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# Eye tracking as a supporting diagnostic tool for Autism Spectrum Disorders

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# Preface

The following thesis is submitted as final examination for the master programme in Interaction Design at NTNU Gjøvik. The research was conducted during the spring semester of 2018.

The idea from which this research started from was about understanding more about the cognitive features of autism (ASD), a complex neurodevelopmental disorder. In particular, the interest of the researcher was focused on the processing of visual stimuli in people with ASD. This interest was driven by the intent of designing more effective Augmentative and Alternative Communication (AAC) systems in the future. However, before thinking more about how AAC systems can support the potential particular visual processing needs of people with ASD, the researcher needed to carry out more information gathering and possibly more research on how this group seems to process the information visually.

In order to narrow down the topic, which could potentially span through several theses and also several years of research, the author and the thesis supervisor, Prof. Frode Volden, agreed that a good starting point would have been to investigate the oculomotor features of people with ASD. Eye movements in humans can highlight the strategies for visual processing of stimuli and also impairments in cognitive information processing. Nowadays, these movements can be recorded accurately and non invasively by high frequency remote eye trackers, an equipment which is available at the university institution.

The author, from his master studies, already knew that experiments with eye trackers can discern between different groups of people basing on their oculomotor performance. A further example of this concept was brought by Prof. Volden, who previously studied the oculomotor differences in people with schizophrenia. Following this reasoning, by studying the oculomotor features in people with ASD, it could be possible that there are particular eye parameters which could help in ASD detection.

The author in his study and professional career had already contacts with clinicians in the ASD field and healthcare institutions, therefore he already knew more or less what are the current diagnostic procedures, and how difficult is to detect symptoms of ASD, especially in small children. Moreover, he also kenw that the current procedures for ASD diagnosis are behavior based, therefore prone to clinicians' subjective interpretation. Therefore, an objective measurement of the children's gaze patterns could improve the reliability of the current diagnostic procedures.

Summarizing, the study of the oculomotor performance of people with ASD, and in particular of children, seemed to be the first step towards various goals: from a more reliable and quick diagnosis to the design of more effective AAC systems, to the design of interfaces (both analogical and digital ones) tailored on the specific needs of people with ASD.

The early diagnosis of ASD is the first research field in which this preliminary study on oculomotor could have its application.The author explored further this first intuition in the autumn semester studies in 2017, by conducting literature review about eye tracking parameters and methods for ASD investigations (for the IMT4898 Specialisation in Interaction Design course), and a series of interviews about eye tracking and ASD diagnosis (for the IMT4215 Specialization Project). From the data collected in these prevous courses, it was evident that, especially since a decade, there is a noticeable interest in the scientific community about the usage of eye tracking technologies as a support tool for early ASD diagnosis. However, the findings in literature seem to be still scattered and sometimes contradictory. For this reason, the main purpose of this master thesis is to build a framework which could put some order in the research field, by highlighting the eye tracking parameters and the procedures which show the most potential for ASD detection.

This Master Thesis report could be read by researchers interested in eye movement tracking, specific features of ASD, new approaches to clinical practice and cognitive assessment. Readers are assumed to have a basic background in scientific research, statistical analysis and some general knowledge about ASD.

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G.D.

# Abstract

Autism Spectrum Disorders (ASD) are a complex neurodevelopmental condition which affects behavior, communication and social functioning. Literature suggests that eye tracking technologies can provide objective measurements of divergent developmental patterns and subtle traits in children's eye movements, and that these parameters can support early detection and diagnosis of ASD.

An eye tracking framework is developed for children in the age group 12-24 months, and consists of a rationale of relevant eye parameters and the methodologies to assess them. A set of stimuli is programmatically designed and generated to assess smooth pursuit and saccade eye parameters.

A first computerized diagnostic test procedure is designed and tested on three typically developing children (15, 24 and 9 months of age) in order to assess the overall feasibility of the application of the framework, with no aim of statistical significance and diagnostic predictive value.

The results from this first experimentation suggest that the developed eye tracking framework and procedure elicit the expected gaze patterns in children belonging to the target age group, and perhaps even in younger children. Improvements need to be made on the procedure in terms of timings and quantity of recorded data. Further research is then outlined, in order to prepare the framework for the systematic collection of eye tracking data on wider samples. Systematic data collection would pave the way for future validation studies in order to support clinical diagnostic decisions.

**Keywords**: autism spectrum disorders, ASD, eye tracking, eye movements, gaze pattern, eye parameters, test design, diagnosis, assessment, children, infants.

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# 1 Introduction

The aim of this Master Thesis is to understand how eye tracking technologies can be used for the detection of Autism Spectrum Disorders (ASD). The project methodology is near to a traditional Human-Computer Interaction experimentation, starting with an in-depth literature review about the eye tracking parameters which have already been detected in previous studies as potential markers of group differences between groups of people with Autism Spectrum Disorders (hereinafter: ASDg) and Typically Developing groups (hereinafter: TDg). An eye tracking framework grounded on literature is then developed, consisting of a rationale of relevant eye parameters and guidelines for measuring them. Basing on the framework, an experimental procedure for measuring specific eye parameters about saccades and smooth pursuit eye movement on small children (12-24 months of age) is developed. Appropriate visual stimuli for eliciting the eye parameters under investigation are generated programmatically using the Processing 3 software. A first experimental protocol is developed, guiding the researchers in the arrangement of the experimental facility and equipment, and the protocol is assessed in relation to a series of research questions. Three tests with small children (9, 15 and 24 months of age) are then performed and the results of the experiments are discussed

The American Psychological Association (APA, 2017) describes the Autism Spectrum Disorder as a complex neurodevelopmental condition that affects behavior, communication and social functioning. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) enlists the diagnostic criteria for ASD (APA, 2013), describing for example the presence of deficits in social-emotional reciprocity (e.g. failure of normal back-and-forth conversation), deficits in nonverbal communicative behaviors used for social interaction (e.g. abnormalities in eye contact and body language or deficits in understanding and use of gestures) and deficits in developing, maintaining, and understanding relationships (e.g. difficulties adjusting behavior to suit various social contexts). The neurodevelopmental abnormalities are present at birth and continue to evolve from the earliest months of life (Zwaigenbaum et al., 2005). Autism spectrum disorders are also described in the ICD-10 diagnostic manual (World Health Organization, 2016), which also describes that the diagnosis of childhood autism (F84.0) implies "the presence of abnormal or impaired development that is manifest before the age of three years".

As Boraston and Blakemore (2007) summarize, autism was first described in 1943 by the psychiatrist Leo Kanner, but in the past decade it has been suggested that autism is not a categorical disorder, but instead lies on the continuum of the autism spectrum disorders, along with Asperger syndrome and Pervasive Developmental Disorders not otherwise specified. ASD manifestations can range from individuals with severe impairment (who may be silent, mentally disabled, and locked into repetitive behaviours) to less impaired individuals who have active but distinctly strange social approaches and communication style, and narrowly focused interests (Pensiero et al., 2009).

As Wilkes et al. (2015) describe, the oculomotor system controls volitional eye movements by incorporating visual information into appropriate motor outputs to the extraocular muscles. Therefore, assessing abnormal oculomotor performance of subjects is useful to investigate neurodevelopmental disorders, since the measurements can provide insights into aberrant neural circuitry.

As Samad et al. (2017) report, currently there are no diagnostic biomarkers for ASD and, therefore, this disorder is commonly identified through direct visual observation of atypical behaviors. However, these methods are limited in identifying subtle behavioral traits, which could be very relevant to identify specific abnormalities in behavior and social communication skills related to ASD. Automated computer vision-based tools, like eye tracking, may assist in detecting eye movement parameters. These technologies can reduce the time and expenses currently needed for screening behavioral markers in subjects with ASD and facilitate the computation of the severity and prognosis of the disorders. Associating oculomotor performance with core features of ASD can also provide suggestions for sensorimotor interventions on ASDg (Wilkes et al., 2015).

Current eye tracking systems capture the light reflected from eye cornea and feed raw data to the software components, in order to make heatmaps and plots (Subrahmaniam, 2013; Baxter et al., 2015, p. 437). This data provide objective and quantitative information about which parts of the scene the subject are orienting their gaze to (Pensiero et al., 2009), providing insights into the strategies the subjects could be using to complete tasks (Boraston and Blakemore, 2007), cognitive responses to specific set of visual stimuli (Subrahmaniam, 2013) and provide information on the way the brain processes the visual environments at a relatively high spatial and temporal resolution (van der Geest et al., 2002). As Subrahmaniam (2013) summarizes, eye trackers can measure several parameters of eye movements (e.g. timestamp of the gaze data, X-Y coordinates, distance of the eyes from the stimuli or display monitor, indexes of events, etc) which can be analyzed by softwares for making plots, graphs, heat maps etc. There are different kinds of eye tracking devices, each one with specific features best suited for specific experimental designs. The Human-Computer Interaction research field, and in particular the development of technologies for diagnosis and intervention on disabilities, is strongly multidisciplinar. Cognitive sciences and software engineering are closely intertwined (Benyon, 2014, p. 13; Lazar et al., 2010, p. 17). Interaction designers are experts in developing interactive systems, both from the design and implementation perspectives. They can effectively contribute to the study of physical and cognitive impairments (ASD included), by developing practical research and assessment tools starting from reviewing scientific research and teaming up with clinicians in the field.

On a meta-research level, eye tracking can provide a way of communicating scientific results to non-specialist stakeholders. It is conceivable that eye tracking can be used as an integrated part of screening and diagnostic assessments in the future (Falck-Ytter et al., 2013). Technology-based research into ASD is more likely to drive awareness and policy changes, as it appears more rigorous and convincing to the public, and it has therefore more potential to receive media coverage (Bölte et al., 2016).

This study is not intended to be conclusive, but it is meant to provide a basis for further research about the usage of eye tracking technologies in the field of cognitive sciences and clinician-based practices.

A box with a list of the key points of the sections is provided in the first three chapters of this report. These chapters are particularly dense of contents and go very much in detail in some parts. A summary is provided in order help the reader to keep in mind the big picture.

## 1.1 Eye tracking and early ASD detection

Section 1.1 highlights

- Eye movement patterns could be considered as early indicators of atypical development.
- Early detection and intervention on impaired eye movement patterns could stop the divergent developmental cascade.
- Eye tracking methodologies shows potential in aiding early ASD diagnosis on small children since they are unobtrusive.
- Eye tracking, used in combination with traditional behavioral assessment, can lower the average age for ASD diagnosis.

As Bölte et al. (2016) summarize, eye tracking technologies have been becoming more viable during recent years and the number of published articles increased exponentially all over the world. The substantial interest in eye-tracking technology is due to the fact that this technology is currently viewed as having the highest direct clinical potential for early pediatric screening of ASD. This is possibly because it is not intrusive and can provide information on various aspects of development (Bölte et al., 2016; Falck-Ytter et al., 2013; Subrahmaniam, 2013; Sasson and Elison, 2012).

Sasson and Elison (2012) illustrate that eye tracking is an objective and accessible tool for examining perceptual characteristics of psychiatric disorders, which facilitates research into the abnormal visual attention and oculomotor patterns that contribute to clinical characteristics of ASD. A particularly promising application is the study on young children, in order to capture early-emerging developmental mechanisms in this critical period in the development and providing information about the early course and characteristics of ASD. Indeed eye tracking has already been largely used in studies on people with ASD (for some recent reviews, see Boraston and Blakemore, 2007; Brenner et al., 2007; Falck-Ytter et al., 2013; Papagiannopoulou et al., 2014; Chita-Tegmark, 2016; Johnson et al., 2016; Bölte et al., 2016; Frazier et al., 2017).

Diagnosing children with ASD means that, from that moment on, a rehabilitation and education path will be developed for the subjects (APA, 2017). People with ASD, especially children, who had early diagnosis and intervention improve long-term prognosis (Vargas-Cuentas et al., 2016). Quicker and more thorough and evidence-based ASD diagnosis can lead to earlier treatment which can help the children to develop adaptation skills which allow them to attain a better level of integration into society, reducing the intensity of the condition (Martineau et al., 2011; Towle and Patrick, 2016). Not only the subjects with ASD would experience a better life experience, but also their families will improve the quality of their everyday life.

As Anderson et al. (2006) explain, early infancy can be a particularly advantageous time to investigate the primacy of deficits, since the deficits would presumably be less influenced by the environment and secondary deficits. For example, the preferential attention to social stimuli might be a precursor to joint attention (which seems to emerge between 6 and 12 months of age), which in turn might be a precursor to theory of mind (which seems to emerge during the fourth year of life). Differences in the neurological structures underlying a precursor could be the cause of impairments in later developing skills, therefore is important to identify early impairments in precursor skills. Various signs of diverging development in cognition and behaviors can be observed within the first 18 months of life (for a detailed description, see Shultz et al., 2015). Indeed, researchers have become very interested in a downward age extension in ASD-specific detection tools that can be applied clinically (Towle and Patrick, 2016).

Analyzing specific eye movements could uncover when a child is missing valuable learning opportunities, and these kind of early indicators of atypical development are functional for research and for early interventions designed to improve social-communication in children with ASD (Birmingham et al., 2017). Impairments in ocular motor control in ASDg, such as planning, timing or accuracy of eye movements could have deep influence on visual perception, visual-motor integration, social imitation and social attention (Brenner et al., 2007; Johnson et al., 2016). Indeed, oculomotor studies provide a strategy for evaluating the functional integrity of several brain systems and cognitive processes in autism (Takarae et al., 2004).

Summarizing from Kemner et al. (2004) and Smyrnis (2008), endophenotypic markers are measurable features (e.g. neurophysiological phenomena) which are intermediate variables measuring one aspect of the complex disorder and linking the phenotype of the disorder to the corresponding genotype. These markers can be measured in a relatively objective way and can provide insight into the underlying neurophysiology, and they are probably more associated with the biology of the disorder than clinical traits. Oculomotor function variables could serve as biomarkers of the disorder and they could be used in the evaluation and the development of treatments. So far, no neurophysiological abnormalities discovered in autism have fulfilled the criteria for being elected as an endophenotypic marker. In this perspective, eye tracking investigations can provide a form of documentation aimed to understand if impairments in eye movements (as endophenotipic markers of different neurological functioning) have the potential to trigger the "developmental cascade" (Towle and Patrick, 2016) which leads the children with ASD to develop differently than TDg (as described further in Section 3.7.2). Therefore, detecting early markers of ASD can be crucial to implement treatments at earlier ages and to correct the identified causal developmental pathways (Young et al., 2009).

Even though literature highlights the need of early ASD diagnosis, as APA (2017) reports "Although ASD can be diagnosed as early as 15 to 18 months of age, the average age of diagnosis is about 4.5 years, and some people are not diagnosed until adulthood". By the time most children with autism come into the clinic for an evaluation, they already have major problems with social engagement and language, as well as repetitive behaviors (Bourzac, 2012). Several articles (Boraston and Blakemore, 2007; Jones et al., 2008; Zwaigenbaum et al., 2005) point out that unobtrusive eye tracking tests done on babies could provide an effective tool for early diagnosis (even in the first 24 months), without waiting for the babies to develop further communication skills before undergoing an ASD evaluation, as well as understanding what are their opportunities for learning and development (Falck-Ytter et al., 2013). Eye tracking can also provide information longitudinally (Zwaigenbaum et al., 2005), and it shows potential to highlight responses to intervention, such as occupational or pharmacological therapies (Johnson et al., 2016).

As Samad et al. (2017) discuss, placing electrophysiological sensors on different body parts can significantly constrain the natural body, hand, and head movements of the subjects. Many of the subjects diagnosed with ASD show anxiety and phobia related to novel experiences, therefore intrusive procedures and restrictions may overwhelm the subjects and eventually inhibit or bias their natural response data. Minimal intrusion and stress is necessary for a psychophysical studies on ASDg. In this regard, eye tracking technology shows potential in aiding early ASD diagnosis by virtue of the fact of being unobtrusive measurement technologies (Bölte et al., 2016; Falck-Ytter et al., 2013), which not require electrodes positioned on eyes or head-mounted devices, record data in a relatively short time (few minutes instead of about one hour for EOG or VOG procedures) (Giordano et al., 2017).

Even though there are many eye tracking studies done currently on ASDg, the methodologies, the paradigms and the results seems scattered and sometimes contradictory. Currently it seems that no combination of technologies have improved the reliability or validity of diagnostic procedures or the efficacy or effectiveness of interventional practices in ASD Bölte et al. (2016). The framework developed in this Master Thesis (as described in detail in Chapter 3 attempts to assemble a cohesive procedure which can be applied in the clinical practice and provide more data about specific eye parameters which might prove to be related significantly with ASD when measured on large sample groups.

As described further in detail throughout the whole Section 2.1, currently the most widely used instruments for ASD detection and diagnosis are clinician-based behavioural methods. The framework developed in this Master Thesis aims to introduce a technology-based assessment for early ASD detection without completely replace traditional or gold-standard practices, acting as a supplement which benefits earlier and more accurate ASD diagnosis or even preliminary screening (as Liu et al., 2015 also propose).

Summarizing, eye tracking has the potential to describe the complex picture of ASD by trying to explicitly connect the underlying neurocognitive networks to everyday function and dysfunction (Falck-Ytter et al., 2013), and indeed it shows significative results in distinguishing TDg and ASDg (e.g. Boraston and Blakemore, 2007; Papagiannopoulou et al., 2014; Bölte et al., 2016; Johnson et al., 2016).

## 1.2 Research questions

The research questions this study tries to answer, and the operationalization of them, are the following:

1. Which eye tracking parameters, that so far have been investigated in literature, seem to be reliable for detecting ASD symptoms in small children (12-24 months)?
2. What kind of experimental design (methods and stimuli) could reveal the eye tracking parameters of interest?
3. Is the outlined procedure applicable to the target children?

3.a. It was possible to conduct it until the end.
3.b. The percentage of tracking ratio for each visual stimuli is >50% (Sasson and Elison, 2012).
3.c. The percentage of repetitions performed entirely over the total number of repetition displayed is >50%.
3.d. The diagrams of the eye tracking data show qualitatively the gaze patterns which the methods were aimed to elicit.

The research questions 1 and 2 find their answer in Chapter 3. The research question 3 finds its answer in Chapter 5 and Chapter 6. Given the abstract nature of question 3, an operationalization is needed. In order to consider the procedure as "applicable to the target children", it has to:

1. Be suitable to be performed from the beginning to the end (3.a), keeping the children interested
2. Manage to provide enough eye tracking data to analyze (3.b). Sasson and Elison (2012) indicate a 50% proportion of missing data as signal of lack of overall attention to the stimuli.
3. Provide data on a good amount of repetitions (3.c). Repetitions are important to assess the consistency of the eye movement data. If the tracking does not cover consistent parts of the recorded dataset, it would be difficult to assess the internal consistency of the data. The 50% threshold is taken by affinity with 3.b;
4. Elicit the expected gaze patterns, which should be similar to a reference measurement. For example, sinusoidal motion target should elicit sinusoidal eye movements.

# 2 Background

The background of the current study embraces two interdisciplinary areas, namely the clinical praxis for the assessment of ASD (Section 2.1), belonging to the healthcare and psychology research fields, and the measurement of specific eye parameters with eye tracking technologies (Section 2.2), belonging more to the human factors and HCI research fields. The eye tracking framework presented in the next chapter (3) builds upon and tries to make a synthesis of these two research areas. Some of the information in this section were collected by the author during the literature review for the IMT4898 Specialisation in Interaction Design course and the interview study for IMT4215 Specialization Project, in the autumn of 2017. Therefore some concepts can be found in those previous reports. The essential literature review (initially started during the IMT4898 course) retrieved a total amount of around 160 relevant papers. The researcher narrowed down to the amount of papers reported in the reference list of this thesis by following a traditional approach (Jesson et al., 2011, pp. 74-76) with a focus on the meta-analysis of eye parameters, user sample characteristics (primarily age and diagnosis), methods, stimuli material, experimental procedure and outcomes. No systematic approaches were practiced, therefore no claims of scientific evidence are made on the literature. The review provides only the researcher's point of view on the state of the art of the research field.

## 2.1 Clinical assessment of ASD: current setting, problems and perspectives

In order to understand the context in which eye tracking technologies might find their application, in this section some notions about the clinical assessment of ASD are reported, including the current practices, tests and problems. Clinicians already assess the children's gaze behavior as an important index of risk related to ASD, and they already collect a series of behavioral information through the administration of specific tests which provide a rich qualitative description of the children's status. Eye trackers can provide a further quantitative measurement tool which should be used together with the current diagnostic praxis.

### 2.1.1 Clinical practice

Section 2.1.1 highlights

- Current clinical screening and diagnostic procedures for ASD detection are based on behavioral assessment.
- Subtle symptoms, comorbidity, lack of instrumental diagnostics and strict procedures make ASD detection difficult in children younger than 24 months of age.
- Technology-based assessments can support current clinical practice.

Current clinical practices base the ASD diagnostic procedure on a variety of well validated and specific behavioral screening and diagnostic tests, which are described in detail by Towle and Patrick (2016), Magán-Maganto et al. (2017) and Charman and Gotham (2013). As these articles further describe, these instruments can be used, and seem to start to be most useful, during the second year of the children (12 months of age to 24, up to 36 for some tests). However, as highlighted by an interview with Simone Minichiello[1](Minichiello, S., personal communication, November 12, 2017), 24 to 32 months of age is the period in which more children are brought to specialistic structures for receiving a diagnosis of neuropsychiatric disorders. Before 22-24 months of age is quite rare to find children in this kind of diagnosis and rehabilitation structures. Therefore, from a clinical perspective and with the current methods, the early diagnosis happens around 22 and 24 months of age. Before this age threshold, the early symptoms of ASD (especially the ones related with social interaction) can be too subtle both for parents and for the general practitioners, and also the screening tests might not be sensitive enough to subtle signs of early ASD. After 33-36 months it is easier to diagnose ASD since the symptoms are already pervasive, clear and evident. The more the children is young and ASD symptoms are not severe, the more complex is the diagnosis process.

