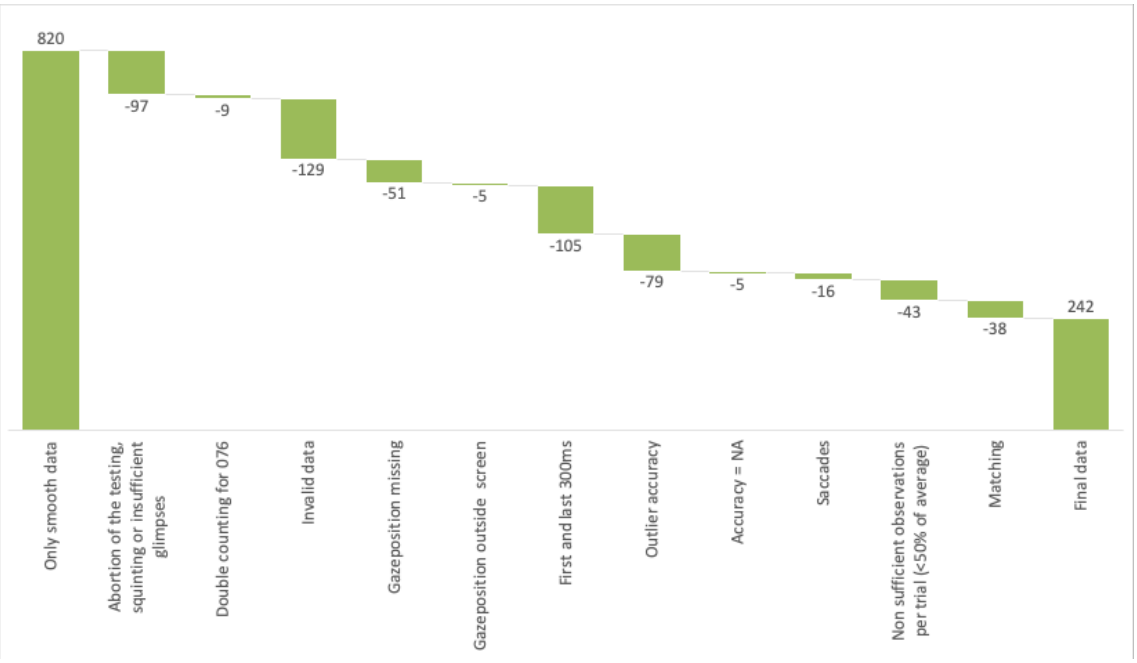

***Figure 4.3 Row count during data cleansing**, in 1000*

Because of the dependency of the gains of one run of one participant, we aggregated the data per participant and run for our models (dataset 2). This dataset contained 463 observations.

4.7 Statistical analysis

For all investigations a significance level of $p < 0.05$ was set. We matched groups (ASD vs. TD) based on *developmental age* and *sex*.[106,132] To test for the influence of covariates on our results we used linear models of the mean gain per participant. Linear models are used to account for the influence of independent variables on the dependent variable in statistical analysis.[133] We included the covariates *target direction, developmental age* [months], *chronological age* [months], *IQ* and *sex*. Group differences in the smooth pursuit gain were analyzed using linear mixed models. In these models, smooth pursuit gain was the dependent variable. The classification variables were coded as follows:

- target direction 1 ≙ vertical 0 ≙ horizontal
- group 1 ≙ ASD 0 ≙ TD
- sex 1 ≙ female 0 ≙ male

5 Results

5.1 Gain between groups

As shown in the tables below we found that children with ASD achieved a gain of 0.848 and typically developing children (TD) achieved a gain of 0.870 before and after matching. After matching (see table 4), there was still a developmental age difference of about 6 months and a chronological age difference of about 12 months. Additionally, there was still an IQ difference of approximately 39 points with higher scores in the TD group.

Chronological and developmental ages were brought closer by the matching, while the p-value for the gain decreased. The differences in gain were still not significant at the 95%-confidence interval. In table 4 one can see the results after matching by developmental age, sex and additionally, chronological age. The values didn't change significantly.

***Table 4 Overview groups after matching**, covariates used for matching displayed in thick font*

Variables	ASD (Mean value)	TD (Mean value)	P-value (Welch Two Sample t-test)
Gain	0.847	0.870	0.209
Developmental age [months]	29.8	35.7	0.045
Chronological age [months]	47.4	35.6	<0.001
IQ	62	101	<0.001
Sex [percentage of females]	21	42	0.066

5.2 Correlation between questionnaire results and gain

As explained earlier, we used several questionnaires to screen for ASD in the participants. For further analysis, we then performed analyses of variance for the CBCL, RBS-R and SRS-16. This was based on a data set of 66 records; one per participant. A mean gain per participant was calculated before.

$$mean\ gain \sim group\ +\ developmental\ age\ +$$
$$sex + questionnaire\ score$$

The CBCL, which is not a specific ASD-questionnaire checks for difficulties in behavior and emotion.[120,123] The RBS-R, checks for restrictive repetitive behavior and the SRS-16 analyzes the everyday behavior. Both are specific for ASD.[118,134,135]

The F-value is a measure of the coincidence of the variation in the sample. The larger the F value, the more significant influence on the gain.[136] In the three questionnaires only the sex of the participants presented a significant influence on the gain value. Regarding the questionnaires no significant result could be shown. Additionally, sex remained the only covariate being significant in F- and p-value (see tables below).

Table 5 ANOVA results CBCL

Variables	F-value	Pr(>F)
CBCL	0.29	0.592
Group	1.71	0.196
Developmental age [months]	0.55	0.461
Sex	11.00	0.002

Table 6 ANOVA results RBS-R

Variables	F-value	Pr(>F)
RBS-R	0.95	0.333
Group	0.33	0.566
Developmental age [months]	0.34	0.563
Sex	7.86	0.007

Table 7 ANOVA results SRS-16

Variables	F-value	Pr(>F)
SRS-16	1.66	0.202
Group	0.60	0.442
Developmental age [months]	0.13	0.723
Sex	6.49	0.013

5.3 Descriptive analysis

The following results refer to dataset 1 as described in chapter 4.6.

5.3.1 Gaze velocity

In figure 5.1 we displayed the distribution of gaze velocity. We excluded data with an absolute velocity greater than 40°/s, which represented saccades (see chapter 4.4.2). The ASD group shows higher peak amplitude in the gaze velocity.

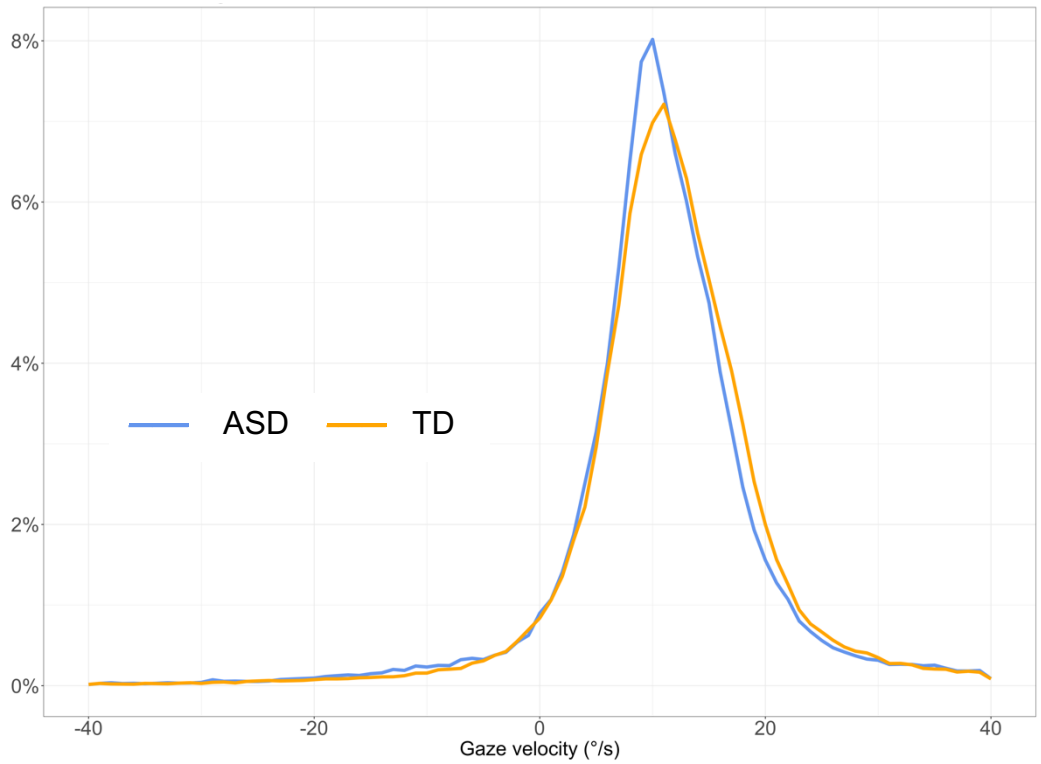

Figure 5.1 Distribution of gaze velocity, *with gaze velocity rounded to 1°/s*

The following figure presents each group's gaze velocity over time. Gaze velocity for both groups decrease after 1 second. The ASD group has a slightly lower gaze velocity than the TD group.

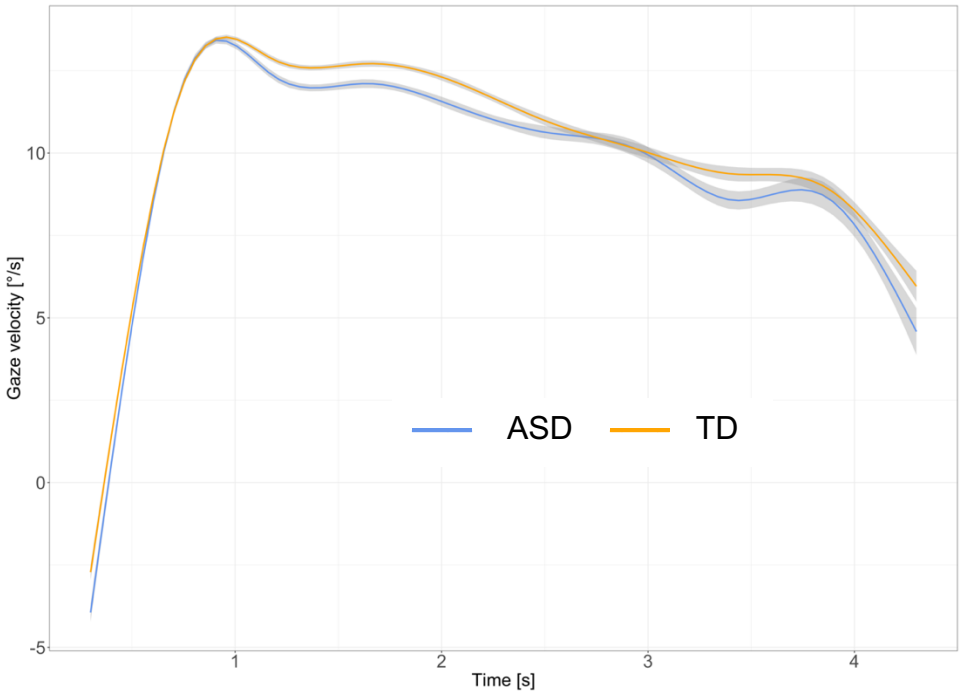

Figure 5.2 Gaze velocity per group over time for 1st trial

Figure 5.3 shows the gaze velocity per group per trial. The black lines here represent the target velocity, which was constant throughout a trial but increased with each trial. The faster the target became, the shorter became the duration of the trial (shown in figure 5.3). The velocities are displayed in px/s; the time is pictured in seconds. The odd-numbered figures represent the horizontal trials, while the even-numbered represent the vertical ones. Although we excluded the first and last 300ms from the analysis, it can be seen that the participants in both groups needed time to reach the target velocity. After an average of approximately 0.7s the gaze velocity reached the target velocity. From then on, the velocity fluctuated around the target velocity. Both groups fluctuated more in vertical trials.