From the same interview emerged that diagnosing ASD in the first 24-30 months of life of a child poses particular challenges to clinicians, for example:

- Behaviors related particularly to social interaction, the usage of language and how the child perceive and act towards the world become more evident and clear only when the children are a bit older (after the 24th month of life (Orlandi et al., 2014; Bocchi et al., 2012)). Indeed, as also Vargas-Cuentas et al. (2016) describe, problems related to early detection of ASD are the difficulty for the parents to detect subtle symptoms like those that characterize ASD in early stages (especially in the first child), the lack of information from pedia-

[1]Simone Minichiello is a logopedist expert in clinical diagnosis and rehabilitation of children with neuropsychiatric disorders (among which ASD). He currently works at the Centro Ferrarese di Neuropsichiatria, Neuropsicologia e Riabilitazione - Piccolo Principe (Ferrarese Center for Neuropsychiatry, Neuropsychology and Rehabilitation - The Little Prince), in Ferrara (FE), Italy. The full transcript of the interview is available in the IMT4215 Specialization Project (autumn 2017) report written by the author of this study.

tricians and other professionals to detect ASD early, and the assessment tools currently in use by specialists sometimes are inadequate (too specific or not specific enough, as Minichiello describes).

- Comorbidity is relatively frequent, meaning that other neurodevelopmental problems are present along with ASD.
- Currently there are not instrumental diagnostics for ASD (e.g. no blood sampling, EEG or MRI which can detect ASD). As also Samad et al. (2017) describe, due to the fact that currently there are no diagnostic biomarkers for ASD, the disorder is commonly identified through direct visual observation of atypical behaviors. These methods have limitations in identifying subtle behavioral traits which may gradually lead to more complex behavioral impairments over the developmental period of the child with ASD.
- There are not strict procedures for ASD diagnosis. Clinical procedures are aimed to describe the symptomatology and at the same time intervene with therapy, waiting for providing a prognosis until the symptoms are clearer.

As Minichiello further explains, the result of these issues is that it is difficult to asses the ASD symptom severity in this particular moment of the children lifecycle. Only if the ASD behavioral symptoms are very severe, it is easier to formulate a diagnosis. Due to the complexity of ASD and that the diagnostic behavioral tests are prone to subjective interpretation, a team of specialized clinicians (e.g. child neuropsychiatrist, developmental psychologist, logopedist, neuro-psychomotrist) need to review together the information and the tests about the child, in order to reduce the risk of incorrect diagnosis. Great benefit could come from providing instrumental and objective assessment tools (and relative procedures) developed specifically for this age group, which can assist the current diagnostic practices. As Bölte et al. (2016) discuss, objective technology-based techniques of research into early ASD have potential to reveal unknown subtle atypicalities in the developmental processes leading to ASD, and to be used in paediatric and psychiatric clinical practice. This is because these technologies seek to identify biological markers of ASD for earlier diagnosis and biologically defined treatment goals.

### 2.1.2 Current ASD screening and diagnostic instruments

Section 2.1.2 highlights

- Technology-based assessment can provide information about subtle atypicalities related to ASD. However, the screening and diagnostic tools in use are observational and behavioral.
- The efficacy of screening and diagnostic tests is computed through indexes of sensitivity, specificity and positive predictive value.
- For small children there are two levels of screening tools: level 1 (population level) and level 2 (applied to children at risk).
- Diagnostic tests are used to structure the information-gathering through standardized protocols. However, diagnosis is not based only on the tests, but also on clinical judgment.

As (Bölte et al., 2016) summarize, there are two main groups of methods for assessing the development in the first months and years of life of children, as well as responses to interventions:

1. Informant and clinician-based behavioural methods (e.g questionnaires, observation scales, interviews developmental tests), which are observational, subjective and sometimes qualitative.
2. Technology-based and/or measurements of basic cognitive or neurological processes and structures (e.g. eye tracking, electroencephalography (EEG), event-related potentials (ERPs), magnetic resonance imaging (MRI), positron emission tomography (PET), transcranial magnetic stimulation (TMS), retrospective video analysis, preferential looking experiments, etc), which are direct, objective and mostly quantitative. These methods show potential to reveal previously unknown subtle atypicalities in the developmental processes leading to ASD, useful for paediatric and child and adolescent psychiatric clinical practice.

The current clinical practice is based on the first group of methods, the observational screening and diagnostic tests, some of which are considered the gold-standards. Some tests are aimed to detect a series of signs of high probability of ASD, then others are carried out in series in order to rule out symptoms which are shared with other conditions and to reach a clinical diagnosis (Vargas-Cuentas et al., 2016).

As Magán-Maganto et al. (2017) explain, over the last two decades more than 20 screening instruments aimed at prospectively identifying children with ASD have been developed and made available internationally, even though these instruments are not yet at an optimal level. The major issue is the difficulty in determining which constructs (e.g. language delays, repetitive behaviours, social interaction, interest in others, joint attention, etc) are essential for discerning between children who are at risk for ASD, at risk for other developmental disorders and typically developing children. Therefore, if construct validity is at debate, practitioners and researchers cannot tell if the different screening tools are measuring the same behaviors. In ASD, the major construct which score higher seem to be social interaction, interest in others, joint attention and atypical eye contact, while motor abnormalities cannot discern clearly between ASDg and children with other other developmental disorder. Moreover, also the content validity of these instruments is largely related to the opinions of the people performing the validation. In order to assess the efficacy and utility of the screening instruments, the following parameters are computed (Charman and Gotham, 2013): (1) sensitivity (the proportion of individuals with a disorder who have a positive screen result), (2) specificity (the proportion of individuals with a disorder who have a negative screen result), (3) positive predictive value (the proportion of individuals with a positive screen result who have the disorder).

Towle and Patrick (2016) illustrate how in the age range between 18–24 months and 30–36 months there are two levels of **screening instruments**, which aim is to identify children in need of further monitoring or diagnostic evaluation:

- Level 1: They are intended to screen at a population level (i.e all children regardless of their risk level for developmental disabilities). Examples of these screening instruments are the Modified Checklist for Autism in Toddlers (M-CHAT), Infant-Toddler Checklist (ITC) and First-Year Inventory (FYI).
- Level 2: They are applied to children at risk (showing signs of ASD or another type of delay or disability, detected by the parents or pediatrician), in order to route the children to more thorough evaluations. Examples of these screening instruments are the Screening Test for Autism in Two-Year-Olds (STAT), Parent Observation of Early Milestones Scale (POEMS) and Autism Detection in Early Childhood (ADEC).

Charman and Gotham (2013) describe the **diagnostic instruments** in use for ASD, which are used to structure the information-gathering from both parents and identified children within a diagnostic assessment. Some examples are Autism Diagnostic Observation Schedule (ADOS, a semi-structured, standardised observation of children and adults interacting during a series of protocols of activities, useful from 12 months and up; Lord et al., 2000), Autism Diagnostic Interview-Revised (ADI-R, a standardised semi-structured interview useful from 12 months and up; Rutter et al., 2003) Diagnostic Interview for Social and Communication Disorders (DISCO, useful at all ages) and Developmental, Dimensional and Diagnostic interview (3Di, useful on unselected clinical and general population samples). Both the screening and diagnostic instruments enlisted are often limited in their power to correctly discern ASDg and TDg, especially for marginal cases. Even though some of the diagnostic tests have strong predictive validity (e.g. ADOS and ADI-R if used together), clinicians do not rely solely on these assessments in order to formulate a diagnosis. Experienced clinical judgment and training with the instruments still impact on the accuracy of the diagnosis, regardless the valuable standardization provided by the tests.

### 2.1.3 Where eye tracking could fit in the screening and diagnostic process

Section 2.1.3 highlights

- It is fundamental to have a behavioral evaluation along with the eye tracking measurements.
- Oculomotor performance can be assessed precisely through eye tracking, while constructs related to social attention are too complex to be measured directly.
- Eye tracking assessment should be repeated at precise intervals, in order to track the developmental trajectory of the children.
- Eye trackers can be part of a portable psychoanalytical unit.

Given the clinical practice framework illustrated in the previous section (2.1.2), eye tracking tools can seen as a supporting diagnostic instrument, and maybe also as a supporting Level 2 screening instrument. The required basic training with the technology, and the economical investment of buying it, probably does not make eye trackers suitable to become a Level 1 screening instrument to be used at population level. At the current state of the research, it is required by the clinicians to notice at least show some sign of possible developmental disorders (among which ASD) in the children before using eye trackers as specific measuring tools. This is also due to the fact that eye tracking alone cannot provide a definitive picture of the ASD condition in small children, for a series of reasons.

As Minichiello (Minichiello, S., personal communication) explains, aberrant gaze behaviors are present also in other pathologies, like in severe dyspraxias or in case of motor problems which affect ocular motor mechanisms, which can be mistaken for ASD indicators. Therefore, it is fundamental to have a behavioral evaluation along with the oculomotor measurements. Moreover, during the encounters between the children and the clinicians in an diagnostic setting, clinicians already pay close attention to children's social and communicative gaze behavior, since it is considered an important index of possible disorders. Joint attention (triadic relation between object-parent-child), gaze following and gaze initiative, are already considered diagnostic parameters and they are already assessed on a behavioral and qualitative level. However, these constructs are probably too complex to evaluate through a controlled experimental setup with eye tracker, since ecological validity plays a fundamental role in assessing the validity of the paradigms used in the experiment (as discussed more in deep in Section 3.7. Eye trackers require a controlled setting in order to provide reliable and replicable measurements. On the other hand, eye trackers can provide measurements on eye movements which are impossible to assess with naked eye (e.g. saccades, smooth pursuit), and eye tracking is probably more useful in assessing these eye movements.

Due to these reasons eye tracking should be seen as a supporting tool for ASD diagnosis, which is meant to be used together with the already validated behavioral diagnostic praxis. In the clinical field, the technologically advanced tools should enhance the diagnosis, by integrating clinicians' experience (mainly qualitative knowledge) with non-invasive quantitative measurements (Orlandi et al., 2014).

Discussing further with Simone Minichiello, it emerged that this kind of eye tracking assessments are possibly suited to be carried out during the first evaluation (anamnesis and diagnosis) and then repeated every 3 or 6 months during the clinical follow-up, basing on the type or treatment. The repetition of the assessment is functional to the observation of the speed of the improvements: the more the changes happen quickly, the less likely they are related to such a severe disorder as ASD. Small children change and develop their behaviors quickly, with evident differences emerging even monthly, especially if the children are already undergoing a somewhat heavy training (in ambulatory, at home, at school) after the clinicians suspected for the first time the presence of ASD and started a treatment program.

According also to his point of view, we hypothesize that—given the unobtrusiveness of eye trackers—validating this technology as a supporting tool for ASD diagnosis should not be a too hard challenge from a technical point of view. A possible first approach to start a validation process requires to:

1. Define the steps of age during which making tests with the children (e.g. 18-24-36 months of age);
2. Record a series of eye tracking measurements on a typically developing children population, in order to collect baseline data and assess the reliability of the measurements;
3. Administer the same procedure on ASD children, in order to assess differences between groups and the internal and external validity of the method.

A possible scenario of use of eye tracking technologies in a clinical setting is outlined by Subrahmaniam (2013); a stand-alone equipment can be developed, acting as a psychoanalytical unit and consisting of a high-end computer with installed:

1. Eye tracking hardwares and softwares;
2. Psychometric/psychoanalytical software: built with the help, guidance and supervision of experts in psychoanalysis and psychiatry. The algorithms should

compute and objectively analyze psychometrics from the eye tracking;
3. Visual stimuli supply engine: a software which fetch from a repository of of media types and deliver visual stimuli content on-demand.

Indeed, Bocchi et al. (2012) already developed this kind of stand-alone automated solution for medical doctors or other non-technical operators, in order to collect and store on a shared server behavioral information (general movement analysis, cry analysis, behavioral analysis) on infants siblings of children diagnosed with ASD, defined to be as "high risk". The data acquisition protocol they outline is also made for being iterated at specific time ranges. Integrating further this kind of qualitative and quantitative technology-based information collection with eye tracking could be promising in providing a more accurate picture of the children's condition.

Recently, Giordano et al. (2017) at University of Catania (Italy) developed a software tool which enables physicians and scientists to design and carry out procedures based on eye movement analysis for both diagnostic and research purposes, without the constant support of expert computer programmers. The system is structured to create, measure and analyze a wide variety of cognitive tests related to smooth pursuit eye movements and visually guided saccades. It does not seem to be tailored specifically on the particular kind of tasks of interest for the present study. However, the basic software and hardware infrastructure the authors describe –which is similar to the one outlined by Subrahmaniam (2013)– shows evident potential to be expanded with the framework developed in this Master Thesis. Moreover, the overall aim of their research is analogue to the one of this study, that is to overcome the complexity and the cost of creating tools for disease-specific eye tracking tests, widening the application of these technology for diagnostic purposes. Therefore, integrating the insights and preliminary results from the present study with the work from Giordano et al. (2017) could be a next step in order to create a psychoanalytical unit which can assess the specific eye parameters for early detection of ASD. The authors also have already tested the system with children with ASD, but with different tasks (attention deficit test, target vs distractor fixation measurement) and with children in an older age group than the one of interest for this thesis.

## 2.2 Eye parameters

Section 2.2 highlights

- Eye movements are distinguished by different anatomical and neural circuits and they serve specific purposes. The different types of eye movement can be operationalized and measured through eye tracking.
- Fizations, saccades and smooth pursuit eye movements are the types of eye movement most extensively studied in ASD.
- Divergent patterns in ASDg eye movements from TDg could indicate potential delays and deficiencies.

In order to understand in which way eye trackers can be useful for early ASD diagnosis, it is fundamental to define and operationalize the eye movements of interest which need to be measured. In the context of this thesis, all the measurements of variables (e.g. velocity, amplitude, etc) related to categories of eye movements (e.g. saccades, smooth pursuit, etc) are defined as “eye parameters”, in order to highlight their purpose of indicators of cognitive or motor differences between groups of subjects. The various eye parameters provide insights about the possible divergent development of the involved neural circuitry.

As Leigh and Zee (2015, pp. 2-5) summarize, there are different categories of eye movements, which are basically rotations of the eye globes aimed to position the image fairly steadily on the central foveal region of the retina (within 0.5 deg from the center of the fovea), where the photoreceptor density is greatest. Eye movements can be distinguished basing on how they support vision, their physiology and anatomy. The categories of eye movements are vestibular movements, visual fixations, optokinetic movements, smooth pursuit, nystagmus quick phases, saccades and vergence. Each functional class of eye movements is suited to a specific purposes and the classes are distinguished by different anatomical and neural circuits. Gaze-shifting eye movements, such as saccades, point the fovea towards the target. Gaze-stabilizing reflexes, such as smooth pursuit, keep the fovea of each eye pointed at the target whenever the head is moving.

Eye trackers can measure and record directly some of these eye movements, such as fixations and saccades, while for others a further computation is needed in order to describe them, such as smooth pursuit eye movements. Moreover, in addition to the movements of the eye globes, eye trackers can compute more eye-related events like the pupillary dilation and the eye blinks. Each type of eye movement or event is then operationalized depending on its specific features (e.g. timing, velocity, accuracy) in order to allow the researchers to measure its characteristics.

Saccades, smooth pursuit eye movements and fixations are the categories of eye movement most extensively studied in ASD so far (Johnson et al., 2016), and therefore the ones which are of most interest for this study, since research provides enough material to try to build a framework on.

Leigh and Zee (2015, pp. 2, 170, 290) describe further these eye movements:

- Fixations are eye movements aimed to hold the image of a stationary object on the fovea by minimizing ocular drifts, even though ocular tremor happens in order to prevent habituation.
- Saccades are rapid eye movements which shift the line of sight between successive points of fixation and which bring images of objects of interest onto the fovea. Saccades are characterized by fast acceleration to high velocity, followed by a quick deceleration of equal magnitude (Wilkes et al., 2015).
- Smooth pursuit movements are generated continuously in order to hold the image of a small moving target on the fovea, by keeping the line of sight congruent to the line of movement of the target. Visual smooth pursuit movements are slower and gradual (Wilkes et al., 2015).

In addition to these parameters, pupil dilation and eye blinks are discussed in literature and they will be described.

Falck-Ytter et al. (2013) provide a quick overview of how the oculomotor system develops in TDg children: at birth infants can direct their gaze throughout the environment primarily using saccadic eye movements (often performing several hypometric saccades). As infants grow older, saccade latencies decrease and fewer corrective saccades are needed. Around two months of age, infants can perform smooth pursuit with the frequent use of saccades to reposition the eyes on the target, and by four months of age they can track objects smoothly on the horizontal plane. Predictive tracking is visible between two and four months of age. The oculomotor system continues to improve over the first year of life. Vertical and two-dimensional tracking matures over the first years and saccade latencies decrease continuously during infancy and childhood. Basing on this overview, it should be possible to assess saccades and smooth pursuit after the first year of life of the children, as well as potential delays and deficiencies.

As Wilkes et al. (2015) discuss, studies show that high-functioning adults with ASD have relatively typical, if more varied saccade function, but abnormal visual smooth pursuit. Less has been done on children, and some patterns are not as clear as in adults.

Even though the number of retrieved articles researching with eye trackers on ASDg is high (as described in Chapter 2, the following sections had to be based on a rather low number of papers which provide detailed measurements of specific eye parameters. Moreover, not many studies investigating on specific eye parameters have been done on infants or toddlers at risk or who eventually have been diagnosed with ASD. Some of the studies reported as follows have been done on children belonging to an older age range, or even adolescents or young adults. This factor might not let the results of these studies to be fully valid for infants in early diagnosis range (defined here as between 12-24 months old), due to the children's development over the months. However, these studies or reviews are the ones which studied subjects in the nearest age groups to the target one (or the studies were cross-sectional or longitudinal, including children), and which described in sufficient detail the ASD group characteristics. ASDg adults are a subject group potentially very different from infants or toddlers for obvious development reasons. However, evidences of abnormal eye parameters in older age might provide hints about earlier impairments which have not been treated by the education and the therapies which the subjects undergone during their lifetime.

In the next sections the various types of eye movements and parameters are described in detail, as well as their potential relation with early ASD diagnosis.

### 2.2.1 Smooth pursuit

Section 2.2.1 highlights

- Smooth pursuit requires the correct functioning and integration of several brain regions (among which the cerebellum). Smooth pursuit impairments could highlight neurodevelopmental disorders.
- Smooth pursuit articulates in two phases: open loop ($\leq$ 100 ms, visually guided) and closed loop (>100, predictive).
- The main smooth pursuit parameter is the gain (position or velocity difference with the target motion).
- Smooth pursuit is present in children since 2 months of age, and it improves while the children grow.
- ASDg show significative abnormalities in smooth pursuit gain.

As Takarae et al. (2004) describe, smooth pursuit requires rapid, temporally precise integration of activity within several brain areas in order to visually track moving targets in the space, making studies of visual pursuit suitable for evaluating functional brain connectivity in ASDg. Neuroimaging studies highlight how the relevant brain circuitry includes the extrastriate areas of visual cortex devoted to the processing of visual motion information, cortical eye fields and cerebellum that are involved in translating sensory information to motor commands, and the striatum and brainstem which are involved in initiating motor commands.

As Brenner et al. (2007) summarize, smooth pursuit is a process which articulates on two phases: a first phase, called open loop, takes place in the first 100 ms after the presentation of the stimuli–which is the time that a pursuit eye movement take to be initiated (Leigh and Zee, 2015, pp. 298) –and the control of pursuit is almost exclusively dependent on sensory analysis of visual motion (Takarae et al., 2004). After this first phase, there is the closed loop phase of sustained pursuit, in which feedback, such as predictive or performance-based information, rather than an analysis of visual motion (Takarae et al., 2004), is used to update eye movement. Smooth-pursuit movements must me generated in response to local optic flow on the fovea but not on the rest of the retina, and this requires the brain to not process visual motion save for the one happening in the fovea (Leigh and Zee, 2015, pp. 290). Takarae et al. (2004) explain that the prediction mechanism is fundamental since once a moving stimulus is tracked, its movement relative to eye velocity should become near zero, and therefore it provides insufficient information to drive further smooth pursuit. They also describe that the frontal eye fields and cerebellum are believed to play a crucial role during closed-loop predictive and performance-based pursuit, and abnormalities in the cerebellum are one of the most consistent histopathological findings in ASD. Cerebellum is believed to make a large contribution to the adaptation of smooth pursuit (Leigh and Zee, 2015, pp. 326).

As Wilkes et al. (2015) describe, smooth pursuit eye movements have slower acceleration and velocity than saccades, and they cannot be performed in the absence of a moving visual stimulus. Two parameters are commonly studied:

- Gain: maximum degree of displacement of the eye as compared to the maximum degree of displacement of the target visual stimulus;
- Phase lead/lag: mean degree of displacement by which the eye leads or lags behind the target stimulus. The less phase difference between eye and target, the more the smooth pursuit movement is accurate.

As Kemner et al. (2004) show, smooth pursuit gain can be computed as position gain (i.e. eye position as a linear function of the target position) or, more commonly, as velocity gain (i.e. how accurately eye velocity matches the velocity of a moving target (Johnson et al., 2016)). Neither fixations nor smooth pursuit eye movements physiologically can have a velocity higher than 100 deg/s (Larsson et al., 2015).

von Hofsten and Rosander (1997) conducted a study which illustrates how smooth pursuit tracking develops in TD infants, and which serves as a basis in order to understand if and how ASDg behaves differently. They measured eye (saccades and smooth pursuit) and head movements in 11 healthy and full-born TDg infants at 2, 3, and 5 months of age, through EOG (Electro-oculography, 200 Hz). The gaze was estimated as the sum of eye and head positions. The subjects were presented with a sinusoidal and triangular target moving horizontally by different amplitudes (12.5 deg or 25 deg of visual angle) and frequencies (0.2 Hz and 0.4 Hz) (Fig. 1). Saccades were detected when the eye velocity was higher than 50 deg/sec of the tracking velocity amplitude, and they were eliminated from the composite eye movement record, in order to obtain two different set of records, one for the smooth pursuit movements and the other for the saccades. Regarding smooth pursuit development, they observed that all the infants displayed some smooth eye tracking. Smooth pursuit gain increased with age: at 2-3 months, the lag of the smooth pursuit was small for the sinusoidal motion but large for the triangular one. These differences might be due to a velocity-based local analysis process in the infants, which works better for prediction of the continuous sinusoidal motion but not for the abruptly changing triangular motion, preventing accurate predictive tracking. They found a higher proportion of smooth pursuit at the lower amplitude and frequency. The authors suggest that the ability to track sinusoidal motion emerges some time between 1 and 2 months of age. At 5 months tracking become clearly more predictive: smooth pursuit was leading the sinusoidal motion and the lag for the triangular one was small. Head tracking increased substantially with age and its lag was always large. Head always lagged the target by at least a quarter of a second on average, which suggests that prediction does not affect head tracking. Head gain increased significantly over the time and consequently the gain of eye movements decreased. Eventually, the coupling between head and eye movements always allowed for the pursuit gain to be close to 1. Regarding saccade development, they observed that saccades occurred regularly and often came in bursts at the higher velocity parts of the motion. Saccadic amplitude varied as a function of target velocity. The triangular motion elicited a higher number saccades, of wider amplitude and frequency than the sinusoidal one. At 5 months, the relative proportion of saccades was similar to the one present in adults.