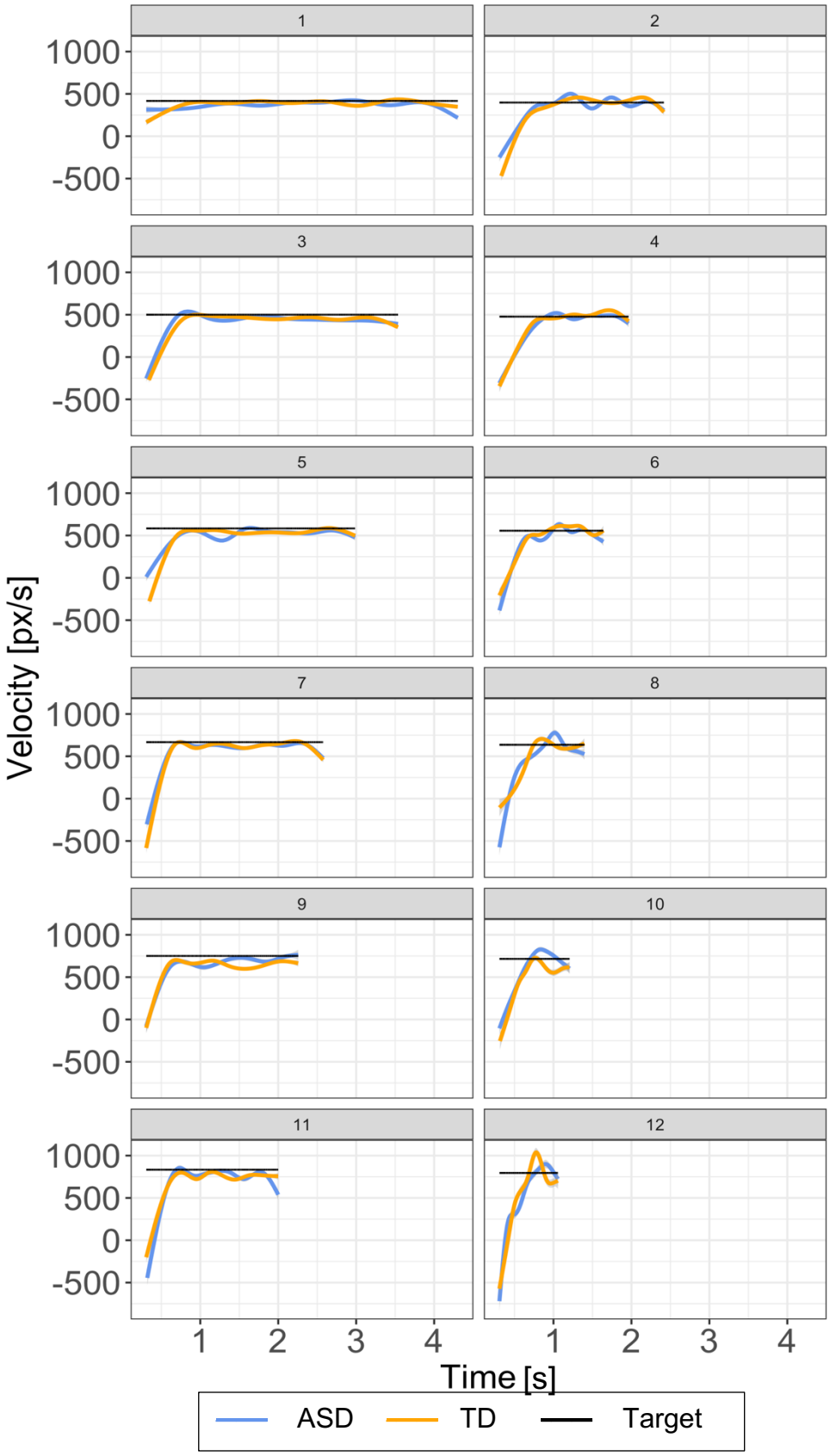

Figure 5.3 Overview gaze velocities and target velocity per trial

5.3.2 Gain

5.3.2.1 Gain with trial duration

In figure 5.4 we see a clear increase in gain in the first second for both groups. Thus, it takes both groups around one second to reach an optimal smooth pursuit gain of 1 (i.e., SPEM-velocity equals target velocity). At about 1 second, the gain values begin to oscillate around 0.9 before dropping off at about 4 seconds.

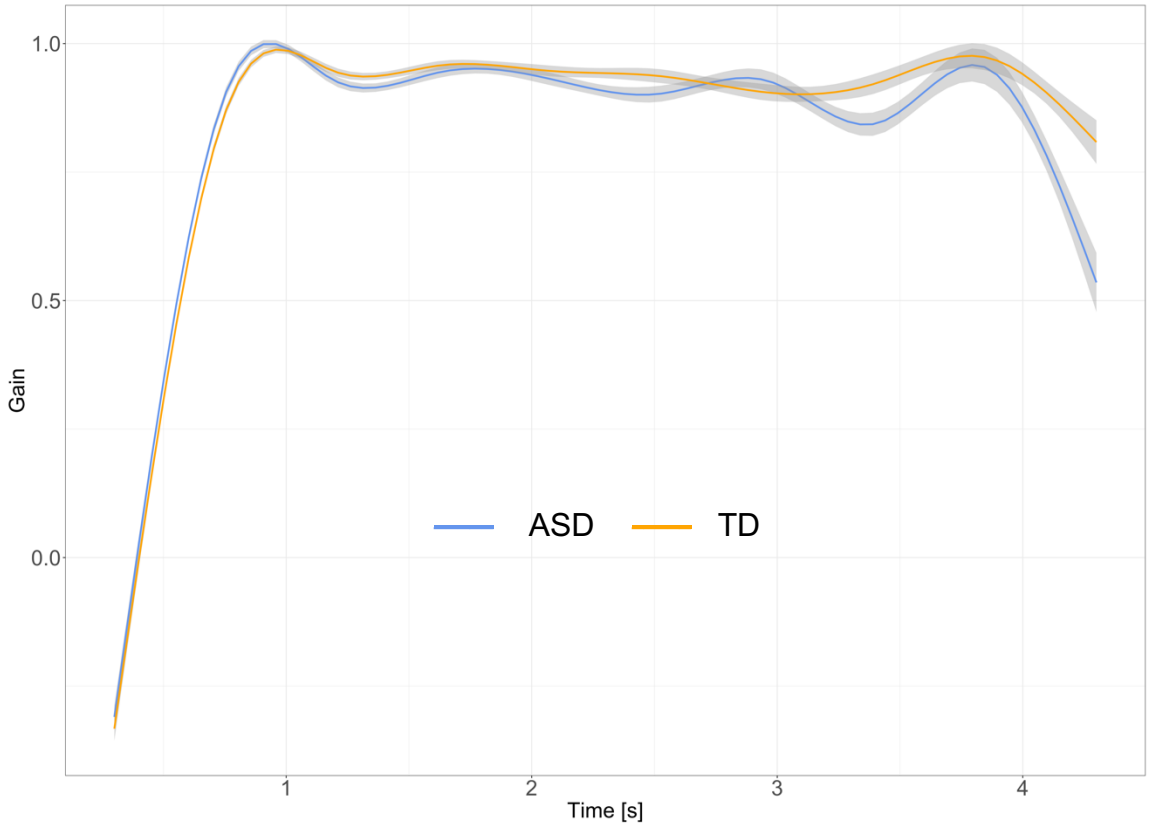

Figure 5.4 Gain per group over time

5.3.2.2 Gain in last trials

As can be seen in table 8, there were 10 observations with gain values less than 0.5. 8 of these were the last and thus the trials with the fastest vertical target velocity (trials 8, 10, 12). Of the 10 observations, 8 are different participants. Such low gain values are observed only in the last trial of the participant. Furthermore, only TD participants behaved this way. Out of the 10 observations we found only one horizontal trial.

Table 8 Overview findings when gain <0.5

ID	Group	Target velocity [px/s]	Target direction	Trial index	Gain	Comment
906	TD	795	vertical	12	0.461	last vertical trial
913	TD	636	vertical	8	0.375	last vertical trials
913	TD	715	vertical	10	0.348	last vertical trials
917	TD	715	vertical	10	0.374	last vertical trial
920	TD	795	vertical	12	0.475	last trial
921	TD	636	vertical	8	0.259	last vertical trial
927	TD	636	vertical	8	0.451	last vertical trial
937	TD	715	vertical	10	0.398	last trials
937	TD	750	horizontal	9	0.452	last trials
943	TD	477	vertical	4	0.482	last vertical trial

5.4 Statistical analysis

The following results refer to dataset 2 as explained in chapter 4.6.

5.4.1 Gaze velocity

Gaze velocity substantially oscillates even after smoothing. For further analysis we used the data of the first trial. Mean and standard deviation are shown in table 9. A t-test showed no significant difference of gaze velocity between the groups (p-value: 0.187).

Table 9 Comparison gaze velocity over groups for 1st trial

Variables	ASD	TD
Mean of gaze velocity [°/s]	8.38	8.89
SD of gaze velocity [°/s]	1.12	1.21

5.4.2 Gain

Table 10 shows the mean and standard deviation of gain for ASD and TD. A t-test didn't result in a significance difference between the groups (p-value: 0.14).

Table 10 Comparison gain over groups

Variables	ASD	TD
Mean gain	0.88	0.92
SD gain	0.11	0.08

5.4.3 Gain over target velocity (Linear models)

The data used for these analyses was aggregated to data per trial and group. We analyzed smooth pursuit gain by target velocity between groups (see table 11). We applied linear regression models (gain ~ target velocity) per group and target direction to predict smooth pursuit gain based on target velocity across groups. We found that smooth pursuit gain decreased with increasing target velocity.