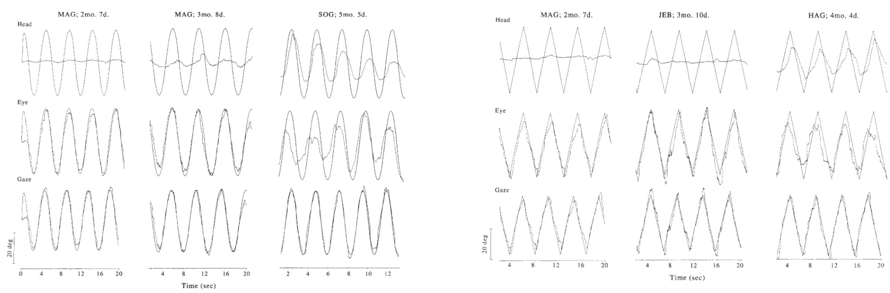


Figure 1: Smooth eye pursuit visualization of sinusoidal and triangular motion stimuli. Images retrieved from von Hofsten and Rosander (1997).

ASDg seem to show significative abnormalities in smooth pursuit movements. Johnson et al. (2016) reviewed results from studies reporting open loop gain measurements (on a total of 101 ASDg and 140 TDg) and closed loop gain measurements (on a total of 114 ASDg and 154 TDg) finding strong evidences for significant deficits of pursuit gain in both open- and closed-loop phases of pursuit eye movements in ASDg. Even though the authors state that these results are one most robust indicators of smooth pursuit impairments, the subjects of the reviewed studies had a mean age ranging from 16.3 and 24.5 years old, and therefore they were either adolescents or adults.

Takarae et al. (2004) compared pursuit eye movements of 60 high-functioning ASDg (children, adolescents and adults, mean age 20.05 years old, SD 11.24) and 94 TDg using foveofugal step-ramp, pure-ramp and oscillating target tasks. They observerved that ASDg showed normal pursuit latency, but reduced closed-loop pursuit gain in all the tasks (which was consistent and not increasing across target speeds), and these abnormal parameters become more evident after mid-adolescence (>16 years), suggesting a reduced development of the pursuit system (Fig. 2). ASDg also showed lower open-loop pursuit gain in the initial catch-up saccades during a foveofugal step-ramp task, when the targets moved into the right visual field. This lateralized effects was more pronounced in younger ASDg. Lower open-loop gain suggests disturbances in the transfer of visual motion information from sensory to sensorimotor systems, which affects the fidelity or resolution of visual motion information, but not the speed through which the information is transferred, since open-loop latency was comparable to TDg. The authors suggest that the reduced functional connectivity within the visual pursuit system–which is caused by disturbs in the development of the brain like the possible disruption of open-loop pursuit in the right hemifield and involving the cerebellum, and the possible developmental failure in the sensorimotor systems mediating closed-loop pursuit–appears to be a fundamental characteristic of ASD.

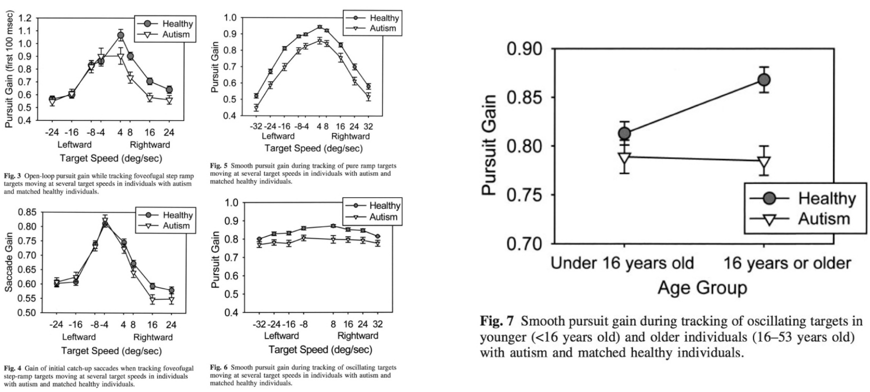


Figure 2: Diagrams from Takarae et al. (2004) showing differences between ASDg and TDg smooth pursuit performance. This study was also included in the review from Johnson et al. (2016).

Even though smooth pursuit parameters seem to be discern ASDg from TDg in a reliable way, there are some contrasting results in literature.

Wilkes et al. (2015) investigated on saccade and smooth pursuit performance in 16 high-functioning ASDg children between 6 - 12 years old (mean age 104 months, SD 23, IQ > 70) and 24 TDg. They used VOG goggles (I-Portal/Neuro-Kinetics, 100 Hz) to record eye movements while presenting a red laser-light as stimuli in a dark room. The stimuli moved both on an horizontal and vertical axis. They observed that ASDg had significantly lower mean smooth pursuit phase for vertical smooth pursuit at .10 Hz (where pursuit is typically more accurate) with a trending group difference at 0.50 Hz, but no differences in mean gain or phase for horizontal smooth pursuit conditions. They observed greater variance horizontal smooth pursuit phase in ASDg. They argue that the more evident difference in group means for phase in vertical, but not horizontal conditions, can be related to the relatively infrequent use of visual pursuit in the vertical plane, since in daily experience tracking objects continuously in the vertical plane is more rare than tracking objects in the horizontal plane. Differences in phase implies that the fovea is not on target but in the periphery.

von Hofsten et al. (2009) made a study on 10 ASDg children, between 3 to 6 years old (mean age 4:8 years, range 2:10–6:1 years) compared to 1 and 3 years old TDg, evaluating their ability to track an object with smooth pursuit and their ability to anticipate the reappearance of a temporarily occluded moving object, looking for indicators of impaired motion perception or predictive ability. They used cornea reflection eye tracking (Tobii 1750/Tobii Technology, 50 Hz).They observed that ASDg tracked a sinusoidally moving object with no significant lag and with the similar smooth pursuit gain as TDg. The authors acknowledge the contradiction with previous results in literature, which reported deficient motion perception in ASDg, by speculating that it could be possible that ASDg are deficient in their ability to integrate local motions into coherent wholes but not in their ability to track single motions. ASDg also shown to be able to anticipate the reappearance of the temporarily occluded moving object. However, these results cannot be fully compared with other papers, since the sampling frequency of the eye tracking equipment was rather low to have precise measurements of saccade and smooth pursuit movements. Smyrnis (2008) advices to use sampling frequencies of at least 200 Hz for saccade and smooth pursuit measurements, while here the authors used only 50 Hz.

Acknowledging the findings in literature of abnormalities in smooth pursuit eye movements in ASDg, Kemner et al. (2004) investigated on smooth pursuit in the group of children with the more generic diagnosis of pervasive developmental disorder (PDD) in order to assess the presence of endophenotypic markers of general genetic factors predisposing for psychopathology. They observed 16 children (9 diagnosed with PDD, 7 diagnosed with ASD, mean age 10.9 years old, SD 2.0) and 18 TDg during smooth pursuit task and and 14 children (7 diagnosed with PDD, 7 diagnosed with ASD, mean age 11.1 years old, SD 2.1) and 15 TDg during visually guided saccade tasks. They used electro-oculography (EOG, 85 Hz, nine points calibration) to record the smooth pursuit eye movements while displaying a target moving at a constant velocity in triangular motion, and horizontal and vertical saccade tasks. In smooth pursuit, they found that position gain decreased significantly at target velocities greater than 16 deg/s and that the number of saccadic intrusions increased at target velocities between 8 and 24 deg/s and then assessed at around 2.7 saccades/second. In saccades, amplitude, scatter in amplitude, duration and peak velocity increased significantly with increasing amplitude between the targets. No differences in smooth pursuit or saccade parameters were found between the groups, indicating that eye tracking is normal in children with PDD (and reached maturation to a normal levels in children with PDD of about 10 years of age), suggesting that smooth pursuit eye movements are not a neurophysiological marker of PDD. Their findings of normal of smooth pursuit eye movements are not consistent with the literature presented above (Takarae et al., 2004; Johnson et al., 2016). As also the authors acknowledge, in this study the sample was a mixed group of children diagnosed with PDD and ASD. The high variability of condition of the children and the also small sample could have lead to a high variability in the results. Moreover, the level of noise in the EOG system might have influenced the results, which might not be fully comparable to the measurements done by other studies with high-frequency IR eye tracking (as discussed also in the previous paragraph for von Hofsten et al., 2009).

### 2.2.2 Saccades

Section 2.2.2 highlights

- Saccades are basic components of the oculomotor system and their impairment can affect development of sensorimotor, attentional, and cognitive functions in children.
- Saccades can be volitional or reflexive, and their parameters are amplitude, duration, latency, accuracy (gain), peak velocity
- The study of saccades in ASDg can reveal different functioning of parts of the brain like brainstem and cerebellum.
- ASDg does not show consistent impairment in primary saccade parameters, but just in standard deviation of saccade gain (saccade dysmetria), which could be reliable predictor of ASD.

As Leigh and Zee (2015, pp. 170-171) summarize, abnormalities of saccades are often distinctive and highlight disorders of specific mechanisms, and they can describe aspects of cognition such as memory, attention, motivation, reward, prediction and decision making, as well as neurological and psychiatric disease. There are several types of saccade movements, but basically they can be grouped in two macrocategories: volitional (i.e. made as part of purposeful behavior) and reflexive (generated by novel visual, auditory or tactile stimuli, which unexpectedly occur within the environment). Saccades do not last much longer than 100 milliseconds, which is about the time it takes for new information to be processed by the visual system and transformed into a new motor command.

Brenner et al. (2007) summarize several parameters which can be computed from saccades:

- Amplitude: the size, or angular rotation, of the saccade.
- Duration: the time taken for the eye to reach the target. The duration of a saccade is approximately linearly related to their amplitude for amplitudes between 1 deg and 50 deg (Leigh and Zee, 2015, p. 172).
- Latency: the time which elapses between the appearance of the target and the onset of a saccade in response to that target. As Smyrnis (2008) summarizes, saccades can be defined accordingly to their latency (in milliseconds): anticipatory saccades ( $\leq 80$), express saccades ($80 < x \leq 120$), fast regular saccades ($135 \leq x < 180$), slow regular saccades ($180 \leq x < 400$) and late saccades ($400 \leq x < 700$).
- Accuracy: how precisely the saccade directs the fovea to the target, by executing saccades of correct amplitude (Pensiero et al., 2009). It is determined in relation to the expected saccade amplitude: insufficient (hypometric) or excessively high (hypermetric). Saccade gain is an index of saccade accuracy, and it is described as the ratio between target displacement and saccade displacement (Johnson et al., 2016).
- Peak velocity: as Leigh and Zee (2015, pp. 171-172) describe, peak velocity is the top speed of the saccade. The relationship between amplitude, duration and peak velocity is consistent enough in humans, and it is defined as main sequence relationship. Saccades which differ from the main sequence can be seen as an indicator of abnormal behavior. For saccades lower than 20 deg of amplitude, the relationship between amplitude and peak velocity is linear, while for larger amplitude saccades the peak velocity saturates and flattens itself. Through the main sequence it is possible to investigate the working of the premotor system (if the burst cells producing the recorded saccade correctly, independently of the direction, amplitude and timing) (Pensiero et al., 2009).

As Pensiero et al. (2009) describe, saccades are basic components of the oculomotor system and they are already present in infancy. If saccades are impaired, they could affect the development of sensorimotor, attentional, and cognitive functions of the infants. For example, saccades can help in investigating on brainstem, which is considered to be the center of eye movement (and saccades in particular) generation.

Literature presents contradictory findings about abnormal saccadic eye movements in ASDg, even though there seem to be evidences of impairments. Some studies report lower peak velocity in autistic children, other no differences in terms of accuracy, velocity, or latency, others saccadic dysmetria consistent with reports of histological abnormalities in the cerebellum. Freedman and Foxe (2017) suggest that differences in the structure of the cerebellum in ASDg could critically impact visuo-sensorimotor development in early infancy. Saccade adaptation and accuracy can be seen as a good candidate metric of different functioning of the cerebellum in ASD or in other developmental disorders, and these metrics can be assessed in children as young as 10–41 months of age.

However, in their review, Johnson et al. (2016) found that mean peak velocity, mean latency and mean accuracy (computed though gain) of saccades seem to not significantly differentiate ASDg from TDg, suggesting that ASDg does not show significant impairments in shifting and orienting visual attention as well as controlling and sustaining fixation. However, in part of the studies investigating saccades (on a total of 93 ASDg and 147 TDg, mean age of ASDg ranging from 11.2 to 20.5 years old, mean IQs above 95.9 points), ASDg show consistently a significant greater variable error of saccades (standard deviation of saccade gain), which indicates saccade dysmetria (i.e. the tendency of overshoot or undershoot the target) in visually guided saccades tasks with target amplitudes ranging from 5 deg to 30 deg.

Pensiero et al. (2009) investigated saccades in ASDg children 14 ASDg children (5 to 12 years old, mean age 8.1 years old, high severity, IQ > 60) and in 20 age matched TDg, in order to assess possible alterations of saccades at an early stage. They used an eye tracker (500 Hz) to collect data about amplitude, duration, latency and peak velocity, in order to compute main sequence relationships. They used LED lights targets blinking in random positions on an horizontal axis, avoiding to use social stimuli in order to measure only the features of the generation of saccadic movements. They kept the head of the children on a chin rest. Eventually, only 1 ASDg participant showed abnormalities of the main sequence. The others did not show clear alterations of the saccadic features. However ASDg produced more blinks before and during fast eye movements, shown tracts of saccadic initiation failure and changes in the saccadic velocity profiles (which happened 37% of the times at 20-25 deg amplitudes, compared to the 18% of TDg) that could be due to an alteration of the brainstem. It has to be noted that the kind of experiment setting used by the authors might not be suitable for early ASD diagnosis on very small children. They indeed tested older children, who were also able to be continuously prompted to follow with their gaze the illuminated LEDs. This kind of verbal prompting might not work on infants. However, their results suggest that, if there could be alterations in small children's saccades, they might get compensated over the time during development.

At the moment it seems that the saccadic parameters involved in the main sequence do not differentiate clearly ASDg from TDg, However, some secondary parameters, like the standard deviation of saccade gain, seem to be consistent and a reliable predictor of ASD.

### 2.2.3 Fixations

Section 2.2.3 highlights

- Fixation parameters in ASDg are comparable to TDg.
- Fixations on areas of interest (AOI) showing social contents have been investigated extensively in ASDg.
- Ecological validity impacts on the social relevance of the experimental stimuli, rendering difficult to find consistent results in literature.
- It is impractical to assess fixations in the eye tracking framework under development, therefore they are not investigated further.

Fixations are identified when the point of gaze remains within 1 degree of visual angle for at least 100 milliseconds (Boraston and Blakemore, 2007).

As Johnson et al. (2016) describe, overall fixation parameters in ASDg are comparable to TDg, however it presents disturbs in stabilization and fixation maintenance, highlighted by a more variable amplitude of microsaccades. Moreover, ASDg seems to not be characterized by enhanced visual processing.

As Pensiero et al. (2009) summarize, eye tracking technology has been used in investigations on the strategies used by ASDg during tasks involving social information processing. The most common stimuli used for investigating social attention in ASDg are pictures of human faces, but videotapes of social interactions, human voices, and abstract animations have also been employed.

Usually, in order to compute social attention from eye tracking, areas of interest (AOI) are identified in the stimuli prior to the tests. ASDg seems to significantly spend less time fixating social features of faces, like the eyes (Papagiannopoulou et al., 2014; Boraston and Blakemore, 2007). The review from Chita-Tegmark (2016) indicates that the lack of attention on social content in the stimuli, measured by fixation time on social AOIs, seems to be a significant predictor of ASD, and that these difficulties seem to not be affected by age or IQ, but to be a core feature of ASD.

However, defining which AOIs are identifying social contents within a visual stimuli is an arbitrary operation that is strongly related to the ecological validity and above all to the construct validity of eye tracking methodologies for ASD detection, as explained in detail in Section 3.7.2. Presenting a video or a picture on a screen, containing some arbitrarily defined social content, could potentially elicit in the children very different oculomotor responses than the ones they would perform in a natural setting, Highly controlled laboratory settings impact on the social relevance of the experimental stimuli (Papagiannopoulou et al., 2014), and the validity of defining social AOIs as parts of face and body (e.g. eyes or mouth) or the entire figures of people in the visual stimuli is highly dependent on ecological validity.

As a consequence of the different definition of social contents in studies stimuli, literature show contradictory findings, in particulars when children with ASD are the experimental subjects.

In the experiments from von Hofsten et al. (2009), 3 to 6 years old ASDg looked at the social AOIs (faces of the people involved in a conversation) in a video for less time than 1 year old and 3 year old TDg children. However, in the same experiment, ASDg looked at turntaking objects (a video showing objects emitting sounds and moving like if they were having a conversation) in a similar way of TDg, suggesting that ASDg did not have a general attention deficit but that they were less attracted by the social component of the conversation.

The study from Young et al. (2009) suggests that even if there seems to be potential for using fixation towards social AOIs as index of potential ASD development in children, this potential seems to lose predictive value within the first 24 months of life. They conducted a longitudinal study on the gaze behavior of a group on infants at risk for autism with the objective of assessing the diagnostic reliability of the results from of one of their previous study (Merin et al., 2007). In their previous report, a group of those 6 months old children at risk shown an overall decreased amount of gaze to the mother's eye region during a mother-child live interaction. The infants at risk looked less at the mother's eyes. Those results highlighted how this kind of ASD symptoms seem to be present at very early stages of development. However, Young et al. (2009) affirm that the lack of visual attention to the eyes or a lack of shared affect during the first year of life might be related more to risk-status than to diagnostic outcome and may ultimately have poor specificity and poor clinical utility, since the majority of infant siblings of children with autism will exhibit typical development. The authors visited and collected infant behavior and eye tracking data (using a Tobii corneal-reflection eye-tracker, 30 Hz, five point calibration) on a final sample of 49 infants, who were visited at 6, 12, 18, and 24 months of age. AOIs were used to code each fixation frequencies and durations on eye, mouth, and other face regions. Eventually, out of the 49 infants only 3 were diagnosed with autism (1 from the low-risk sibling group, and 2 from the high-risk sibling group). All these 3 infants showed a high proportion of fixation to the eye region and did not exhibit any abnormal face scanning patterns at 6 months. Summarizing, the differences in fixation behavior at 6 months did not predict the development of ASD.

van der Geest et al. (2002) used an eye tracker (Iview Remote / SMI, 50 Hz, nine-point calibration) in order to investigate on fixation (latency, number and time) and scan path length behavior of high-functioning ASD children, in an older age group than Young et al. (2009) (mean age 10.6 years, SD 2.1 years). The stimuli were cartoon-like scenes that included neutral objects and a human figure. Their results indicate that fixations on human figure of ASDg was comparable to age- and IQ-matched TDg, suggesting that ASDg does not process socially loaded visual stimuli in a different way, even when they grow up. All the children looked longer and more often to the human figure than to the neutral objects, took the same time to first fixate the human figure and put the same effort in inspecting the pictures. Even though the experimental setting lacked ecological validity (it was not a real time interaction between humans in the environment) and the stimuli (full-color cartoon-like images) probably lacked social validity, still all the children looked more at the human figure than other parts of the scene, attributing them some special or social meaning. The authors suggest that abnormal gaze patterns in ASDg everyday life is not related to the nature of the visual stimuli but that other factors, like social interaction, may play a decisive role.

From these studies, it is evident that eye tracking studies on fixations on social vs. non-social stimuli can yield very different results. Moreover, a series of practical reasons would make the eye tracking measurements on fixations impractical.

Clinicians already assess the “social gaze” in their behavioral tests, in a rather complex situation like the shared play between the child and the evaluator (Minichiello S., personal communication). Possibly, the measurements on the gaze behavior with an eye tracker should be done in such kind of rich and playful environment in order to simulate an accurate gaze behavior in the children. However, this kind of experiment would imply to use mobile wear-on eye trackers on the children, since their head movements need to be not constrained and they need to be free to look ad interact at 360 deg in the environment. This kind of equipment might not be suitable to be used on very small children, or toddlers. Putting a device on the face or on the head of the child implies biasing their behavior to some extent, especially if they never worn a pair of glasses before.

Moreover, the video footage and the eye tracking data need to be checked manually by the evaluators or by using a rather complex video analysis software, in order to code the AOIs in such a dynamic environment. This kind of heavy posttest analysis might not suit the purpose of aiding the diagnosis process, letting it become even more bulky and expensive and causing attrition towards the technology itself.

An experimental setting in which the child is required to watch to a screen is less ecologically valid than presenting the child some stimuli in a playful environment. However, it could allow to perform quicker data analysis, since the stimuli are presented in a controlled environment and the software can compute AOIs or eye parameters in the same way for each testing.

Due to all these reasons, fixations will be not investigated further by the eye tracking framework developed for this study. The focus will be more on saccades and smooth pursuit parameters, which can be measured in detail in an experiment with controlled setting, in which ecological validity should not impact significantly on the measurement of these basic oculomotor functions.

The choice of not investigating further on fixations is explained even further in Section 3.7.2.

### 2.2.4 Eye-related events

Section 2.2.4 highlights

- Pupillary responses and eye blinks are interesting parameters, but for now they are not included in the framework due to methodological and ecological validity issues.
- ASDg seem to show smaller pupil size while attending face stimuli, while TDg show dilation, and overall ASDg show lower mean pupil size.
- Pupillary response is influenced by the amount of light in the environment and by a series of setting-related issues.
- ASDg shows lack of eye blink synchronization with speakers who are acting in video clips.
- Eye blink synchronization is particularly related to the ecological validity of experimental setting and stimuli, and to the ability to process verbal communication and language.

Current eye trackers, as for example the SMI RED250mobile used in this study, have algorithms which can detect pupillary responses and eye blinks along with eye ball movements. These further parameters can provide information about emotional reactivity to stimuli and signs of rapport between conversational partners. ASDg seem to show reduced pupillary responses to non-conscious emotion processing and to visual stimuli (Nuske et al., 2014; Martineau et al., 2011) and difficulties in synchronizing eye blinks with another speaker (Nakano et al., 2011).

However, since there are not many studies investigating these eye related events and that their measurement is impractical to be added in an eye tracking procedure for early ASD detection, these eye parameters are not added in the eye tracking framework.