Table 11 Dependency gain on target velocity

		Estimate			
Group	Target direction	Intercept	Target velocity [10^{-6} px/s]	P-value target velocity	R^2
ASD	Horizontal	0.91	-69	0.17	0.27
ASD	Vertical	0.95	-264	0.04	0.60
TD	Horizontal	0.95	-126	0.15	0.30
TD	Vertical	1.10	-491	<0.01	0.80

In table 11 and figure 5.5 we see that vertical trials show a greater dependency on the target velocity than horizontal trials. ASD show lower gain performance than TD (see figure 5.5). Additionally, the values decrease faster in the TD group. Thus, figure 5.5 indicates a possible interaction between group, target direction and target velocity, especially for vertical trials.[137]

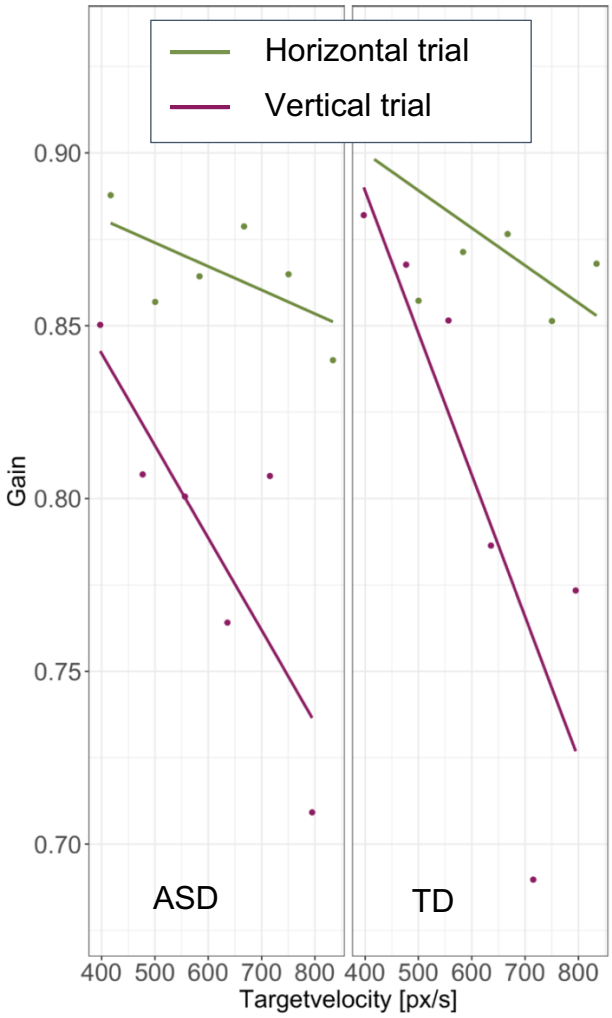

Figure 5.5 Gain over target velocity per trial, *one dot representing aggregated data per trial per group*

5.4.4 Linear mixed model

We calculated a linear mixed model to check for the gain's dependence of target velocity, group and target direction including interactions between target velocity and group:

$$gain_{scaled} \sim target\ velocity_{scaled} * group + target\ direction + sex + developmental\ age + (1|id)$$

As seen in the table below we found a significant group influence on the gain when considering interactions between target velocity and group (p=0.041). Additionally, sex is a significant predictor for gain, meaning that females showed a significant higher gain than males.

Table 12 Overview linear mixed model

Variable	Estimate	Pr(>|t|)
Intercept	-0.194	0.372
Scaled target velocity	-0.216	<0.001
Target direction	-0.253	<0.001
Sex	0.256	0.010
Scaled target velocity x group	0.085	0.041
Developmental age	0.003	0.562
Group	-0.019	0.795

Next, we checked for the trend per group regarding scaled target velocity. Here, we can see that the gain values in the TD group decreased 2.3 times faster with increasing target velocity than the ASD group.

Table 13 Estimated marginal means of linear trends

with TD = 0, ASD = 1 and CL = confidence level

Group	Trend regarding scaled target velocity	Lower CL	Upper CL
0	-0.30	-0.41	-0.19
1	-0.13	-0.26	-0.01

6 Discussion

The aim of the present study was the analysis of smooth pursuit gain in preschoolers with ASD and TD. After excluding participants for the criteria (see chapter 4.1), cleaning the data (see chapter 4.4) and matching (see chapter 4.5) we compared N = 33 ASD and N = 33 TD.

6.1 Outcomes

The data showed that it took participants a few milliseconds to reach the target velocity after initiation (see figure 5.3). Rashbass et al.[138] discussed that there did not appear a specific intent to reach the target position in both groups. In further research this could be analyzed.

We found that gain decreased with increasing target velocity. It might be more difficult for participants to track faster targets. Lencer et al.[2] undermine this: they

state that adequate SPEM can generally occur at target speed limits of 100°/s, but ideal gain values are achieved at target velocities of about 15-30°/s.[2] Other existing data confirm that there is a maximum smooth pursuit velocity of ca. 20-30°/s).[138–143]

Additionally, declining concentration/motivation in participants over time could play an important role. The literature reports reduced attentional skills in children with ASD.[144,145] However, typically developing children may also perform worse at the end of the task due to declining interest and motivation.

The analysis also showed that gain decreased more in vertical trials than in horizontal trials (see figure 5.5) for both groups.

In the descriptive data shown before (see table 8) only the TD group showed gain values smaller than 0.5. It is striking that the vast majority of these observations came from vertical trials (9 out of 10). Eight of these were the last and thus the trials with the fastest vertical target velocity (trial index 8, 10, 12). Of the ten observations, eight are from different participants, so this effect is not caused by an outlier but represents a more common behavior. This could indicate a possible difference between the groups regarding vertical trials with high target velocities. Buizza et al.[146] present a linear relationship between SPEM and target velocities up to velocities of 75°/s (≈ 3000px/s). Similar data were published by Salman et al.[147] They present a difference between horizontal and vertical smooth pursuit gain values of 0.16 at 0.25 Hz and 0.28 at 0.5 Hz.[147] Salman et al.[147] and Collewijn and Tamminga[142] suggest that better performance in horizontal than in vertical smooth pursuit could be explained by its greater importance in everyday life. Most objects move in a horizontal direction and thus enable more experience here. Collewijn and Tamminga[142] suggest that exercise could enhance vertical performance. Rottach et al.[148] state that gain values in horizontal trials were higher than in vertical trials. The only exception was counterclockwise target motion.[148] We found that vertical trials depend more on the target velocity than horizontal trials (see figure 5.5). This could indicate a greater importance of the horizontal eye movements' study.