#### Pupillary responses

As Nuske et al. (2014) describe, pupillary responses seem to be a reliable marker of emotional arousal and they are known to be functionally linked to the amygdala, allowing for comparisons with neuroimaging studies. Martineau et al. (2011) add that pupil size assessment has been used to evaluate neurological functioning, alertness, cognitive functioning and information processing, and it seems to be more reliable and sensitive than other autonomic measurements.

Anderson et al. (2006), investigated visual scanning and pupillary responses to face and non-face stimuli, by using an eye tracker (ASL 504 / Applied Science Laboratories, the authors do not state the sampling frequency, five-point calibration) on 6 ASDg and 9 TDg children (age range 12 to 72 months, mean age 49.6 months). The stimuli consisted of colored photographs of children's faces, animal faces, toys and landscapes, and they computed AOIs (in order to determine time tracked, duration of fixations, and average duration of fixations) and average pupil size for stimulus and interstimulus slides. They observed that ASDg showed significant lower time tracked, total time fixating, and average duration of fixations only for the landscape stimulus, which also contradicts findings in literature of reducing scanning to people's faces (which is considered to be an indicator of social content). ASDg showed pupillary constriction to the overall and internal region of the children's faces stimuli, while TDg showed dilation. ASDg showed similar pupillary responses to non-face stimuli (landscapes and toys). Therefore in their study, scanning measures to the landscape stimulus and pupil dilation on children's faces stimulus significantly differentiated the ASDg from TDg. Due to the inconsistent results with literature for the visual scanning (as also already discussed in Section 2.2.3), the authors argue that pupillary responses might be a more sensitive indicator of ASD, and which is worth investigating further this parameter on infants with familial risk for ASD.

Martineau et al. (2011) conducted a study which seems to confirm the hypothesis that pupil measurements can provide useful information for discerning ASDg to TDg even in children belonging to an older age group than Anderson et al. (2006). They recorded with an eye tracker (FaceLAB, 58.82 Hz) the mean pupil size and pupil waveform (average pupil size computed every 250 ms and then plotted over time) during a visual scanning task of still color photographs showing neutral faces, virtual faces (avatars) and objects, and the black slides separating the photographs (in order to test differences between dark and light conditions). The subjects were 19 children with ASD (mean age 118 months, ranging between 41 and 181 months), 19 mental age-matched TDg (mean age 87 months; range 44-178 months) and 19 chronological age-matched TDg (mean age 118 months, range 41-136 months). The mean pupil size was significantly smaller in ASDg than in both TDg, both during the presentation of black and all the different stimuli slides with pictures. Pupil size correctly classified in 89% of the participants in the ASD group, in 63% in the mental age-matched TDg in 63% in the chronological age-matched TDg. The mean pupil size in ASDg was significantly higher when seeing the picture stimuli compared to when they were seeing the black slides, while TDg showed opposite behavior. Saccade waveforms were significantly different between ASDg and TDg when analyzing individually group, stimulus type and time, but not when analyzing together group - time - stimulus, meaning that overall the saccade waveform does not differ totally in the two groups. ASDg mean pupil size was significantly higher when the stimuli were faces compared to objects, but not to avatars. Changes in pupil waveforms did not vary according to the stimulus used. Both TDg showed significantly higher mean pupil size when when the stimuli were faces than when they were objects, but not when they were avatars for mental age-matched TDg. While analyzing the changes in pupil size as a function of time, no significant difference emerged between groups, indicating that the modulation of pupil changes does not differ between ASDg and TDg. The pupil waveform varied according to time, highlighting three phases of pupil response: a first rapid dilation (< 1 s, indicating a change of perception), a second rapid constriction (< 1 s, a photo-motor reflex) and a third slow increase in pupil size (starting from  1.25 s, the analysis of the stimuli) to eventually reaching the baseline. The authors argue that pupil dilation shows to be a potential biomarkers of ASD, if tested further on smaller children.

However, even if pupillary responses seems to provide useful results in discerning ASDg from TDg, this parameter relies on a couple of conditions which are not ideal for being used in an early ASD assessment setting. Even though pupil movements are used for investigating clinical aspects of subjects, the basic function of pupil constriction and dilation is to respond to the change of intensity of the ambient lightning, in order to optimize retinal illumination and maximize visual perception (Adler, 2011, p. 502). Therefore, in order to collect reliable and comparable measurements of pupil movements there is a need to have consistent ambient lightning in all the experiments. Considering the fact that ideally the portable eye tracking system for early ASD detection should be used ideally in a variety of clinical environments or even at the home of the children, such a strict control over the ambient illumination is difficult to achieve. Moreover, accommodation, convergence and pupillary constriction are controlled, synchronized and associated eye movements, even if they are not caused by each other (Adler, 2011, p. 508). Therefore, it would be necessary to control over the setting and the children's movements in a way that would prevent pupillary constriction and dilation to be influenced by other eye movements, thus isolating it and measuring it thoroughly.

In addition, the same issues concerning how to define what is an ecologically valid social content (explained in Section 2.2.3 and Section 3.7.2) apply to the definition of what can be an emotionally significative stimuli which could elicit trustworthy emotional responses in the subjects. Pictures and videos shown on a display monitor, which could allow a sufficiently controlled environment for accurate eye parameter measurements of pupil diameter, do not involve interaction or emotional sharing between two conversational partners. This would question the content and the construct validity of such measurements.

For these reasons, even though pupil diameter seems to be an interesting parameter to assess in small children, it is not included in the eye tracking framework.

**Eye blinks**

As Nakano et al. (2011) explain, measurements on eye blinks can provide insights on interactional behavioral synchrony between conversation partners, for example. It seems that listeners tend to synchronize their respiration, posture and eye blinks (especially at breakpoints of speech) with their conversation partners, as possible signs of rapport and connectedness, leading to effective social communication.

Nakano et al. (2011) investigated on the ability of ASDg to synchronize eye blinks to the speaker's ones in different video clips. Hypothetically, this ability should be impaired due to deficits in social interaction and communication. They used EOG to detect eye blinks and a remote eye tracker (Tobii x50 / Tobii Technology, 50Hz) to detect gaze position in 18 ASDg adults (mean age 29 years old, SD 7.1) and 18 TDg (mean age 23 years old, SD 2.1). TDg showed significant increase of eye blinks after the speaker's eye blinks, while ASDg did not, under any condition. The two groups did not differ significantly in terms of viewing time on the speaker's eyes and mouth, therefore the lack of synchronization showed by ASDg should not be accounted to abnormal gaze behavior.
However, it is difficult to determine if the kind of laboratory setting used in the study really accounts for ecological validity. Indeed, the authors affirm that the results contradict the general finding that adults with ASD spend less time viewing other people's eyes, and that the stimuli consisted in a video in which a single speaker talked with no mutual interaction between the listener and the speaker, while being in an environment with few distractor objects. Therefore, it is not possible to affirm that the contents of the stimuli represented a situation which is similar enough to everyday social communication. Anyway, given the results of similar gaze patterns but differences in blink synchronization, the authors speculate that ASDg does not seem to show imitation of the conversation partner but rather deficits in temporal coordination of blinks, which may impair effective social communication with others.

As also discussed in Section 3.7.2, if the kind of construct which can be measured with eye blinks is related to the social content of the stimuli, the controlled laboratory experimental setting needed for the precise measurement of eye movement can be too artificial to elicit trustworthy responses. Moreover, between 12 and 24 months of age the children might not have the good command of the language needed for performing verbal communication and language processing tasks (e.g. turn-taking, synchronization with another speaker, etc). Nakano et al. (2011) indeed collected eye blink data on ASDg adults.

Therefore, at the moment these conditions seems to not make eye blinks a reliable parameter to discern ASDg from TDg, and it is not included in the eye tracking framework.

# 3 Framework

In this section, the information from the previously discussed literature is compiled into a tentative framework for early ASD detection. The framework consist of a set of eye parameters measurements and test procedures, which eventually yield specific objectively measured outcome variables, which are needed in order to assess the reliability and the validity of oculomotor function measurements (Tab. 1). The review article from Smyrnis (2008) strives to provide guidelines for the standardization of oculomotor function tests in psychiatric research, and it is used as a canvas upon which the framework is built on.

Literature describes several established methods for eliciting eye movement responses in ASDg (reported for example by Johnson et al., 2016; Brenner et al., 2007; Zalla et al., 2016; Falck-Ytter et al., 2013; Papagiannopoulou et al., 2014, etc), like visual search tasks, embedded figures test, visually-guided saccade tasks and step-gap-overlap paradigms, paired visual preference paradigm, semi-naturalistic and naturalistic settings, etc, and each method demands specific types of stimuli materials. The following framework keeps into account only the methods which specifically elicit the eye parameters selected in Section 2.2 as most probable indicators for early ASD detection, and which can be applied to the target age group 12-24 month.

The experimental setting and procedure protocols are just drafted in the framework. This is due to the fact that the present study serves more as pilot test which is not meant to provide standardized and replicable guidelines at the current stage. As explained in Section 5. Results and Section 6. Discussion, the framework seems to be applicable to the target children, but there is still a noticeable amount or research to do before providing standardized procedure for ASD diagnostics with eye trackers, including experiment setup, stimuli, measurement calculations and outputs. It is worth remembering that at this stage the framework is based completely on findings in literature, therefore it can show only theoretical, face, content and construct validity, as explained in Section 3.7.

## 3.1 Subjects

Given that the period in which clinicians can formulate an ASD diagnosis by using behavioral assessment is when the children are around 24 and 32 months old (Minchiello, personal communication), providing information which could lead to an earlier detection of ASD in an earlier stage than the usual one is a key point

**Framework executive summary**

1. Subjects: Children between 12-24 months of age
2. Apparatus: Eye tracker, infrared pupil detection, sampling frequency $\geq$ 250 Hz
3. Eye tracking parameters
   - 3.a. Standard deviation of saccade gain
   - 3.b. Open-loop smooth pursuit gain
   - 3.c. Closed-loop smooth pursuit gain
4. Methods
   - 4.a. Smooth pursuit assessment: Step ramp task, sinusoidal and triangular motion tracking
   - 4.b. Saccades: Visually guided saccades task, step paradigm
5. Data analysis
   - 5.a. Keep measurements records with less than 50% proportion of missing data
   - 5.b. Smooth pursuit: Compute pursuit velocity gain as primary parameter. Report target speed, amplitude, frequency, cycles
   - 5.c. Saccades: Compute standard deviation of saccade gain as primary parameter. analyze the different types of saccades separately. Report central fixation duration, peripheral target duration, amplitudes, number of trials

   Experiment setting and testing procedure
   - 5.a. Sober furnishing, dim lightning but not darkened room, no loud sounds, experimenters positioned out of the participant's view, children may sit on the lap of the accompanying caregivers.Stimuli should be concise and compelling, interstimulus materials should be entertaining, administer calibration between tasks
6. Reliability and validity
   - 6.a. Reliability: Implement multiple automatic calibration routines. Report data related to the eye tracking measurements, and information collected through clinical anamnesis.
   - 6.b. Validity
     - 6.b.i. Eye tracking are unobtrusive and provide insights on cognitive processing and development. Face and content validity
     - 6.b.ii. Cross-reporting between qualitative assessments and quantitative eye tracking measurements will provide criterion validity
     - 6.b.iii. Construct validity of the assessment of oculomotor functions for the detection of early ASD has still to be fully proven and shared within the clinical community
     - 6.b.iv. Ecological validity is not achievable in laboratory experiments, but it should not impact on the participants' oculomotor responses. However, it does not allow to assess directly constructs like social attention
     - 6.b.v. The analysis of eye parameters shows construct and content validity for determining whether some neural circuits are selectively affected by ASD

Table 1: Framework executive summary

of an eye tracking framework. Children in the age group of 12-24 months seem suitable candidates for the framework.

Indeed, as Towle and Patrick (2016) explain, different timing patterns of symptom emergence among ASDg make the ages before 12 months to 18 months particularly ambiguous. Phenotypic variability (quantity and quality of visible symptoms) and the variable degree of overall severity are a known feature of ASD, and young children with milder symptoms are more difficult to diagnose under 24 months of age. Moreover, the observable behavioral ASD markers become more evident from about 12 months on, and they can be interpreted either as the result of earlier divergent neurocognitive processes and also a divergent foundation that may produce further ASD symptoms. As explained in Section 2.1.3, the eye tracking framework is meant to be used together with the already validated behavioral diagnostic praxis. Therefore some divergent behavioral patterns in children should be noticeable by the clinicians in order to collect qualitative information along with the quantitative eye tracking measurements.

Therefore there is a need for more precise early detection instruments for ASD particularly below the 24 months of age threshold, which is the period of life of the children in which it is more difficult to spot subtle signs and symptoms, and above 12 months of age, moment from which some symptoms are visible and that can raise suspect of ASD insurgency and provide qualitative assessments.

## 3.2 Apparatus

Summarizing from Smyrnis (2008), the apparatus for measuring eye movements available to the researchers nowadays are electrooculography (EOG), infrared limbus or pupil detection, video camera capture with pattern recognition algorithms, and contact lenses with search coil. Between all the apparatus, the one which seems the most viable for testing with small children is the infrared pupil reflection one, in which the infrared light emitted by the device illuminates the eyes and the reflection from within the pupil is detected by photodetectors. A video camera capture of eye movements with pattern recognition algorithms of the pupil is also a good option, even if low sampling frequency can be an issue. Using eye tracking systems with sampling frequencies below 100 Hz is detrimental to the quality of results. EOG needs skin electrodes placed around the eye and it is prone to artifacts from the movements of the muscles in the face area (which the infrared apparatus do not show). The contact lenses with search coil are too invasive and can cause distress.

Sasson and Elison (2012) provide recommendations on the usage of eye trackers on small children with autism. They advice to avoid head stabilization (e.g. chin-rest or head mounted systems), preventing the children to oppose resistance. Remote eye trackers are preferable, since they also allow for minor head movements. Eye trackers integrated within the display monitor or table-top are preferable, since relatively unobtrusive. Sampling rates of 50 Hz are useful only in visual scanning tasks, while sampling rates of $\geq$250 Hz are necessary for investigating more subtle oculomotor behaviors like smooth pursuit and saccades.

## 3.3 Eye tracking parameters

Summarizing from the results and the reflections from the literature included in Section 2.2 it seems that so far the most reliable parameters which could discern ASDg from TDg, and which could potentially be helpful in supporting the early diagnosis of ASD in small children are:

1. Open-loop smooth pursuit gain;
2. Closed-loop smooth pursuit gain;
3. Standard deviation of saccade gain.

## 3.4 Methods for eliciting the selected eye tracking parameters

As described preliminarily during the literature review of the single eye parameter, each eye parameter of interest can be measured by a series of methods (Tab. 2), which are here summarized together with guidelines for setting up the experiment stimuli and procedure.

### 3.4.1 Smooth pursuit assessment

Here it follows a summary of the recommendations (and the rationale behind them) provided by Smyrnis (2008) in function of what emerged from literature about the use of smooth pursuit tasks for testing oculomotor functions for early ASD detection on the target children. The sampling frequency of the eye tracking apparatus should be at least 200 Hz.

The open-loop condition can be assessed by using a step ramp task, in which the stimulus makes a sudden movement (the “step”) to a peripheral location of the visual field, then moves with constant speed in the opposite direction (the “ramp”) and finally stops (Fig. 3). This task is useful for measuring the initial acceleration of the eye, which is aimed to catch up with the stimulus after the step when the ramp begins. The study from Takarae et al. (2004) used this method, along with pure ramp and oscillating target tasks. However, they observed ASDg showing lower open-loop pursuit gain in the initial catch-up saccades only during the step-ramp task, while in the other tasks only the closed-loop gain was reduced. Therefore only the step ramp task is taken into consideration for this framework.

The preferable closed-loop condition use triangular motion, ranging in speed from $\leq$10 deg/s and the high end of 20–30 deg/s. However, the relevant studies reviewed by Johnson et al. (2016) use sinusoidal motion stimuli, and the study

| Article / eye parameters | Methods | ASD prediction |
|---|---|---|
| **Smooth pursuit** | | |
| Johnson et al., 2016 | Step ramp<br>Pure ramp<br>Sinusoidal pursuit | Yes |
| von Hofsten & Rosander, 1997 | Sinusoidal and triangular motion on TDg | No |
| Takarae et al., 2004 | Step ramp<br>Pure ramp<br>Oscillating target tasks | Yes |
| Wilkes et al., 2015 | Horizontal and vertical axes pursuit | No |
| von Hofsten et al., 2008 | Sinusoidal motion stimuli | No |
| Kemner et al,. 2004 | Triangular motion | No |
| **Saccades** | | |
| Johnson et al., 2016 | Visually guided saccades tasks | Yes |
| Pensiero et al., 2009 | Led blinking on horizontal axis | No |
| Kemner et al., 2004 | Horizontal and vertical saccade tasks | No |

Table 2: Summary of the methods reported in literature for the eye parameters of interest.

from von Hofsten and Rosander (1997) uses both sinusoidal and triangular motion stimuli. This latter study provides measurements done on TDg infants, which can be useful to compare with ASDg development patterns. Therefore, also a closed loop condition using sinusoidal motion should be tested, at the same conditions of the triangular motion one. As Smyrnis (2008) explains, different stimulus profiles lead to different interpretations of the results:

- In the sinusoidal velocity profile the target speed varies continuously in a sinusoid fashion determined by a single frequency, and this stimulus is useful to determine the acceleration saturation of smooth pursuit to predictable target motion and is also for measuring overall pursuit performance. Since the target speed varies continuously (ranging from 0 deg/s to $n$ deg/s), it is not directly comparable to the speed for triangular or trapezoidal target motion.

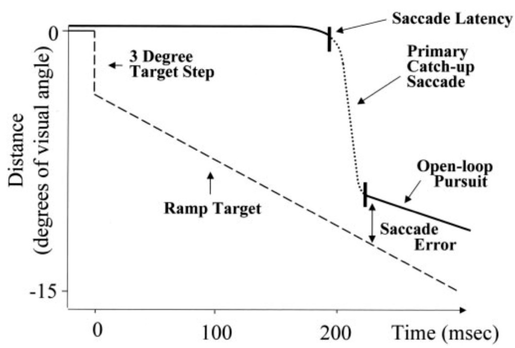


Figure 3: Schematic representation of step ramp task. The solid line represents a typical eye movement response, while the dashed line represents target movement. Image retrieved from Takarae et al. (2004)

- In the triangular velocity profile the target moves with constant speed and changes direction abruptly at the end of each run, and it is useful for for determining the steady state pursuit velocity and velocity saturation. This profile is not useful for determining global pursuit performance, since the strategy through which the subjects recover the pursuit after the abrupt change of target direction can vary considerably.
- Trapezoidal velocity profiles have not been found in the background literature, so they are not considered in this framework.

Given the young age of the target subjects for the framework, keeping their attention focused on the moving target during smooth pursuit tasks can be a challenge. As Smyrnis (2008) highlights, manipulating the shape of the target in order to facilitate performance of the task by driving the individual's attention to the stimulus, however it makes difficult to evaluate the impact of the target transformation and compare the results across studies, making even harder to identify possible parameters as endophenotypes. Therefore, the shape of the target needs to be interesting enough to the infant without changing/transforming during the smooth pursuit task, in order to keep the stimuli stable and at the same time encourage the subjects to keep following the target without further prompting.

The task duration for sinusoidal and triangular motion stimuli is determined by the number of cycles. A cycle is completed when the target moves towards one direction and then goes back to reach the starting point. The more cycles are performed by the subject, the more measurements of pursuit performance are available, resulting in a more reliable measurement. However, it is not clear from literature what is the minimum number of cycles for each stimulus speed. There might be an unknown balance between having a reliable measurement and adding practice effects, due to the subjects' habituation to the task. Smyrnis (2008) advices at least five, which is similar to what von Hofsten and Rosander (1997) did in their experiments.

### 3.4.2 Saccades assessment

Johnson et al. (2016) explain the need to distinguish between visually-guided saccades from volitional saccades, due to the involvement of different cortical, subcortical and cerebellar networks when performing each class of eye movement. In visually-guided saccade tasks, participants are presented with a central fixation target and then a peripheral target appears concomitantly to the central fixation target disappearing.

Brenner et al. (2007) describe visually-guided saccades also as reflexive, non-predictive. Visually-guided saccades tasks are therefore designed to assess target-elicited saccades, which are driven by exogenous stimuli. These tasks are used in opposition to intentional-saccade tasks (e.g. memory-guided, predictive, anti-saccade tasks). Johnson et al. (2016) add that anti-saccade task is frequently used to examine top-down control of saccades, since they ask the participant to suppress a reflexive saccade to a visual target and to make a volitional saccade in the equal opposite position.

Due to their nature, antisaccade tasks (but also the other kinds of volitional saccades) are impractical to do with small children, since the researcher would need to instruct the child to purposely not look at the target and to look at the opposite direction. Young children may be unable or unwilling to follow verbal instructions to look to specific locations on the screen (Sasson and Elison, 2012). Therefore, antisaccade tasks are not considered in this framework.

Summarizing from Zalla et al. (2016), the Step, Gap and Overlap paradigms are well-validated visually guided saccade tasks:

- Step paradigm: the subject fixates a central fixation target and as soon as it disappears a lateral target appears, requiring the subject to make a lateral saccade. When the lateral target disappears a new central fixation target is presented, starting a new trial.
- Gap paradigm: follows the same routine of the Step paradigm, but the central fixation target disappears before the onset of the peripheral stimulus.
- Overlap paradigm: follows the same routine of the Step paradigm, but the central fixation target remains on display when the peripheral stimulus is shown.

Gap/Overlap paradigms are useful to assess attention shift and disengagement between the central and the peripheral targets, by analyzing saccade latency (basically the response time).

Here it follows the discussion around the recommendations for assessing saccades from Smyrnis (2008) in function of early ASD detection on the target children. The sampling frequency of the eye tracking apparatus should be at least 200 Hz.

It is better to avoid complex stimuli and gap or precues between stimuli which change the performance. Therefore, the peripheral target onset needs to occur synchronously with the central fixation offset (step paradigm), not before (introducing overlap) or after (introducing gap).

Stimulus should appear both at right and left directions and at multiple amplitudes within the range of 10 deg, avoiding targets appearing too close to the central fixation target ($\leq$ 2 deg) or too far ($>$15 deg). Johnson et al. (2016) report that the standard deviation of saccade gain is expected to be significantly different in ASDg at target amplitudes ranging from 5 to 30 deg, therefore a compromise is to show targets between 5 to 15 deg of distance from the central target.

A sufficient number of trials can be within 30 and 100, but not greater in order to avoid practice and fatigue effects.

## 3.5 Data analysis

In this section, tentative procedures are outlined in order to compute and assess the eye parameters measured with the tasks described in the previous paragraph. However, due to the fact that complex algorithms and softwares need to be developed for discerning, isolating and computing specific eye parameters–as shown for example by Giordano et al. (2017); Jansson and Medvedev (2013); Larsson et al. (2015)–engineering level software programming and mathematics are required. For example, the signal characteristics of fixations and smooth pursuit movements overlap to some extent, therefore the classification of fixations in the presence of smooth pursuit movements is complex (Larsson et al., 2015). Giordano et al. (2017) already implemented basic data analysis algorithms for smooth pursuit (Fourier transform of the Euclidean distance between eye gaze position and target position, i.e. positional gain) and for visually guided saccades (percentage of fixation points matching the target position), however they might not be sophisticated enough. Moreover, as Smyrnis (2008) discusses, there is still considerable variation of task procedures and outcome measurements in literature, which does not ease the process of finding few well-defined parameters that can be repeatedly used in genetic and clinical studies, and that there is need of standardization.

For these reasons, a further collaboration with experts in these fields is required in order to complete the framework. The results of the measurements done in the current study will stay in a raw format, waiting for further developments of the framework in the future. The diagrams automatically generated by the eye tracking software are be inspected visually and commented in Chapter 5.

As a general consideration about data analysis, Sasson and Elison (2012) explain how children with ASD, and in particular the ones with impairments in sustaining attention, often exhibit more missing gaze data than controls, due to less focus on the stimuli or excessive blinking. It is useful then to compute results as a proportion of gaze time on screen instead of in absolute values, and control for participants who have exceeded a certain amount of missing data (a 50% proportion of missing data should already be considered suspect), as a signal of lack of overall attention to the stimuli and to the experiment in general.

### 3.5.1 Smooth pursuit data analysis

Here it follows the discussion around the recommendations from Smyrnis (2008) for analyzing smooth pursuit data, in function of the framework for early ASD detection.

All pursuit performance parameters are affected by target speed. The average target speed is calculated basing on the frequency and the amplitude of target motion, therefore the amplitude of target motion needs to be reported, as well as the amplitude covered by the moving target to the right and left of the central fixation point. Pursuit performance seems to deteriorate with increasing speed.

Pursuit gain should be used as the primary outcome parameter (as also the studies reviewed in Section 2.2.1 do) and other parameters such as frequency of catch up saccades, anticipatory saccades and square wave jerks can be used as secondary outcome. Gain needs to be defined as the ratio of eye velocity to target velocity (i.e. if pursuit performance is perfect this value should be equal to 1), and it should be preferably time weighted. The mean or the median value of pursuit gain for each target speed needs to be reported.

In a sinusoid stimulus the target velocity changes constantly, so for each segment the target velocity needs to be computed, while in triangular and trapezoidal patterns eye velocity (distance traveled divided by time) is computed for each "saccade free" segment and then divided by the constant target velocity. In order to time weight the pursuit gain, gain values at each segment are multiplied by the corresponding time and then summed. The sum of the products is then divided by the total time duration of these segments.

Since eye pursuit involves the integrated function of both the pursuit and the saccadic system, it is necessary to distinguish between smooth pursuit movements and saccades in the pursuit task records. Lower quality of pursuit could be due to two qualitatively different effects: the inability to follow the target with the same gain or the inability to suppress the saccadic system function during pursuit, resulting in intrusive saccades during pursuit.

In order to discern the records of smooth pursuit movements and saccades, it is better to use combined criteria for describing the saccades parameter thresholds (e.g. amplitude, velocity and acceleration). Once saccades onset and duration are detected they can be separated from pursuit records. Simpler criteria are not enough detailed for having a clear separation.

Smyrnis (2008) strongly emphasizes that there is therefore a need for the definition of the saccade movements involved in smooth pursuit (Fig. 4) and their operationalization in precise (and possibly standard) metrics:

- Catch up saccades: small amplitude eye movements in the direction of target motion that bring the eye close to the target when pursuit gain is low. They serve a different purpose than intrusive saccades.
- Anticipatory saccades: eye movements that are in the direction of motion, take the eyes ahead of target, have amplitudes of 5 deg or more and are followed by a time interval during which the eyes virtually remain stationary.
- Backup saccades: eye movements performed after an anticipatory saccade, in the opposite direction, in order to bring the eyes back to the target with a saccade.
- Square wave jerks: pairs of small saccades 0.5–3 deg in amplitude separated by a 200–400 ms interval. Differences in definitions are found in literature about if these movements should be of opposite direction, and if they interrupt, precede or follow smooth pursuit.

Due to the different nature of these movements, computing the frequency all saccadic eye movements during pursuit as indicator of pursuit integrity means grouping together qualitatively different parameters, rendering the saccade frequency parameter not really useful.

Differences in literature about quantitative and qualitative parameter definitions of saccadic movements in smooth pursuit highlight the need for standardization, in order to analyze and compare systematically the results of eye parameter measurements. However, this issues goes beyond the scope of this study, and it is the next step for further development of the framework and the next objective to reach in order to strengthen the reliability and the validity of all the eye tracking methodology.

Discarding the pursuit data close to the direction shift points (Fig. 5) allows to analyze eye movements only on a central window around the primary eye position (e.g. upward-left/right, downward-left/right), avoiding to take into account the different strategy effects in the points of a direction shift. Close to these points the pursuit of the target becomes more erratic and intrusion saccades are more

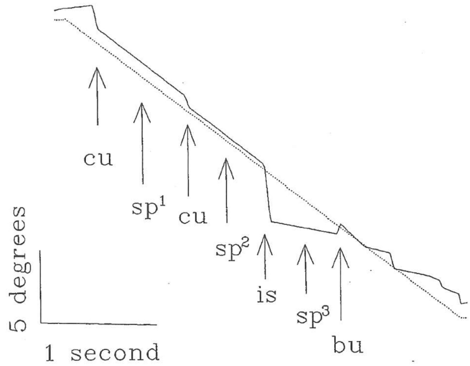


Figure 4: Visual example of different types of eye movements (cu = catchup saccades, sp = smooth pursuit, is = intrusive saccades, bu = backup saccades) happening during a smooth pursuit task of a trapezoidal moving stimuli. Image retrieved from Ross et al. (1993).

frequent.

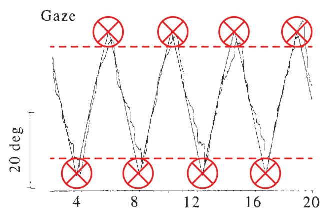


Figure 5: visual example of removal of the data close to direction shift points. Original picture from von Hofsten and Rosander (1997)

In addition to discerning smooth pursuit eye movements and saccades, artifacts (such as blinks) in the pursuit record needs to be removed (Fig. 6). Literature does not report a preferential way to discard artifacts, but it can be done by visual inspection or by using a pattern recognition program (using visual inspection to validate the program decisions). Probably the latter option is the more suitable for this framework, but it implies advanced computation beyond the scope of this study.

As Takarae et al. (2004) illustrate, in order to measure the performance in the open-loop phase of pursuit gain with a step ramp task, it is necessary to compute gain of the first catch-up saccade (defined as the ratio of eye movement amplitude to target distance) and pursuit gain during the first 100 ms after the initial saccade (defined as ratio of the average velocity of pursuit eye movement to target velocity).

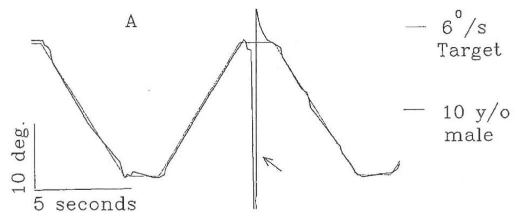


Figure 6: Example of blink artifact in smooth eye pursuit on trapezoidal motion stimuli. Image retrieved from Ross et al. (1993)

For smooth pursuit tasks it is valuable to report stimulus speed (deg/s), amplitude and number of cycles.

### 3.5.2 Saccades data analysis

Johnson et al. (2016) report that the only parameter expected to differ between ASDg and TDg is the standard deviation of saccade gain. Here it follows the discussion around the recommendations from Smyrnis (2008) for analyzing saccades data, in function of the framework for early ASD detection.

Similarly to what stated in Section 3.5.1, combined criteria (e.g. amplitude, velocity and acceleration) needs to be used to define and describe with sufficient detail the saccades, and therefore to detect their onset and duration in the record. This level of detail allows to exclude from analysis (or analyze separately) predictive saccades (latency $\leq$ 80 ms) and very slow onset saccades (latency >500 or 600 ms). Rejection of artifacts can be done by visual inspection or if using a pattern recognition program (with the clinicians' supervision).

Once the refinement process is done on the saccades records, saccade parameters prove to be easier to compute from the raw data than the smooth pursuit ones. Pensiero et al. (2009) show two diagrams (Fig. 7) which visualize examples of good and poor tracking during saccade tasks.

Since no other saccade parameter seems to help in differentiating ASDg to TDg, only the saccade gain (defined as the mean or preferably the median ratio of saccade amplitude to target amplitude) should be used as primary performance outcomes in the saccade task. With the gain mean and the number of sampled saccade records it is possible to compute the standard deviation of the gain, as index of saccade dysmetria Johnson et al. (2016).

It is valuable to report central fixation duration (ms), peripheral target duration (ms), amplitudes of the locations for the peripheral target presentation (in degrees) and the number of trials.

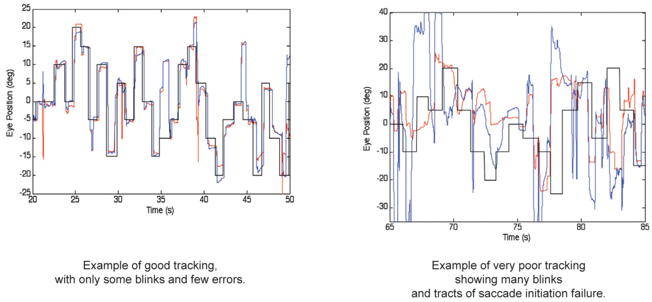


Figure 7: Examples of good and poor tracking from Pensiero et al. (2009). In the graphs are plotted the stimulus position (black), right-eye position (red) and left-eye position (blue).

## 3.6 Experiment setting and testing procedure

Sasson and Elison (2012) provide practical guidelines for setting up the experimental environment and the testing procedure for eye tracking studies involving young children with autism, which are also suitable for small children who has not been diagnosed yet. The guidelines are summarized as follows.

1. Sober furnishing and dim lightning help to keep the children's attention on the screen. It is better to avoid to test in a completely darkened room or using loud sounds to avoid to make the children uncomfortable. The experimenters should position themselves out of the participant's view or put a partition between themselves and the eye-tracking station, while still keeping a view on the participant.
2. Children should be accompanied by a caregiver throughout the testing session and the researchers should wait for the child to be acquainted and comfortable with the research environment. Having children's videos or cartoons playing on the display monitor can help with this task, and also it gives the opportunity to position the equipment at the right distance from the child and proceed with the calibration.
3. Especially when the children are very small (and they require body support) they can sit on the caregiver's lap, ensuring that only the children's eyes are captured by the eye tracker.
4. Calibration should use animated stimuli accompanied by sound, which should be more effective in capturing the children's attention. A 5-point sequence should be brief enough to retain the child's attention while also providing an accurate calibration.
5. The visual stimuli and the task should be concise and compelling enough to maximize the children's attention, requiring minimal effort (e.g. passive

viewing tasks). Adding inter-stimulus animated materials can help to recover the children's interest and keep them entertained. Re-calibration should be administered between tasks, checking and correcting possible calibration drift (3 degrees of visual angle)

These guidelines are easier to follow in a controlled laboratory, however it is not impossible to meet these requirements also in a home environment, which can be suitable for making the child and the caregiver feel more at ease during the whole procedure and therefore providing more chances to collect more complete measurements. Remote eye trackers, especially if mounted on a laptop computer acting as a portable measuring station, can be quite resilient to environment changes and subject positioning if the ambient lightning is suitable.

## 3.7 Reliability and validity

Using eye tracking technologies in the context of clinical evaluation of the neuropsychiatric condition of small children poses not only methodological problems, but also specific reliability and validity issues. Reliability issues involve calibration loss and the need of thorough reporting of quantitative and qualitative data about the children and their eye movements. Validity discussions are due to the choice of not assessing directly constructs like social attention (a key factor of ASD impairments) in an ecologically valid setting, but oculomotor functions in a controlled experimental setting.

The various types of reliability and validity are defined and described by Leedy and Ormrod (2012, pp. 89-92) and Smyrnis (2008).

### 3.7.1 Reliability

As Giordano et al. (2017) summarize, eye-tracking has been applied successfully to evaluate ocular movements, especially in children/infants for whom it is usually difficult (or even impossible) to sustain attention during the medical examinations. This is possible also because current eye tracking technologies are capable to compensate effectively head movements without losing track of the eyes, providing the flexibility needed to make precise measurements without constraining the children and the setting, both in terms of procedures and equipment.

However, calibration failures have been reported in literature as a potential data loss pitfall (Birmingham et al., 2017), even though more dated or invasive eye trackers (e.g. eye tracking goggles) are more prone to this issue. Nevertheless, losing calibration during the procedure means jeopardizing both test–retest reliability and internal consistency of the data, ultimately rendering impossible to compare data within and between tests and studies. This specific issue can be particularly relevant in the context of clinical evaluation of small children. The eye tracking tests conducted by following the outlined framework are meant to be as quick as possible, due to the children's attention span and interest, but they impose the evaluators to be flexible and prepared to take breaks and to provide the children with entertainment between the measurement trials. Therefore, after the first eye tracker calibration, it is predictable that the children would not stay still and sit in the same position throughout all the experiment, which is a potential threat to the precision of the calibration. Multiple automatic re-calibration routines in between tests and interstimulus materials are recommended (Sasson and Elison, 2012).

In literature, the lack of systematic reporting about important parameters, like ASD symptoms severity (Chita-Tegmark, 2016) or the kind of training under which the participants have been exposed in their life prior to the experiments (Boraston and Blakemore, 2007) prevent data comparison between different studies. Therefore, in the future application of eye tracking technologies for clinical practice, not only the data related to the eye tracking measurements and analysis need to be thoroughly reported (e.g. visual angle, AOIs, size, how missing data were handled across study groups, points of calibration, number of stimuli presented, type of control comparison; Frazier et al., 2017), but also the information collected through anamnesis and the behavioral screening and diagnostic tests, if available.

### 3.7.2 Validity

Some considerations about the validity of the eye tracking framework are directly related to reliability issues, while others are related to the choice of constructs to assess and their inherent validity. Overall, given that the current study is still in an initial phase and that the eye tracking technologies are not used in clinical diagnostic settings yet, this research can show in most part theoretical validity, since the proposals done are based on literature and not on a pool of empirically collected data.

As discussed in Section 1.1, it is a fairly shared opinion in the HCI literature that eye tracking (especially infrared/corneal reflection types) is a relatively unobtrusive technique, which is ideal to be used on small children and which can provide insights on the different cognitive processing of stimuli and development of ASDg and TDg (Subrahmaniam, 2013; Giordano et al., 2017; Samad et al., 2017; Bölte et al., 2016; Falck-Ytter et al., 2013). Therefore, as a measurement technique, eye tracking shows face and content validity.

The thoroughness of the reporting of both the eye tracking and the behavioral assessments (as discussed in Section 3.7.1) allows for the comparison and the integration between the two types of evaluations, making possible to assess if the eye tracking framework is yielding reliable results in detecting appropriate ASD related measurements. Not only this cross-reporting would make the whole framework more complete, reliable and replicable, but also and most importantly it will one day allow to compute the sensitivity, specificity and positive predictive value of this instrument (as discussed in Section 2.1.2; Charman and Gotham, 2013), as it is already done for behavioral screening and diagnostic instruments. These parameters will provide scientific evidence for criterion validity (both predictive and concurrent) of the eye tracking method as a supporting diagnostic tool for ASD, and therefore paving the way for the validation of this technology-based assessment on a large scale.

A concern for the validity of the framework is that it focuses more on the assessment of oculomotor functions (smooth pursuit eye movements and saccades) than the assessment of psychological constructs like attention or communication (e.g. joint attention, social interaction, interest in others, atypical eye contact) which are so far considered core symptoms and important indexes of ASD (Magán-Maganto et al., 2017).

The construct validity of the assessment of dwelling times on social vs. non-social AOIs is based on the concept that if a child does not attend to social stimuli, he or she will not be able to develop basic cognitive functions as joint attention and theory of mind (von Hofsten et al., 2009).

Indeed, Minichiello (Minichiello, S., personal communication) stated that it would be interesting for clinicians to have quantitative measurements about the children's eye movements if the data focus on the social and communicative intent of the children's gaze, rather than providing information about oculomotor disturbances, which are present in other neurological pathologies. Therefore, while the construct validity of eye movement measurements around attention or communication (e.g. fixations on social vs non-social AOIs) seem to be more immediate–even if it is not confirmed by literature, as discussed in Section 2.2.3– the construct validity of the assessment of basic oculomotor functions is still probably not shared enough within the clinical community. This is evidently related to the current behavioral assessment methods for ASD diagnosis.

Ecological validity is strongly related with the construct validity issue. Ecological validity can be defined as the extent to which the stimuli and protocol approximate the real-life situation that is under study (Boraston and Blakemore, 2007). Tailoring the experimental setting for eye tracking methodologies means balancing between two extremes: one extreme is to have an ecologically valid setting, where eye trackers can provide few more information on eye parameters than fixations on AOIs, which by definition are arbitrarily described by the researchers as social or non-social. The other extreme is to constrain the setting for assessing more varieties of eye parameters, but making it too artificial to assess complex constructs like attention and social interactions, which need an ecologically valid setting to be investigated in a trustworthy way.

Video clips with multiple subjects interacting with each other and with objects can be considered more ecologically valid than static photographs (Boraston and Blakemore, 2007), but they are all still a simulation of a real-life situation. Defining what is a socially valid content in such kind of controlled and artificial stimuli is debatable. Indeed, as (Bush and Kennedy, 2015, p. 185) state, seeing a face in the absence of any social context may not reflect how one might view that same face in more naturalistic contexts in which they typically are encountered.

Naturalistic settings can probably be considered the most ecologically valid settings suitable for eye tracking (Bush and Kennedy, 2015, p. 185), which poses additional processing demands like the selection of the relevant parts of the scene. As Birmingham et al. (2017) illustrate, naturalistic settings involve an experimenter who sits across from a child, engages the child's attention by making direct eye contact with him or her, and then the experimenter looks to an peripheral object. The measure of interest is typically the percentage of trials (or pass/fail) on which the child successfully orients attention (by looking) in the direction of the experimenter's gaze. However, the high ecological validity of these settings, with their inherent internal variability, implies to give up on precise measurements of oculomotor performance, which require consistent and strict stimuli parameters.

Another perspective is summarized from von Hofsten et al. (2009), in the real world social stimuli are always dynamic and embedded in a flow of events, which require rapid and accurate perception of the partner's action and anticipation of the upcoming events in the flow of social interchange. Humans show innate attentional dispositions (e.g. to track people's faces and to be attracted by features of faces) which allow the infants to focus their attention on the appropriate information and to enjoy interacting with other people, therefore supporting the development of social perception. ASDg show disrupted social functioning, and this can be related to different functioning of the Mirror Neuron System, preventing the children to project other people's actions onto their own action system and therefore anticipating what is going to happen next in a social context. Literature suggests that in ASDg children the cerebellum functions differently from TDg. Cerebellum is believed to play a central role in the construction of predictive models for behavior and the anticipation of the outcome of events, which might render attention shifts slow, imprecise, and unprepared for what is going to happen next.

Johnson et al. (2016) describe that it is possible that that the widely reported anatomical abnormalities and connectivities in ASDg's cerebellum and higher cortical areas (e.g. V5, see for example Takarae et al., 2014) impact on the ability to track and predict target velocity and trajectory and positions and to integrate these signals with other actions, and these impairments are likely to contribute to a range of daily problems often described in ASDg. Smooth pursuit abnormalities could cause functional impairments in ASDg such as altered spatial awareness in environments with moving stimuli (Wilkes et al., 2015).

As von Hofsten et al. (2009) reflect, the social disabilities of children with ASD could be caused by some lower level dysfunctions–cognitive processes like event prediction and/or more basic perceptual process such as motion perception– which ultimately makes social interaction difficult or impossible.

Takarae et al. (2004) explain that sensorimotor systems are well understood both neurophysiologically and anatomically, and sensory inputs and motor responses are more easily quantifiable than most higher cognitive processes. Investigating these systems allows to collect insights into functional connectivity deficits in ASD and for determining whether some neural circuits are selectively affected by the disorder. These deficits can be responsible for impairments in higher order cognitive and adaptive behaviours. In this respect, eye tracking methods show construct and content validity for the investigation of the neural circuitry of sensorimotor systems in ASD, or possibly any neurodevelopmental disorder.

Given these reflections on construct validity in relation to social content, the framework presented in this chapter does not focus on complex constructs related to social attention. On the other hand, other constructs related to oculomotor control are assessed, which are described in literature as a possible manifestation of the different functioning of neural pathways and neurophysiology in people with ASD. Moreover, for the kind of eye parameters of interest–saccades and smooth pursuit eye movements–eye trackers can be the most reliable measurement tool, due to their high sampling frequency and precision. In this way, the eye tracking can perform its diagnosis support function without providing redundant data with the current behavioral measurements.

# 4 Experimental design and procedure

## 4.1 Participants

The total number of participants was three small children, all female, two belonging to the target age range (15 and 24 months of age) and one younger (9 months of age). Their parents did not report any diagnosis of clinical conditions or vision problems related to the children. In addition, the author made a pilot test on himself in order to provide the “ideal” eye tracking record set, which is used a reference for the comparison on the experimental group record sets. The participant profiles is shown in Tab. 3.

| Characteristics | Participants | | | |
|---|---|---|---|---|
| | P1 | P2 | P3 | Pilot |
| Sex | female | female | female | male |
| Age (months) | 15 | 24 | 9 | 25 years old |
| Test | Random_1 | Random_2 | Random_3 | Random_1 |

Table 3: Participants profiles.