We have shown the trend of the gain in figure 5.4 and gaze velocity in figure 5.2 and figure 5.3 over time in ASD and TD. Declining trends appear in all three plots. Negative gaze velocity results from gaze shifts to the left or up and thus opposite direction to the target. In all three plots this appears only at the beginning of the

trials. Participants may need time to orient and find the target at the beginning of each trial. Once the target is found it is easier to follow it. This could explain why negative values don't appear as often later on.

Matching ensured a more appropriate analysis in an understudied population. We matched the groups based on their developmental age and sex. This resulted in closer values for the covariates. It didn't affect the results in terms of the gain. This should be replicated by studies with a larger sample size.

Previous studies have reported mixed results: Johnson et al.[11] concluded from their meta-analysis that participants with ASD show more difficulties in open-loop and closed-loop pursuit. Aitkin et al.[89] tested anticipatory eye movements and found that there are no disabilities in ASD. Takarae et al.[22] showed a significant difference in smooth pursuit gain between ASD and TD especially in the closed-loop phase. Divergent results may be explained by differences in conduction of and technical conditions in eye tracking: While some authors use chin rests and head fixations, others added a bite bar to avoid excessive head movements.[2,22,89] In the current study we didn't use any kind of these because in toddlers and preschoolers we found a fixation of the head too disturbing for the participants. Some eye trackers offer the possibility to observe head movements with an additional camera. In addition, different eye tracker software and methods of calculating the gaze position are used.[2] This leaves space for further discussion of the most fitting conduction of eye tracking in young children.

The targets in our study moved in one direction per trial. We distinguished between the vertical and horizontal direction and found results in our descriptive data mentioned above. Takarae's group discriminated between right and left visual fields.[22] These results show the lack of clarity that exists in eye movement research in ASD. This undermines the significance of further and more extensive research.

We could show a significant influence of the group on the gain when considering interactions with target velocity. In addition, in the analysis of the estimated marginal means of linear trends the ASD group appeared to depend less on the increasing target velocity compared to the TD group. This undermines the importance of additional studies with fixed target velocity in a larger study population.

6.2 Population

ASD is a disorder affecting approximately 80 million people worldwide. Individuals with this disorder are affected in their daily lives and, depending on their level on the spectrum, may not be able to live independently.[7] To this date, no effective cure has been found.[37,38] Studies have shown that earlier identification and treatment may lead to a reduction in the impact of the disorder.[39–43] Therefore, earlier diagnosis is essential.

Often, children with ASD become clinically evident at an age of 3 years.[5] Studies have shown that intervention at a younger age (from 18 months on) results in not only an improved intellectual but also better social and everyday functioning.[39,41,42] This undermines the importance of diagnostic options for children as young as toddlers.

In our study we found a significant difference between the two groups. It should be kept in mind, that preschoolers still represent an understudied population. Thus, further research with larger sample sizes should follow.

6.3 Procedures

Different instrumental diagnostics for research in ASD are known. The most commonly used are eye tracking, electroencephalography (EEG) and magnetic resonance imaging (MRI).[149] We decided to examine the two study groups via eye-tracking; first of all because we planned on analyzing the eye movements themselves. Promising literature had been published by e.g. Johnson et al.[11]. Eye-tracking allows a free range of movement and no noise interference (see 3.5). It also allows for the direct recording of eye movements.[1] The MRI can give accurate results without the use of radiation. The disadvantages are that the children have to remain still and are in a narrow space. Habitually, they need to be sedated for this examination.[150] EEG is a common method for detecting cerebral abnormalities and has been used in ASD research.[151,152] It should be taken into account that children may not tolerate the electrodes attached to the head. Thus, eye-tracking is an adequate method to examine children with minorly disturbing of them.

In our analysis we differentiated between the trials by target velocity and target direction. Moreover, we tested for a declining performance over time. We

analyzed the mean gain per group over all trials and target velocities. For further examination one should keep the recommendation of Lencer et al.[2] in mind, stating that gain values should be examined across trials with the same target speed and the same target direction.[2]

In the understudied group of preschoolers, we matched our groups for a more accurate analysis. We first matched our participants for their developmental age and sex. This matching resulted in a lower chronological age and developmental age in the TD group, which were values closer to the ASD group. However, there still was a developmental age difference of about 6 months and a chronological age difference of about 12 months. The IQ in the two group differs greatly. The lower IQ in ASD might have different reasons but their limited attention span could play a significant role. The IQ didn't represent a suiting matching variable for the reason mentioned above. It was more suitable to use the developmental age as matching variable; it allows the consideration of the child's level of development calculating an orienting age. No significant changes were found in the results.

6.4 Limitations and Outlook

The current study expands the literature on smooth pursuit gain in preschoolers with ASD compared to TD. Notwithstanding, some methodological limitations must be mentioned.

We divided our study groups into ASD and TD. As explained before (see chapter 3.1) ASD has a wide range of severity. Children who are more severely affected may show a greater deviation in SPG than children who are mildly affected. Thus, further research could compare especially severely affected children with typically developing controls. This may reveal clearer differences between the groups and therefore important hints for clinical work and usage.

We recruited participants on a voluntary basis: Participants were recruited mostly through social media, but also through calls in the local kindergartens. This results not only in a small sample size, but also in a locally influenced group of participants. Additionally, we administered developmental or intellectual tests to all participants. This might attract a certain clientele of families and needs to be taken into account.

Also, families participating in this study could represent overall more motivated caregivers, who might encourage their children more beforehand. Thus, these children could show a lesser impact of ASD. A recommendation for further research could be a bigger public appeal in newspapers and visits of kindergartens and schools. This might lead not only to a bigger study population but also to the possibility of a wider range of clientele in terms of, e.g., the educational status, family size, encouragement of the child and ASD severity.