The recruitment was done by convenience sampling, with a snowball sampling approach (Baxter et al., 2015, pp. 496, 506), looking for parents within the network of acquaintances of the researchers who might have had children in the target age range. This technique was chosen due the following reasons:

- The necessity of collecting a trustworthy informed consent, and therefore clarifying in detail the aims of the experimentation. Due to the fact that the research involves concepts related to ASD, it was of utmost importance to clarify that no evaluation would have been carried out on the children’s performance. This task demanded for personal communication.
- The importance of establishing a relationship of trust with the parents in order to conduct experiments on their babies. The very young age of the participants makes them a sensitive experimental group. Moreover, eye tracking technologies and research methods are not to be expected to be known by parents as general knowledge. Also this task demanded for personal communication.

- The objectives of the experiments did not include statistical significance. Therefore a more personal approach allowed to establish the necessary collaboration with the parents, and involve them as partners (and also stakeholders) in the research. Their help was indeed fundamental.

Originally, only two participants were identified (P1 and P2), who belonged to the target age group. P3 became a participant since she was present at the experimental facility, and her parent proposed and allowed for doing the experiment. This provided the opportunity to test the procedure on children even younger than the target age range of 12-24 months.

## 4.2 Apparatus

The eye tracker used in the experiments is the SMI® RED250mobile™, produced by SensoMotoric Instruments GmbH (Teltow, Germany). It is a remote model, which is to be placed underneath a display monitor and it casts infrared light towards the pupil of the subject in order to track the movement of the eyes. Since it does not produce sounds or movements, and it does not require the subject to wear additional equipment, it gets inconspicuous and unobtrusive. The sample rate was set to 250 Hz, which it is sufficient for tracking saccades, smooth pursuit movements and fixations. It can also track blinks and pupil dilation. The eye tracker software and its experiment suite (SMI Experiment Suite™3.6) are installed on a laptop computer (7th Generation Intel® Core™i7 processor 2.50 GHz; 8GB RAM, NVIDIA® Quadro™graphic card with 2GB dedicated memory; 32 bit colors; 15.6-inch diagonal anti-glare LED-backlit display, resolution 1920x1080px, 60Hz; the monitor size covers 39 degrees of visual angle horizontally and 22 degrees vertically, when it is viewed at 50 cm of distance). This setup is powerful and portable enough to be carried around and used in different settings, according to where the evaluation takes place, either in an home environment, in a clinical structure, or wherever the child feels more at ease. The computer was controlled at distance by using a portable keyboard connected to the experiment computer by a long USB cable. This allowed the researchers to stay out of the participant's sight and at the same time controlling the progress of the experiment. A scheme of the setting is shown in Fig. 8.

No video recordings were set up in order to capture the events happening during the experiment, due to a couple of reasons. The agreement between the researchers and the parents of the participant children was to keep all the information related to the experiment completely anonymized. This key point in the informed consent agreement was particularly important due to the potential for the research to uncover in the future possible clinical conditions of the children. Therefore, protecting the children's identity was of primary importance, regardless the confi-

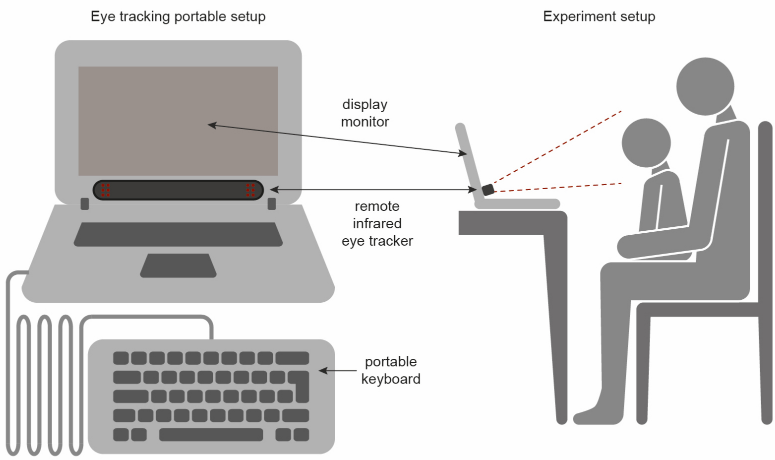


Figure 8: Scheme of the experiment equipment and setting.

dentiality obligation for the researchers. Adding a video recording tool could have prevented the parents to decide to participate in the study. Moreover, a tripod and a camera could have revealed to be an invasive equipment for the home setting. Adding even more technical equipment in addition to the eye tracker and its computer could have made the setting too cluttered, and also would have required an assistant to operate it, making the environment even more crowded. For these reasons the researcher considered having video recorders not to be ideal, even if they would provide a noticeable amount of richer qualitative data, which could have been useful for deepening the analysis on the applicability of the procedure on small children.

## 4.3 Stimuli materials

The stimuli materials for the experiment were all generated programmatically by using the Processing 3 software (https://processing.org), which is based on the Java programming language. The executive files for the generation of the visual stimuli are parametric, meaning that the researchers can input some variables and the software generates a new version of the visual stimuli automatically. For example, all the conversions between pixel and degrees of visual angle measurements units, the drawing of sinusoidal and triangular waves starting from trigonometric parameters, the rendering of the target movement, are automated. This features makes them useful not only for the specific case of the current research on early ASD, but also for other research in need for similar paradigms and visual stimuli.

The eye parameters and the appropriate methods for eliciting them enlisted in the framework (Chapter 3) lead to the development of four kinds of stimuli, which were put together in a single experimental procedure in the SMI Experiment Suite®. In between the presentation of the visual stimuli, a series of interstimulus materials was shown. A summary of the sequence of the visual stimuli and interstimulus materials is shown in Tab. 4.

| Index | Code | Material |
|---|---|---|
| 1 | v1 | Introduction video - Frederick, by Leo Lionni. No data recording. |
| 2 | c1 | Calibration routine - Ladybug target, 5 points. |
| 3 | s1 | Sinusoidal motion visual stimuli - Ladybug target. Eye tracking recording. [Assessment of closed-loop smooth pursuit gain (von Hofsten & Rosander, 1997)] |
| 4 | i1 | Interstimulus video - The Very Hungry Caterpillar, by Eric Carle. No data recording. |
| 5 | c2 | Calibration routine - Bee target, 5 points. |
| 6 | s2 | Triangular motion visual stimuli - Bee target. Eye tracking recording. [Assessment of closed-loop smooth pursuit gain (von Hofsten & Rosander, 1997)] |
| 7 | i2 | Interstimulus video - The Mixed-Up Chameleon, by Eric Carle. No data recording. |
| 8 | c3 | Calibration routine - Snail target, 5 points. |
| 9 | s3 | Step-Ramp pursuit visual stimuli - Snail target. Eye tracking recording. [Assessment of open-loop and closed-loop smooth pursuit gain (Takarae et al., 2004)] |
| 10 | i3 | Interstimulus video - I See A Song, by Eric Carle. No data recording. |
| 11 | c4 | Calibration routine - Butterfly target, 5 points. |
| 12 | s4 | Visually guided saccades visual stimuli - Butterfly target. Eye tracking recording. [Step paradigm for visually guided saccade tasks (Zalla et al., 2016), assessing the standard deviation of saccade gain (Johnson et al. 2016)] |

Table 4: List of stimuli and interstimulus materials.

### 4.3.1 Stimuli

All the stimuli require to input the display monitor sizes and resolution, in order to convert any measurement in pixel units to degrees of visual angle. The degrees of visual angle can be seen as a device-independent measurement unit, therefore it allows to make more precise calculations and to compare the results with literature independently from the type of media on which the stimuli are streamed on. The conversion functions are based on trigonometric calculations made publicly available by Michael Tesar[1] and encoded to suit the Processing 3 syntax. For the experiments, the assumed distance of the participant's eyes from the screen was set to 50 cm.

Given the small size of the display monitor available for doing the experiments, the parameters for the stimuli could not always replicate the stimuli described in literature, which often used supports and media with wider surfaces. Therefore, the stimuli are adapted for being presented on a 15.6" display monitor. Moreover, the parameters for each stimuli (especially the ones related with velocities, repetitions and durations) were manipulated in order to obtain trials short enough to keep the children's interest throughout the stimuli presentation.

The framerate for the stimuli is set to 60 fps in order to ensure a smooth presentation of the moving target and consequent eye movement artifacts due to a low rendering performance of the stimuli videos. This framerate matched also with the refresh rate of the display monitor used for the experiments.

The target pictures (Fig. 9) were drawn by the author starting from a black and white version of the ladybug target by Karen Tyler[2]. The aspect of the targets (bee, butterfly and snail) was kept consistent, changing their colors in order to make them stand out on the medium-gray background (128 on 256 levels), in the attempt to attract as much attention as possible. The target pictures are the only colored element in the stimuli.

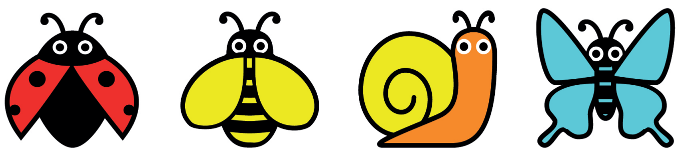

Figure 9: Target pictures for the stimuli

The 5-point calibration routines (c1, c2, c3, c4) used the custom targets, depending on which stimuli they were preceding. The calibration required a precision of <0.5 deg drift to be considered valid. The calibration procedures were semi-automated, for which the researcher needed to input a command in order to start and then the software expected the participant's fixations on the target to pro-

[1]The original codes are available at https://github.com/neuropacabra/VisualAngleCalculator.

[2]The icon is available at https://thenounproject.com/01karent/uploads/?i=469184.The author made the icon available under creative commons attribuition (CC-BY) license.

ceed further. The targets were always 49x49 px, covering 1 degree of visual angle for the display monitor in use. This dimension allows the viewers to foveate the whole target (Leigh and Zee, 2015, p. 2), preventing them to scan inside the target to foveate for further internal details, adding potential intrusive eye movements to the recordings. The Processing 3 scripts allow to export a picture for each frame in the visual stimuli, and then it can import all the pictures in sequence for creating a movie file. The movie file are then chained together in the eye tracker experiment software. Each stimulus material has its own set of parameters and algorithms to be generated. Each Processing 3 script generates a report with the parameters for the drawing of the stimuli, in order to allow the researchers to annotate the parameters and confront them within experiments or with literature. The detailed list of the stimuli for each participant is shown in Appendix D. Here it follows a summary of the algorithms which generate the stimuli.

**Sinusoidal motion visual stimuli [s1, s2]**

These stimuli were drawn starting from the descriptions provided by von Hofsten and Rosander (1997).

Given the limited space available on the 15.6" display monitor, an algorithm for drawing the sinusoidal and triangular motion paths was created in order to exploit all the space available:

1. Input the size and the resolution of the screen in pixels;
2. Convert the size from pixels to degrees of visual angle;
3. Set the wave parameters:
   - 3.1. Chose the number of cycles per trial (direction). This will impact on the wavelength of the wave;
   - 3.2. Set the frequency of the wave (which determines the duration of the trials and the velocity of the wave);
   - 3.3. The amplitude by default is set to be half of the display monitor screen;
4. Set the number of trials (i.e. the wave completes all the cycles toward one direction) within the experiment
5. Chose the target picture and its size
6. Determine the sinusoidal and triangular wave function and use it to move the target. The motion goes from the center-left of the screen to the center-right, and then backwards

The parameters of the waves were made dependent on the number of cycles, in order to allow the researchers to predict how many measurement repetitions could be available from completing all the trials in the visual stimuli.

The frequency of the wave was kept 0.2 Hz, following the values from von

Hofsten and Rosander (1997). However, the velocity of the target motion is not comparable with that study, due to the different dimensions of the waves in terms of amplitude and wavelength.

Before starting to move the target in a wave motion, a focusing animation is played for 1 second in order to direct the attention of the participant toward the initial point of the wave.

The two stimuli are essentially the same (Fig. 10, Fig. 11), but they use two different wave equations (sinusoidal sinusoidal $y(x) = A\sin(2\pi/\lambda * x)$ ; triangular $y(x) = 2A/\pi * \arcsin(\sin(2\pi/\lambda * x))$) and different target pictures.

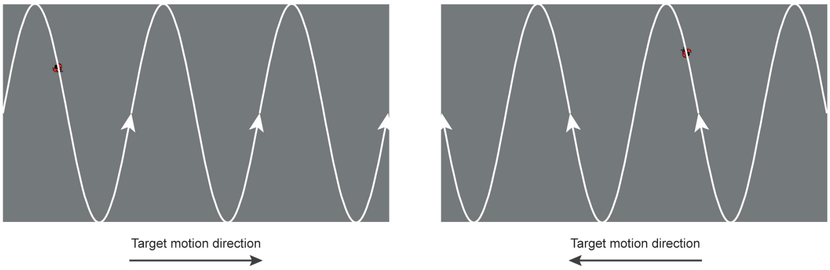


Figure 10: Scheme of the sinusoidal motion stimuli (s1)

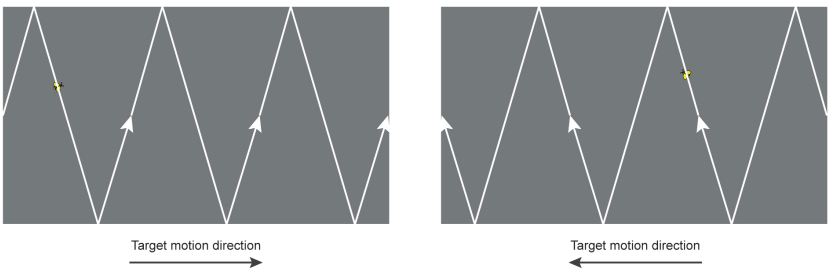


Figure 11: Scheme of the triangular motion stimuli (s2)

**Step-Ramp pursuit visual stimuli [s3]**

The algorithm for drawing a target moving smoothly following a step-ramp paradigm (Fig. 12) was taken from Takarae et al. (2004):

1. Show the central target for a random interval of time between two extremes: 1 s and 2 s. The randomization helps in preventing anticipatory eye movements.
2. Move the target abruptly to a determined distance but random direction on the horizontal axis:

   2.1. 3 deg of visual angle
   2.2. either left or right

3. Smooth movement of the target, at a constant but randomized velocity value, from the step position to a second position, keeping the same direction of the step:
   3.1. from 3 to 15 deg of visual angle
   3.2. at two different velocities: 4 and 8 degrees/second
   3.3. in two different directions: either left or right depending on the step direction
4. When the target reaches the final position, start another trial. Repeat the trial for each velocity by a set amount of times: 2 trials for each velocity.

The Processing 3 code generates an array with all the velocity and direction profiles, then it shuffles the array in order to have always a randomized sequence. This is the only experiment in which the orientation of the target matters. Therefore the snail target turns toward the direction of the movement on each trial.

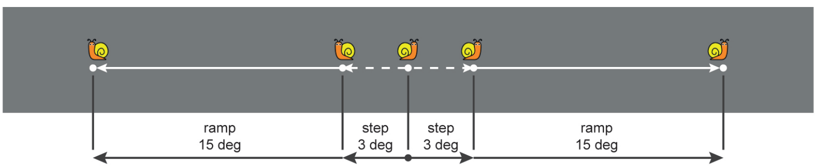


Figure 12: Scheme for of the step-ramp stimuli (s3)

**Visually guided saccades visual stimuli [s4]**

The algorithm for drawing a moving target in space following a step paradigm (Fig. 13) was taken from Zalla et al. (2016):

1. Show the central target for a random interval of time between two extremes: 1 s and 2 s. The randomization helps in preventing anticipatory eye movements.
2. At the same time, hide the central target and show a peripheral target, at a random distance between two extremes, in a random direction:
   2.1. the peripheral target is shown for a random interval of time between 1 s and 2 s
   2.2. in two different directions: either left or right (50-50 proportion)
   2.3. between 5 to 15 degrees of visual angle. The script randomizes both the x and y coordinates of the peripheral target, even if the guidelines did not explicitly state if the random y was needed. However, if the pe-

ripheral target always appears at y=0 (horizontal axis), some prediction mechanism could arise in the subject, who most likely understands after a couple of trials that the target would appear at the same y coordinate. In order to avoid this kind of prediction, the targets are both moved left or right from the central target at a random degree of visual angle in the range 5-15 deg, and also rotated around the central point of a random degree between +45 deg and -45 deg from the horizontal axis (not more, in order to retain the perception horizontal movement direction).

3. When the peripheral target disappear, start another trial. Repeat the trial for a set amount of times: 15 times.

The Processing 3 code generates an array with all the distance and direction profiles, then it shuffles the array in order to have always a randomized sequence.

The number of repetitions was 15, in order to have a total length of the trial ranging from 30 s to 60 s. Smyrnis (2008) advices to have at least 30 repetitions, however in that case the trial would range between 60 to 120 s, which was considered a too long timeframe for a small child for sustaining the attention. Indeed, in this last part of the experiment, the children shown less attention span to the stimuli.

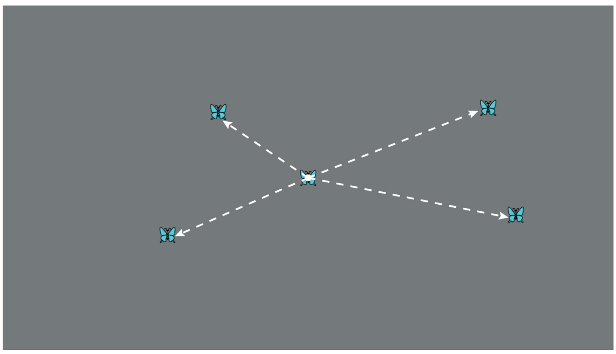

Figure 13: Scheme of the saccade stimuli (s4)

### 4.3.2 Interstimulus materials

The interstimulus materials chosen for the experimentation are a series of videos, which shown animations and storytelling based on famous books for small children: “Frederick” by Leo Lionni, and “The Very Hungry Caterpillar”, “The Mixed-Up Chameleon” and “ I See A Song” by Eric Carle. All the videos are publicly available on the Youtube website. These animations were chosen due to the fact that they are based on stories made for being appropriate for small children and pretty renown internationally for their good contents, and above all they are not frightening or stressing the child in any way. The function of the interstimulus materials is indeed to provide a break in between the stimuli presentation. While the interstimulus videos are shown, the eye tracker does not record data. This can be seen as a potential data loss, due to the fact that analyzing the gaze patterns of the children while they watch the animations can be a source of valuable information. However, the priority in this experimentation was given to the opportunity for the children and their caregivers to relax, have playful stress-relieving activities and granting them freedom of movement. The automatic calibration routines shown after the interstimulus materials correct any possible calibration drift.

Moreover, a specific experimental design should be created around the interstimulus videos if they would be considered experimental stimuli. This task goes beyond the scope of the current research. During the experiment session, it was not necessary to show the first video, “Frederick” by Leo Lionni. The children and their caregivers were already ready to start, and the children were showing interest for the experiment computer. Therefore the experiments started with the first calibration routine right away.

The duration of the interstimulus videos was planned to be around 2 minutes. However during the experiments it become evident that this amount of time was too long, and it distracted the children probably too much. They started losing interest after around 1 minute. However, all the animations showed an introduction, which does not present any animated contents but just texts. Probably it could have been more useful to skip systematically the introduction parts and show shorter parts of animated contents right away.

## 4.4 Experiment setting and procedure

The research protocol for the study follows the guidelines provided by Sasson and Elison (2012) for conducting eye tracking studies on young children with ASD, and by (Rubin and Chisnell, 2008, pp. 98-101) for arranging experiment sessions at a user’s site and the preparation of a minimalist portable test lab.

The informed consent form for the participation in the study and the research protocol document follow more or less the templates provided by the Regional Committees For Medical and Health Research Ethics (2017)(REK), which are suitable for medical-related research. The detailed documents are both available in Appendix A and C. The research protocol was shared and read by the researcher and the assistant before conducting the experiments.

The project proposal and the research protocol has been submitted to REK and, given the purpose of the project to just investigate the feasibility of the procedure and to not generate statistical results, REK notified that the project is not covered by the scope of the Health Research Act. Therefore, their approval was not necessary.

The experiments took place at a private home. Two attempts were made in order to find a spot in the home which was suitable enough to have good calibration, for a couple of reasons:

1. The ambient illumination, mainly coming from the sunshine filtering from the windows during a very sunny and hot day, was too bright in the first location. The calibration was failing repeatedly most likely due to the fact that the pupil size of the children was too small due to physiological constriction.
2. The geometry of the face of small babies is significantly different than the one from adults (i.e. the the pupillary distance is lower), therefore it is possible that the eye tracker software has troubles in detecting the children's pupils correctly.

Figure 14: Experiment setup in the home environment

The second location (Fig. 14), with dimmer ambient lightning, proven to be ideal for calibration. The location was still not fully isolated from distractions, and sometimes it was playfully noisy, with children running around. However, this kind of environment probably contributed to make feel the whole situation more relaxed and near to the everyday life of the children, which can be regarded as a positive feature. As predictable, all the children were easily distracted by the presence of the researchers, as probably they were new people in a known environment and therefore more interesting than the experiment equipments. Even if the researchers stayed out of sight, controlling the computer remotely, every small movement or noise they made captured the children's attention.

Before the experiments all the children were playing outside in the sun with their mothers and then during the experiments they were sitting indoors watching videos on a computer. Probably the change in the settings was pretty abrupt, and it might have impacted on the children's willingness to follow carefully the experiment from the beginning to the end.

The detailed research protocol available in Appendix C shows the timing and the duration of the phases of the experiment and the succession of the stimuli an interstimulus material. Here it follows a summary.

The experiment consisted of different phases:

1. Introduction and setup: The caregiver is provided with a recap of the experimental procedure and an informed consent form. Then she take a seat on a chair in front of the screen at an adequate distance, keeping the child on her lap.
2. Calibration: The researchers check if the eye tracker is detecting the child's pupils. The caregiver is asked to wear sunglasses, in order to prevent the eye tracker to detect her eyes. When the caregiver feels that she and her child are comfortable and ready to start, a first semi-automated calibration routine is shown on the display monitor. The researchers position themselves out of the child's field of sight, using the portable keyboard to control the experiment software.
3. Visualization: The series of stimuli and interstimulus materials is shown, following the sequence shown in Appendix C. The eye tracker records the data only during the stimulus presentation. The procedure is semi-automated, during which the researcher can move forward if needed by using the portable keyboard.
4. Conclusion: When the series of stimuli is over, a message is displayed on the display monitor and the test is ended. The eye tracker recordings are saved in the experiment software.

During the experiment, it was not possible to control constantly if the children's eyes were at 50 cm of distance from the eye tracker (which is the distance assumed in the visual stimuli codes). It was ranging up to 60-65 cm, rendering the sizes of the targets visually smaller than planned.

# 5 Results of the eye tracking experiments

Here it follows the discussion about the data collected on the participants' eye movement during the experiments. As explained previously in Section 3.5, at the current state of this research is not possible to provide quantitative computations on the eye tracking data. Moreover, the eye tracker experiment software does not provide calculation modules for smooth pursuit eye movements. Complex algorithms need to be applied on the raw data in the future. For these reasons, the analysis is mainly based on the visual inspection of the graphs outputted by the eye tracker software. Therefore, the following analysis is qualitative, subjective and based on the researcher's interpretation of the framework and of the measurements. Along with the eye tracker recordings, qualitative data were collected for each participant, in the form of written notes, about how they behaved in relation to the whole procedure.

The graphs shown in the following sections show a series of eye parameters, which are enlisted in the legend on the right side of the charts. In particular, the eye position is not shown by the composite cartesian coordinates (x,y), but the two coordinates are plotted separately. Therefore it is not possible to overlap the graphs with the visual stimuli. There are different units of measure on the chart's axes for the eye positions (pixels), the pupil diameter (mm) and the eye velocity (deg/s). For each participant, a tracking ratio is provided, which reports the percentage of correctly recorded data over the trial total amount.

The eye tracker software also tags the eye movements depending on their features, creating events for fixations, saccades and blinks. However, lacking of the smooth pursuit tag, it is not possible to discern fixations from smooth pursuit eye movements at the moment.

## 5.1 Pilot test [PT]: the reference dataset

Before conducting the experiment, the author conducted a pilot test in order to collect reference data. The data and the eye movement patterns shown in the following charts are the one which are expected to be elicited by the visual stimuli developed for the framework. The author knows all the stimuli in detail, he does not have any clinical diagnosis, and his eyesight is corrected to normal by glasses. Therefore it can be assumed that his performance on tracking the targets is theoretically one of the best achievable. The tracking ratio for the pilot test is $\geq 95.8\%$

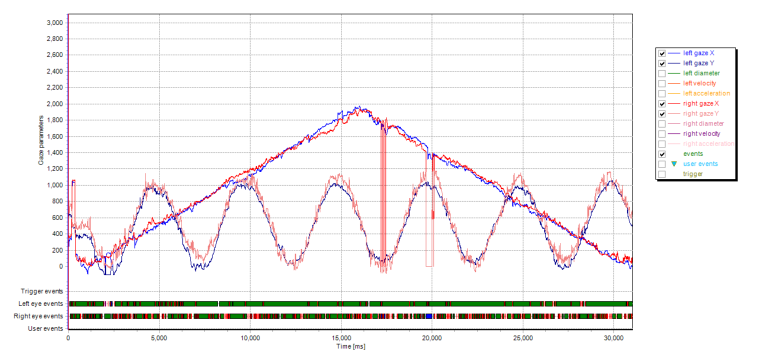


Figure 15: PT_T1 Eye positioning

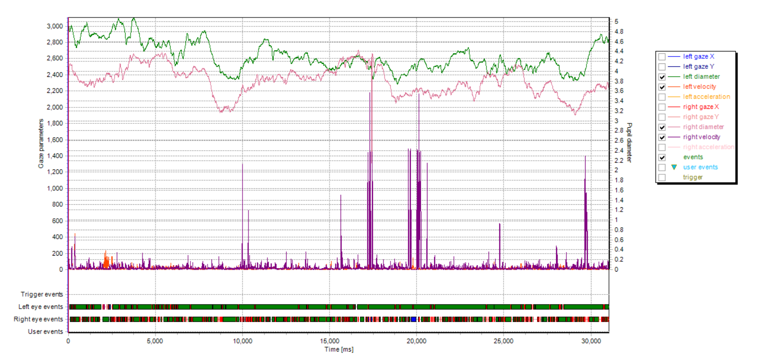


Figure 16: PT_T1 Pupil diameter and eye velocity

### 5.1.1 PT_T1 : Sinusoidal motion visual stimuli

The sinusoidal tracking pattern (Fig. 15) is evident from the plots of the y coordinate, while from the x coordinate plots it can be inferred that in the first half of the experiment the target moved from left to right (increase of x value) and then it travelled backwards (decrease of x value) following the same pattern (no disruption of the sinusoidal y pattern). The eye movements in the first 1000 ms are due to the focus-to-target routine in the stimuli. From the graph it can be seen that during two changes of directions (17.5 and 20 s) large saccades were performed, probably in the attempt to predict larger movements of the target. The left eye tracks smoothly the target sinusoidal movement with more precision, while the right eye is less precise. This is probably due to the dominance of the left eye over the right one in the subject.

Fig. 16 shows that a number of small saccades (the spikes in the eye velocity profile) were performed during the pursuit, and the two groups of larger saccades discussed in the chart Fig. 15 are well highlighted by high peaks of eye velocity.

### 5.1.2 PT_T2 : Triangular motion visual stimuli

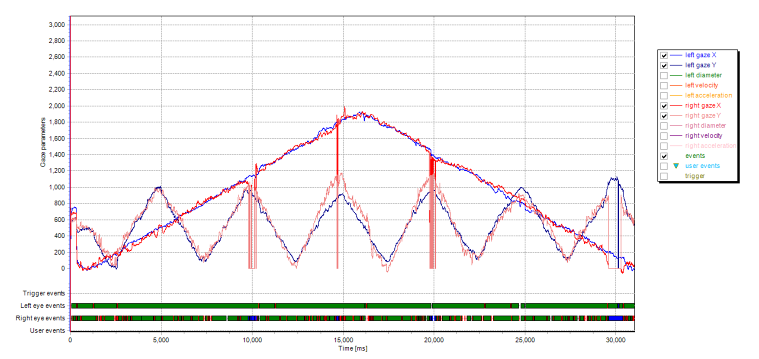


Figure 17: PT_T2 Eye positioning

The considerations made for the sinusoidal motion chart (Fig. 17) apply here to the triangular motion chart. Here it is even more evident the attempt to perform saccades at turning points of the target motion, which are indeed more abrupt than in the sinusoidal pattern.

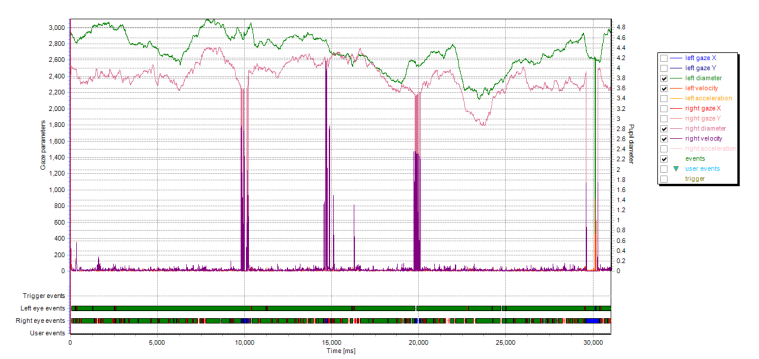


Figure 18: PT_T2 Pupil diameter and eye velocity

In Fig. 18, it is possible to see that the during the smooth tracking the number of microsaccades appears to be lower than in the sinusoidal motion pattern. This is probably due to the fact that the triangular pattern has constant velocity, which should be easier for the oculomotor system to attune to. The three groups of large saccades are highlighted clearly by their peaks in velocity. The last peaks in velocity seem to be due more to a tracking loss.

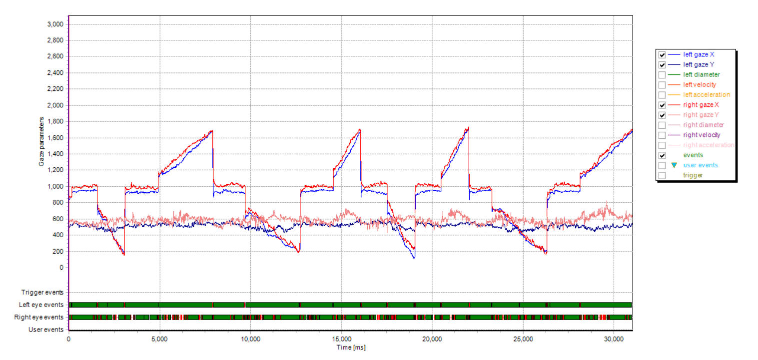

Figure 19: PT_T3 Eye positioning

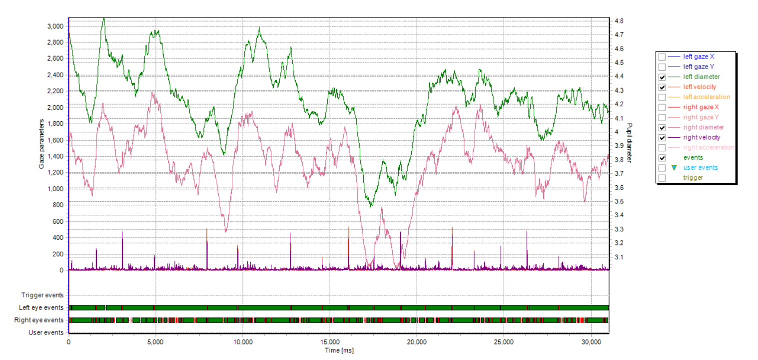

Figure 20: PT_T3 Pupil diameter and eye velocity

### 5.1.3 PT_T3 : Step-Ramp pursuit visual stimuli

In Fig. 19 it is fairly clear to see the step-ramp paradigm in action. The x coordinate have a baseline of 960 px (since the target was displayed at the center of the screen, at half of the size of the stimuli, therefore 1920px/2). The eyes fixates at the baseline value, then they perform a rapid saccade towards the step location of 3 deg (positive or negative, either above or below the baseline), then they follow smoothly the target towards the final location of 15 deg (above or below the baseline depending on the direction) and finally they return to the baseline position at the start of the subsequent trial. The difference in time taken for completing the ramp pursuits is due to the different velocity profiles (4 or 8 deg/s).

The y coordinates of the eye movements are always equal, since the stimuli moves only on the horizontal axis. No large saccades or blinks are visible in the recorded data.

It is important to remind that even during fixations, a number of small eye

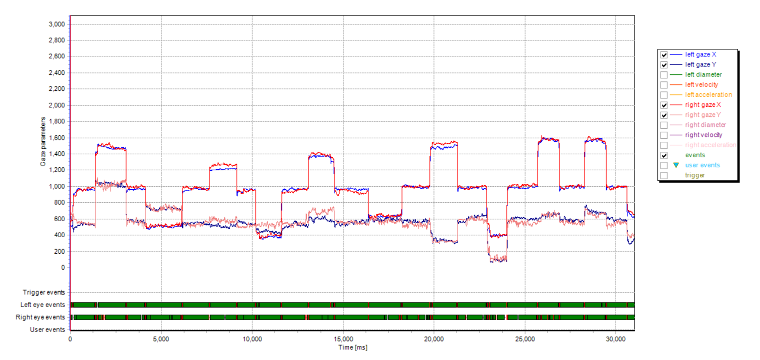


Figure 21: PT_T4 Eye positioning

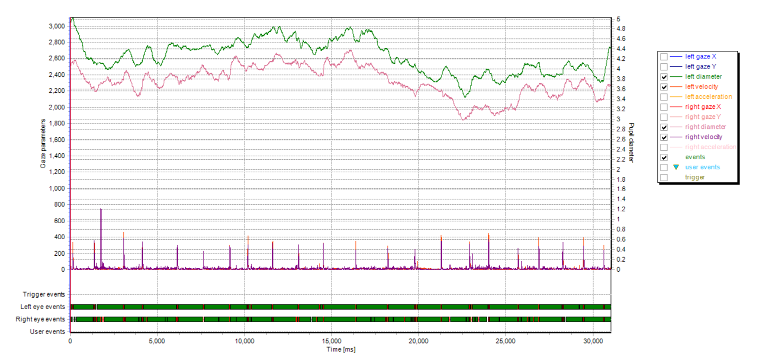


Figure 22: PT_T4 Pupil diameter and eye velocity

movements are performed in order to prevent visual habituation (Leigh and Zee, 2015, p. 3), therefore a completely flat velocity profile is not expected even during fixations.

In Fig. 20 it is possible to see the quick burst of more or less consistent velocity performed by the eyes in order to do the necessary saccade for the step. Then the smooth pursuit during the ramp flattens the velocity profile of the eye movements in a similar way than the fixations before the step do.

### 5.1.4 PT_T4 : Visually guided saccades visual stimuli

Fig. 21 shows how both the x and y coordinates of the eye change abruptly when a saccade is performed in order to track the target moving freely on the screen. The baseline value for the x value is 960 px while for the y value is 540 px (half of the stimulus size, since the target is at the center). The position profile moves upward or downward from the baseline basing on the direction of the target movement.

| Participant (Age monts) | Test | Trial n° | code | stimuli | Tracking ratio (%) | Repetitions (%) | Correct pattern |
|---|---|---|---|---|---|---|---|
| P1 (15) | 1 | 1 | P1_T1 | Sinusoidal motion | 58,8% | ~50% (3/6) | Yes |
| | | 2 | P1_T2 | Triangular motion | 71,6% | ~33.33% (2/6) | Yes |
| | | 3 | P1_T3 | Step-Ramp pursuit | 79,3% | ~75% (6/8) | Yes |
| | | 4 | P1_T4 | Visually guided saccades | 37,9% | −20% (3/15) | Yes |
| P2 (24) | 2 | 1 | P2_T1 | Sinusoidal motion | 78,7% | ~75% (4.5/6) | Yes |
| | | 2 | P2_T2 | Triangular motion | 54,9% | ~33.33% (2/6) | Yes |
| | | 3 | P2_T3 | Step-Ramp pursuit | 10,7% | 0% (0/8) | No |
| | | 4 | P2_T4 | Visually guided saccades | Not performed | - | - |
| P3 (9) | 3 | 1 | P3_T1 | Sinusoidal motion | 23,6% | ~16.66% (1/6) | Yes |
| | | 2 | P3_T2 | Triangular motion | 52,9% | ~50% (3/6) | Yes |
| | | 3 | P3_T3 | Step-Ramp pursuit | 29,1% | 25% (2/8) | Yes |
| | | 4 | P3_T4 | Visually guided saccades | Not performed | . | - |

Table 5: P{1,2,3} experiments results overview.

Since the target stays both in the center and in the periphery for certain amounts of time, it is possible to see the fixation stabilization in between saccades. The trial lasted 43.7 s, but the chart focuses on the first 30 s in order to provide more details.

Fig. 22 shows the bursts of eye velocity while performing the visually guided saccades, and the flat velocity profiles of the in-between fixations. It is interesting to notice that the first eye movement (performed between 1 and 2 seconds) has higher velocity and it is done in two saccades, therefore it was probably less precise. After that one, the other saccades are pretty similar, showing an attunement of the oculomotor system to the visual stimuli.

## 5.2 Experimental group [P1, P2, P3]

Tab. 5 shows an overview of the results from the experiments with the target group (P1, P2 and P3).

### 5.2.1 P{1,2,3}_T1 : Sinusoidal motion visual stimuli

**P1_T1**

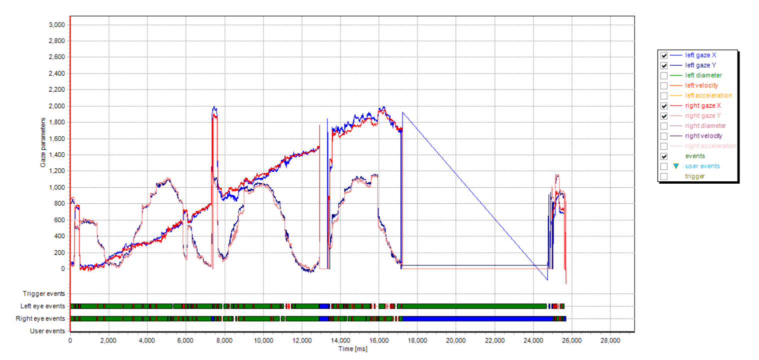


Figure 23: P1_T1 Eye positioning

The visual stimuli elicited a gaze pattern (Fig. 23) pretty close to the one expected for half of the designed repetitions. Indeed, the tracking record show data until the half of the experiment, while the target was moving in one direction from left to right. The graph show how P1's eyes did not perform a very smooth pursuit especially near to the turning points and during the third repetition. Rather, it seems that they performed more of a series of saccades and fixations, drawing a “staircase” profile. The graph also shows the intrusion of more or less large saccades especially immediately after the target turning points, which is consistent with the pilot test data.

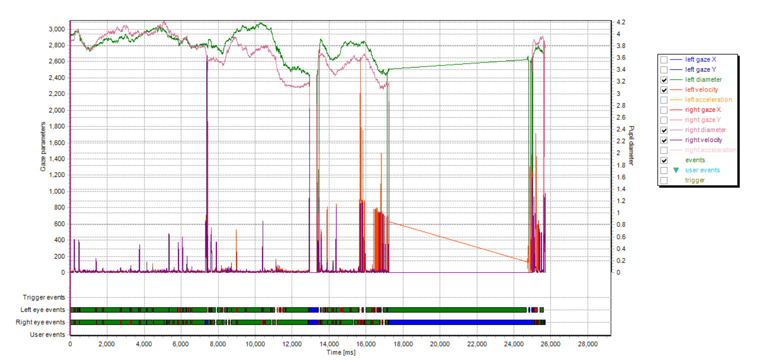


Figure 24: P1_T1 Pupil diameter and eye velocity

Fig. 24 shows that during the smooth pursuit tracking in the first half of the stimuli presentation, P1 performed a series of small corrective saccades with small peaks of velocity, and also three large saccades with bursts of high peaks of velocity after the target turning points, where the eye velocity profile flattens the most since the target velocity is at minimum.

**P2_T1**

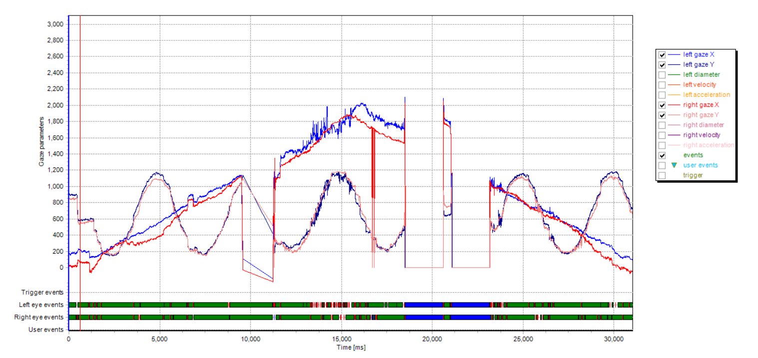


Figure 25: P2_T1 Eye positioning

Fig. 25 shows that P2 tracked the sinusoidal moving target smoothly with noticeable accuracy throughout all the stimuli presentation. The eye tracker lost data on one full repetition and a half one, probably because the child moved a bit far away from the eye tracker or something caught her attention elsewhere. However, she returned to track the target again accurately. Two saccades, a small one and a large one, are visible before the target turning points, when the target starts decelerating noticeably.

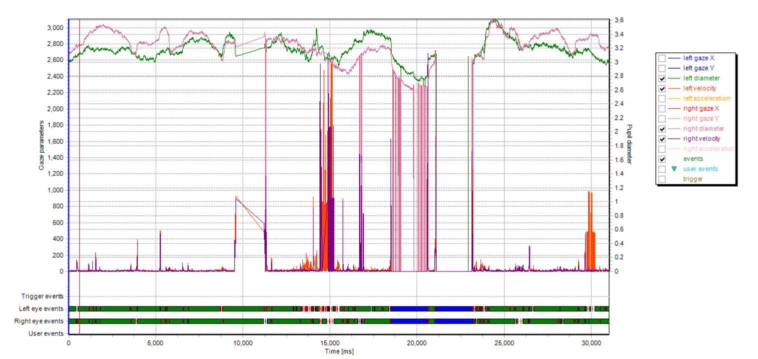


Figure 26: P2_T1 Pupil diameter and eye velocity

Fig. 26 show how during smooth tracking the velocity profile of P2 eyes is near to be flat, meaning that even though the eyes were moving constantly, P2 made no

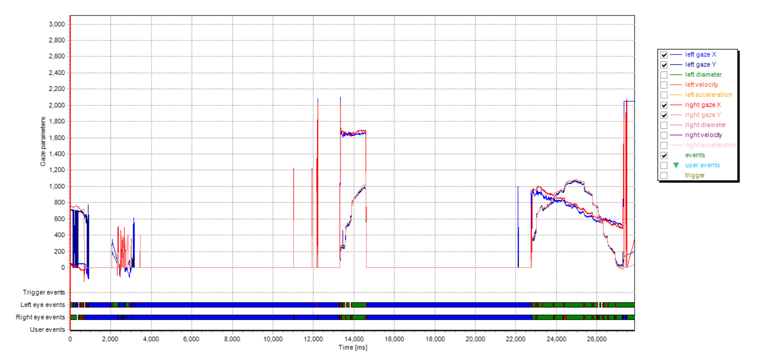


Figure 27: P3_T1 Eye positioning

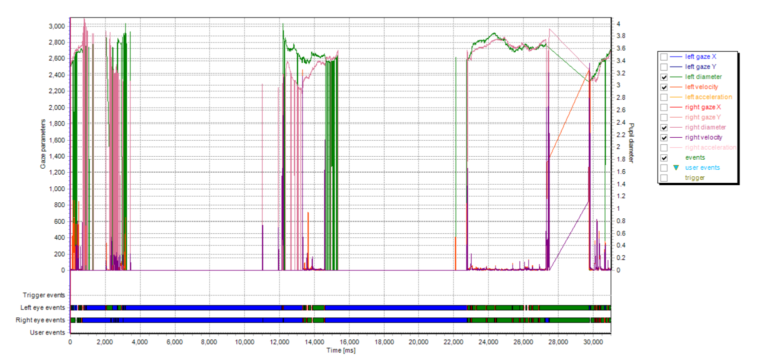


Figure 28: P3_T1 Pupil diameter and eye velocity

saccades or abrupt eye movements. Bursts of high peaks of eye velocity are found during larger saccades intrusions.

**P3_T1**

As Fig. 27 shows, the quantity of collected data from P3 in the first trial is rather low (tracking ratio 23,6%). This is probably due to the fact that the child might become comfortable to sit in a position too far away from the display monitor. Or it can be due to the fact that the child seemed very curious towards the researchers and was more keen on observing them than the display monitor. These events are expected to happen while testing with such a small baby. Therefore, it is not possible to state that the recorded data can be useful for an in-deep analysis. However, in the only full repetition completely recorded as well as in the first section of another one, it is possible to see that the stimuli elicited the expected sinusoidal gaze pattern. Moreover, the smooth tracking shows qualitatively the same staircase profile of P1.