The study design inhibited a double-blind, randomized study design. To still minimize personal influence on the outcome of the study, we assigned encrypted IDs to each participant. Before further analysis, we excluded information on who tested the participants and when. Thus, the final analysis was biased less by personal influence.

The developmental age was assessed via questionnaires. These were generally completed by the participants' caregivers. Consequently, the statements are based on caregivers' estimation. Future studies could include more objective assessments. The intelligence and/or development tests were administered by trained psychological and/or medical personnel. They also agreed on how to analyze the child's performance beforehand. Notwithstanding, slightly different assessments of the child's performance may have occurred during testing.[20,153]

It should be noted that some literature recommends head fixation, e.g. with a chin rest.[2] In order to achieve better compliance, which is especially necessary in young children and is also recommended in the literature (e.g. Falck-Ytter et al.[14]), we did not use such devices. This could lead to a greater spreading in the results because the children may move their head and therefore the measurement of the eye tracking could be less precise.

We excluded saccades in the smooth pursuit analysis based on Lencer et al.[2]. It should be noted however, that other thresholds can be found in the literature, e.g. Bynke et al.[69], Erkelens et al.[154], Ettinger et al.[78], Komogortsev et al.[155], Larsson et al.[156] and Salman et al.[157]. Nevertheless, this does not change the present statement of the available data (see chapter 7.3).

We conducted a nearest neighbor matching to achieve more comparable groups. It should be noted, that after matching there still was a developmental age difference of about 6 months and a difference in the sex distribution of 21% between the groups.

Overall, we showed a significant difference between the ASD and TD group on smooth pursuit gain when including interactions. This interaction is described by the greater dependence of the gain in the TD group on the target velocity than the ASD group: Gain decreased 2.3 times faster with increasing target velocity in the TD group. Additionally, we presented promising ideas for further research. Object for further research could be the investigation of the gain per group at fixed target velocity and fixed target direction with a bigger study population. Smooth pursuit gain might be utilized as an additional and objective marker to improve early diagnostic procedures for ASD in preschoolers.

7 Appendix

7.1 Flyer used for recruitment

Figure 7.1 Flyer Recruitment Participants Page 1

Figure 7.2 Flyer Recruitment Participants Page 2

Liebe Eltern, liebe Kinder,

in der Klinik für Psychiatrie, Psychosomatik und Psychotherapie des Kindes- und Jugendalters führen wir aktuell eine Studie durch, die sich mit der Untersuchung sozialer Kernkompetenzen bei Kindern mit und ohne Autismus-Spektrum-Störung (ASS) im Vorschulalter befasst.

Was genau wollen wir untersuchen? Und warum?

Kinder mit ASS haben Schwierigkeiten in sozialen Kernkompetenzen, wie aufmerksam auf soziale Reize zu schauen (z.B. emotionale Gesichter) oder ein Gegenüber spontan zu imitieren. Diese Schwierigkeiten scheinen bei der Entwicklung von ASS-Symptomen eine Rolle zu spielen und könnten zur Vorhersage des Schweregrads verwendet werden. Die Erfassung sozialer Kernkompetenzen könnte daher einen wichtigen Beitrag zur frühen Diagnostik von ASS leisten. Da es bisher jedoch keine Verfahren gibt, um diese objektiv zu messen, wollen wir eine neue Messmethode untersuchen: Das Eye-Tracking.

Was ist Eye-Tracking?

Eye-Tracking ist ein Verfahren zur Erfassung der Blickbewegungen von Personen mit Hilfe von Kameras. Es ist lediglich das Betrachten eines Bildschirms notwendig. Die Messung ist unauffällig und wird meistens nicht mal bemerkt. Die Kameras ermitteln dabei die Blickbewegungen und Pupillengröße Ihres Kindes, während es verschiedene Videos und Bilder ansieht, die mit sozialen Kernkompetenzen in Verbindung stehen (z.B.: spielende Kinder).

Ablauf der Studie

Die Studie findet an nur einem Termin (ca. 1,5 Stunden) statt und beinhaltet:

- Intelligenz- bzw. Entwicklungstest mit Ihrem Kind
- Ausfüllen einiger Fragebögen durch ein Elternteil
- Eye-Tracking-Messung mit Ihrem Kind

Ihr Kind hat während der Eye-Tracking-Messung keine weitere Aufgabe, außer die kindgerechten Videos und Bilder zu betrachten. Selbstverständlich können Sie während der Untersuchung im Raum bleiben und bei der Testung zusehen.

Wen suchen wir?

Wir suchen Mädchen und Jungen im Alter zwischen 1,5 bis 6 Jahren, sowohl mit als auch ohne ASS.

Was ist der Nutzen Ihrer Teilnahme?

- Ihre Teilnahme trägt zu einem verbesserten Verständnis der spezifischen Probleme und Schwierigkeiten, sowie der Entstehung der autistischen Symptomatik bei Kindern mit ASS bei.
- Die Entwicklung und Anpassung von objektiven Verfahren wird gefördert.
- Ihre Teilnahme könnte letztlich dazu beitragen, die Diagnostik von Kindern mit ASS zu verbessern und früher zu identifizieren.
- **Zusätzlich erhalten Sie auf Wunsch ein Intelligenzprofil Ihres Kindes!**

7.2 Overview demographic data

Table 14 Overview demographic data ASD-group

ID	Sex	IQ	Developmental age [months}	Actual age [months]	Final matched data set
003	male	42	27	64	no
005	female	77	48	55	yes
006	male	84	55	56	yes
011	male	48	25	52	no
012	male	50	27	55	no
013	male	69	41	60	yes
016	male	55	43	65	yes
017	male	49	23	48	yes
018	male	47	25	54	yes
020	male	50	21	49	yes
023	male	39	20	52	no
025	male	70	23	34	no
028	female	53	23	43	yes
031	male	53	16	30	yes
032	male	68	26	38	yes
033	male	54	27	51	yes
034	female	61	23	39	yes
037	male	87	36	38	yes
038	male	59	27	46	yes
039	male	52	23	44	no
041	female	38	23	60	no
042	male	48	25	53	yes
044	female	49	24	50	yes
046	male	75	40	50	yes
047	male	78	28	37	no
048	male	40	24	61	yes
050	female	45	28	62	no
051	male	70	23	34	yes
052	male	41	16	40	no
053	male	75	27	37	yes
054	male	59	20	34	no
055	male	73	51	62	no
059	male	54	19	35	yes
060	male	81	43	50	yes
061	male	62	29	47	yes
062	female	72	51	64	no
066	male	53	24	45	yes
068	male	77	20	26	no

069	male	70	26	38	yes
070	male	55	32	59	no
071	male	93	38	41	yes
072	male	48	24	50	yes
073	female	62	24	39	yes
074	male	45	18	40	no
076	male	40	23	58	yes
078	male	101	66	63	yes
080	female	49	17	36	no
081	male	89	23	26	yes
082	female	43	24	53	yes
083	male	74	29	40	no
084	male	37	23	63	no
087	female	39	24	61	yes
090	male	50	23	47	no
091	male	86	44	50	no
092	male	86	61	59	no
093	male	73	24	34	no
094	male	73	37	45	no
095	male	54	25	47	no
096	male	105	45	42	no
097	male	31	16	51	no
098	female	73	49	60	no
099	male	97	38	30	no
100	male	50	24	48	no
101	male	46	24	54	no
102	male	83	33	40	no
105	male	38	24	64	no
108	male	71	24	34	no
110	male	53	16	31	no
113	male	51	18	35	no

Table 15 Overview demographic data TD-group

ID	Sex	IQ	Developmental age [months}	Actual age [months]	Final matched data set
901	male	105	48	45	yes
902	female	105	80	77	no
903	male	90	43	46	yes
904	female	101	75	68	no
905	female	116	71	56	no
906	male	92	33	25	yes
909	female	116	76	62	no
910	female	105	67	61	no
911	male	105	76	72	yes
912	male	100	33	34	yes
913	male	114	49	44	yes
914	male	94	32	35	yes
916	male	77	27	35	yes
917	male	85	29	34	yes
918	female	104	29	29	yes
920	female	89	31	35	yes
921	female	93	27	29	yes
922	female	94	29	31	yes
924	male	92	24	26	no
925	male	77	24	31	no
926	female	97	48	46	yes
927	female	114	32	29	yes
928	female	91	23	26	yes
929	female	89	24	27	yes
930	female	110	66	58	no
931	male	102	39	39	yes
932	male	100	31	31	yes
933	female	102	37	37	yes
935	female	103	59	55	no
937	male	73	48	68	yes
938	male	117	52	44	yes
940	female	117	28	24	yes
941	female	101	59	55	no
943	female	112	29	26	yes
945	female	100	18	18	no
946	male	117	35	30	yes
947	male	100	28	28	yes
948	male	100	21	21	yes
949	female	105	39	36	no
950	male	122	22	18	yes
951	male	105	23	22	yes

952	female	117	27	24	yes
953	male	96	55	58	yes
954	female	117	54	44	yes
955	female	97	37	38	yes
956	female	128	23	18	no
957	male	100	25	25	no

7.3 Statistical measures after exclusion of saccades through threshold 100°/s instead of 40°/s

Table 16 Overview groups before matching with saccade-threshold 100°/s

Variables	ASD (mean value)	TD (mean value)	P-value (Welch Two Sample t-test)
Gain	0.913	0.902	0.499
Developmental age [months]	29.8	42.2	4e-4
Chronological age [months]	47.4	40.6	0.028
IQ	62	102	2e-16
Sex [percentage of females]	21	54	0.003

Table 17 Overview groups after matching with saccade-threshold 100°/s

Variables	ASD (mean value)	TD (mean value)	P-value (Welch Two Sample t-test)
Gain	0.913	0.900	0.437
Developmental age [months]	29.8	35.7	0.045
Chronological age [months]	47.4	35.6	8e-05
IQ	62	101	2e-15
Sex [percentage of females]	21	42	0.066

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Schriftliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die dem Fachbereich Medizin der Goethe-Universität Frankfurt am Main zur Promotionsprüfung eingereichte Dissertation mit dem Titel

Smooth pursuit gain during eye tracking – a comparison of toddlers and preschoolers with autism spectrum disorders and typically developing controls

am Zentrum der Psychischen Gesundheit, in dem Autismus Therapie- und Forschungszentrum der Klinik für Psychiatrie, Psychosomatik und Psychotherapie des Kindes- und Jugendalters unter Betreuung und Anleitung von Prof. Dr. Christine M. Freitag mit Unterstützung durch Dr. Nico Bast und Leonie Polzer ohne sonstige Hilfe selbst durchgeführt und bei der Abfassung der Arbeit keine anderen als die in der Dissertation angeführten Hilfsmittel benutzt habe. Darüber hinaus versichere ich, nicht die Hilfe einer kommerziellen Promotionsvermittlung in Anspruch genommen zu haben.

Ich habe bisher an keiner in- oder ausländischen Universität ein Gesuch um Zulassung zur Promotion eingereicht. Die vorliegende Arbeit wurde bisher nicht als Dissertation eingereicht.

Vorliegende Ergebnisse der Arbeit wurden bisher nicht veröffentlicht.

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(Ort, Datum) (Unterschrift)