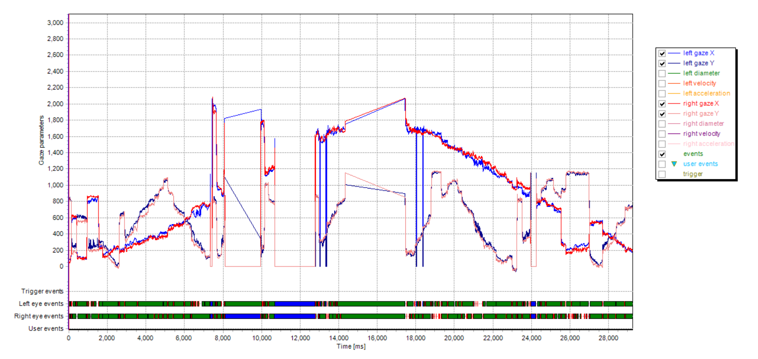

Figure 29: P1_T2 Eye positioning

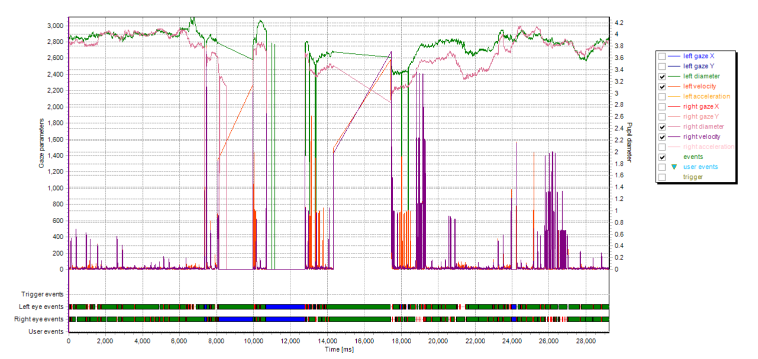

Figure 30: P1_T2 Pupil diameter and eye velocity

In the only two clear record sets available (Fig. 28), it is possible to see that a number of small saccades with low peaks of velocity are performed during the smooth tracking with a more flat velocity profile. The pattern is visually pretty stable, suggesting a good control over the eye movements performed, regardless their performance.

### 5.2.2 P{1,2,3}_T2 : Triangular motion visual stimul

**P1_T2**

In Fig. 29 it is possible to spot the triangular motion pattern, however large and small saccades are present throughout the whole record. A couple of full repetitions are clean from saccadic intrusions. The smooth tracking shows a staircase profile, like for the sinusoidal motion stimuli, but it seems less abrupt in this stimuli. This could be due to the fact that the velocity profile of the triangular motion remains constant, resulting in being more predictable and easier to track smoothly for the

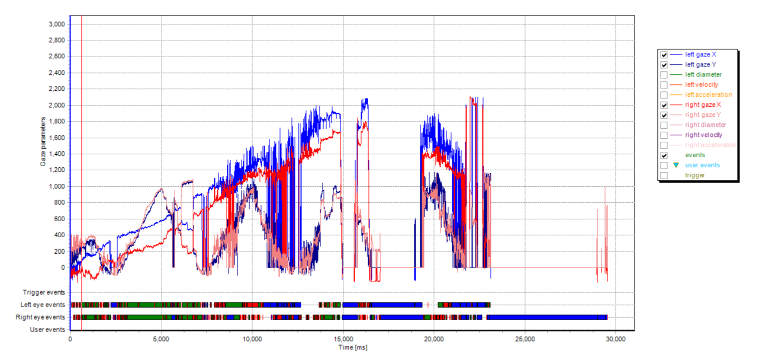


Figure 31: P2_T2 Eye positioning

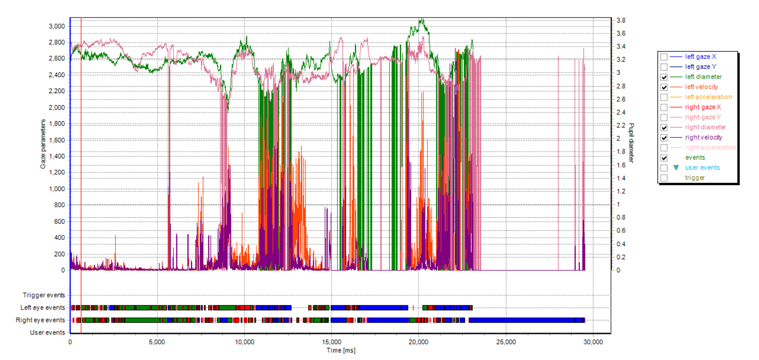


Figure 32: P2_T2 Pupil diameter and eye velocity

child.

Fig. 30 shows the presence of small saccades intruding the smooth pursuit even in the two cleaner repetitions.

**P2_T2**

The graph for the triangular pursuit of P2 (Fig. 31) is particularly rich of artifacts, which are particularly irregular and therefore probably due more to movements of the head or the whole body of the child rather than being caused by only by eye movements. Indeed, the dense repetition of quick eye movements, starting from the second repetition of the triangular wave, can be better explained by the child trying to track the object while keeping moving on the lap of her mother. In the record of the first clean repetition of the stimuli it is possible to see that the smooth tracking is pretty precise for the y coordinate of the eye, while the left eye leads the right one in terms of x coordinate. This might be due to the fact that the child's

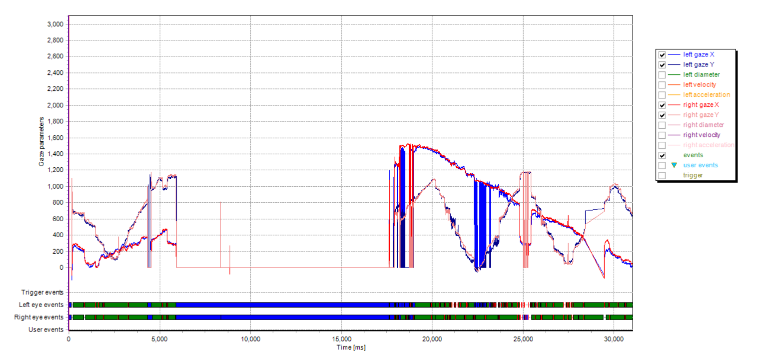


Figure 33: P3_T2 Eye positioning

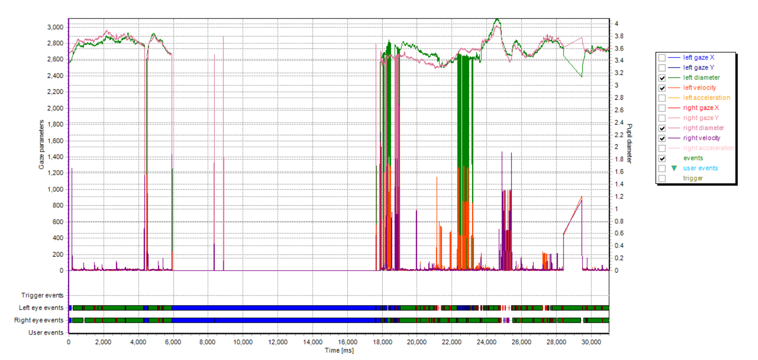


Figure 34: P3_T2 Pupil diameter and eye velocity

head was a bit tilted or the calibration was not precise due to the movements of the child. Overall, the record does not seem to provide many reliable measurements for smooth pursuit eye movements. It is possible that the stimuli was not different enough from the previous one in order to be interesting enough for the child, or she felt uncomfortable to sit still in position at the moment of this trial.

Fig. 32 shows how only the first repetition of the stimuli shows eye tracking with a velocity profile clean an flat enough to be considered smooth pursuit. The rest of the record is too noisy to be considered.

**P3_T2**

The tracking record of P3 (Fig. 33) is pretty accurate, she followed the stimuli mainly during the second part of the presentation. Large saccades are visible at the target turning points, as predictable, both on the horizontal and vertical axes. A staircase profile for the smooth tracking is present also in this stimuli. Overall the

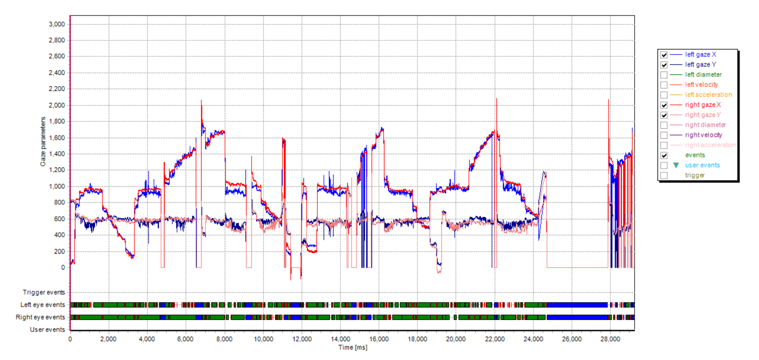


Figure 35: P1_T3 Eye positioning

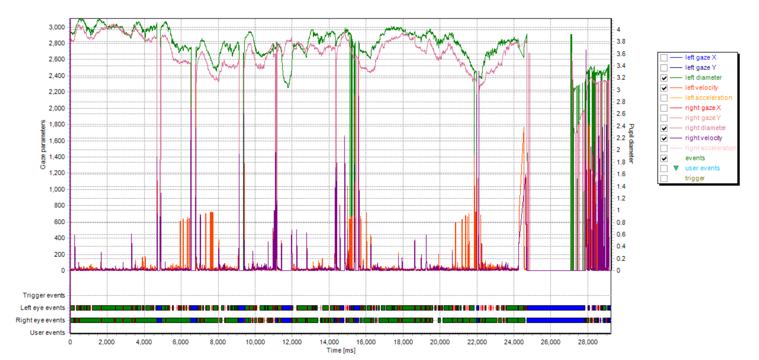


Figure 36: P1_T3 Pupil diameter and eye velocity

stimuli seemed to work well in eliciting the expected gaze pattern. The central part of the record is missing, probably because the child looked away for some time.

Fig. 34 shows how in the first repetition of the stimuli few saccades with small peaks in velocity disrupted an otherwise pretty flat eye velocity profile, suggesting smooth tracking. On the other hand, In the second part of the stimuli more and larger saccades intruded the smooth tracking.

### 5.2.3 P{1,2,3}_T3 : Step-Ramp pursuit visual stimuli

**P1_T3**

Fig. 35 shows pretty clearly that the stimuli elicited the expected eye movements. All the phases of the paradigm are easily detectable (initial *fixation*, *step* saccade, smooth pursuit *ramp*). A number of large saccade is visible, happening in particular moments (e.g. during the step, or when the target returns to the central point after the end of a repetition). Some of them might be also blinks, since they happen in the middle of pursuit tracking, where no competing stimuli or abrupt target movements are shown. The tracking appears accurate, and the staircase pattern is visible only in some parts of the chart.

Fig. 36 shows the presence of a series of saccades with consistent velocity, around 400 deg/s, which happen at during the step phase. The other larger saccades with higher peaks of velocity can be considered as intrusive of either fixations or smooth pursuit. The velocity profile, when not disrupted by saccades, appears fairly flat, indicating somewhat stable fixations and smooth pursuits.

**P2_T3**

The eye tracking data of P2 during the step-ramp visual stimuli are insufficient for being analyzed (Fig. 37). Indeed, at this point of the experiment P2 seemed tired of watching at the display monitor. Probably the experiment was lasting for too long, and she lost interest. Indeed, the researchers and P2's mother decided to stop the experiment and leave the child to go outside to play with her friends. P2 did not perform further trials.

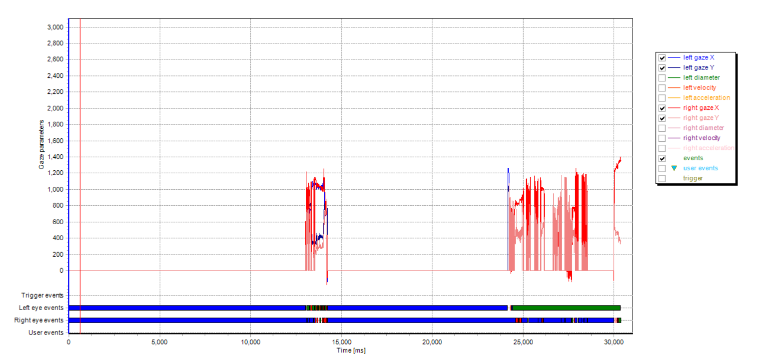


Figure 37: P2_T3 Eye positioning

**P3_T3**

The record for the step-ramp stimuli of P3 stops after the second repetition. After that moment, P3 started interacting with her sister and her mother. She was probably a bit tired to look at the display monitor too. However, the recorded data show interesting patterns.

The two repetitions performed by P3 (Fig. 38) show a gaze pattern which is pretty close to the expected one, with apparent good accuracy. An artifact is present during the ramp of the first repetition, and it could be a blink. While a large saccade performed after the ramp of the second repetition seems more an overshooting of the target.

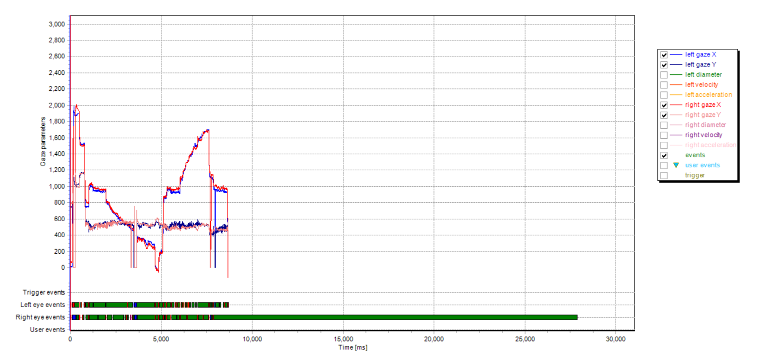


Figure 38: P3_T3 Eye positioning

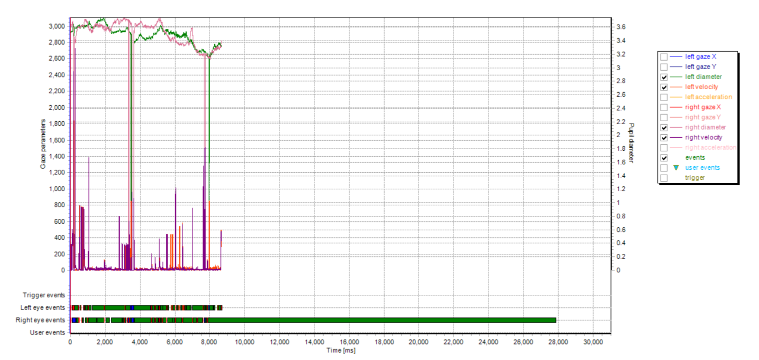


Figure 39: P3_T3 Pupil diameter and eye velocity

Fig. 39 reveals how the velocity profile of the smooth pursuit ramp of the first repetition is overall flat, if not considering the artifact in between the pursuit, indicating smooth tracking. On the other hand, the series of peaks of eye velocity during the second ramp suggest more of a staircase pattern, with saccades and fixations in sequence rather a single smooth pursuit.

### 5.2.4 P{1,2,3}_T4 : Visually guided saccades visual stimuli

**P1_T4**

Fig. 40 show that the stimuli elicited the expected gaze pattern. A series of fixation on different points in the space is disrupted by quick eye movements, which are saccades. The fixation stabilization seems less precise from the pilot test reference dataset, and this could be due to small movement of the baby during the trial, or that the gaze stabilization improves further later in the children's development. Some large artifacts are visible during fixations, and they probably are blinks, since

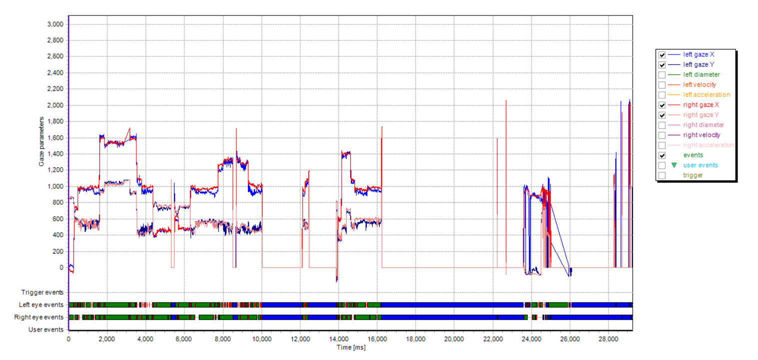


Figure 40: P1_T4 Eye positioning

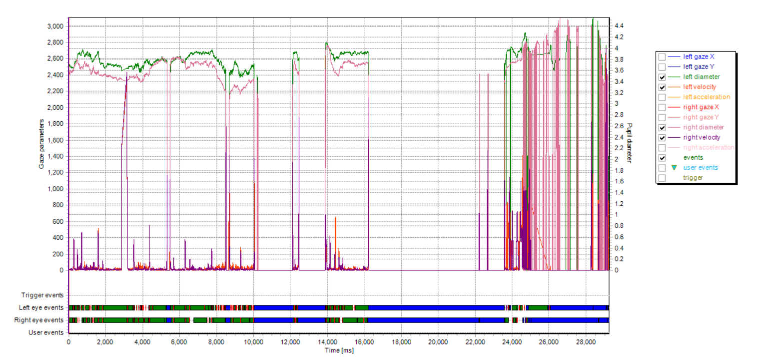


Figure 41: P1_T4 Pupil diameter and eye velocity

they do not happen when the target moves from the center to the periphery or back. The trial should have lasted for 43.7 s, but it has been stopped at 34.61 s since the child was evidently tired and not paying attention to the stimuli anymore. The chart shows the first 30 s, however no more evident gaze patterns are shown after 16 s.

Fig. 41 shows a series of consistent saccades, varying in peaks of velocity according to the amplitude of the saccade required, and in-between flatter velocity profiles of fixations, which however show constant low velocity small movements. Higher peaks in eye velocity are related to artifacts in the record, probably blinks. After 16 s the record seems to be too unreliable for being analyzed.

P2 and P3 did not perform Trial 4 (the visually guided saccades stimuli), and also P1 attended it for around one third of the time according to the tracking ratio. It seems that the experiment lasted for too long at this point, and the children's attention faded in between the third stimulus and the third interstimulus material presentations. This made difficult to record data on Trial 4.

### 5.2.5 Experiment notes

Along with the eye tracker recordings, the researcher took some written notes during the experiments.

After finding a suitable spot in the home environment, P1's calibration routines worked surprisingly good. They were fast and accurate, and the child did not need particular prompting for following the target with her gaze. P2, during the experiment, was not particularly attracted by the first calibration procedure, which prevented to move on to the subsequent stimuli. Her mother then asked the researchers if she could help in directing P2's attention toward the screen. The researchers welcomed the proposal, and the mother started to tell the children sentences like "what there is on the screen?" or "look at the screen", and she pointed with her finger to the target. The mother performed this active reinforcement throughout all the experiment, and allowed to recover the child's focus. The reinforcement was particularly useful during the calibration phases, which became shorter due to the child's precise gaze directioning.

When a stimuli disappeared, the child often said "det er borte!" ("it disappeared!", in English). She seemed surprised from the abrupt change between stimuli and interstimulus materials, especially in terms of the target picture. It is possible that she was expecting to see the same target performing different actions throughout the experiment stimuli. However, not meeting the child expectations fully can be a good way to keep his/her interest.
P2's mother described that the child usually does not watch much television in general.

P3, the youngest participant, seemed particularly pleased with both the stimuli and the interstimulus materials. She giggled briefly when she saw the stimuli for the first time. She seemed very curious about the researchers' presence, which made her turn frequently towards them and not following the stimuli materials on the screen. However, this reaction was expected. She was also younger than the target group, therefore the whole procedure was not completely tailored around children of her age group.

# 6 Discussion

## 6.1 Applicability of the eye tracking framework on the target group

Regarding the research question 3.a (*was it possible to conduct the experiment until the end?*), only P1 managed to reach the last trial, but she did not complete it fully. P2 and P3 lost interest at the third trial, not performing the last one. At the current state of the experimental design, it seems that it lasts a bit too long. Both the stimuli and also the interstimulus materials should be shorter. Shortening the stimuli presentation means showing less repetitions of the stimuli or shortening the durations of expected fixations, if the other parameters of frequency and velocity (particularly important for smooth pursuit) and size of the stimulus remain constant. Lowering the number of repetitions could make the stimuli provide less repeated measurements and therefore less assessments for internal consistency and less reliability of the measurements in general. However, it is probably better to have less repeated measurements than not having measurements at all, as happened for Trial 4, which was not performed by P2 and P3.

Regarding the research question 3.b (*was the percentage of tracking ratio for each visual stimuli >50%?*), 6 out of a total of 12 trials have tracking records for more than half of the total time of the presentation of the stimuli. The tracking ratio percentage does not describe the quality of the data, but it provides a good index of how efficient the eye tracker in collecting data during the experiments. Considering the lack of control over every potential distractor in the environment (e.g. participants children free to move while sitting on the lap of their caregiver, people free to pass by the experiment location, researchers out of the sight of the participant but still present in the location, etc) and the fact that probably the stimuli lasted for a bit longer than the necessary (increasing the total amount of time which the tracking ratio percentage refers to), collecting data for half of the trials can be considered satisfactory for this first experimentation. P1 (15 months of age) and P2 (24 months of age) data records already show noticeable high percentages of tracking ratio, and indeed their records are pretty complete in some tasks. All the participants though show a decrease of tracking ratio the more the experiment proceeded, resulting also in P2 and P3 not performing the last task. P3 (9 months of age) records are overall much shorter than P1 and P2. This might be due to a series of factors (e.g. a shorter attention spans at her very young age, more difficulties to sit still for long periods of time) but, regardless the motivation, the procedure collected more data for the two children in the target age group than the younger one. The research question 3.c (*is the percentage of repetitions performed entirely over the total number of repetition displayed >50%?*) is closely related with 3.b, but it tells more about the quality of the recorded data rather than the quantity. As explained before, the number of repetitions is important to ensure reliable measurements. 4 out of 12 trials collected tracking records of at least half of the repetitions designed in the visual stimuli, indicating that very frequently the children lost interest in the stimuli or started to behave differently (e.g. moved to far away from the experiment computer or sat in different positions) during the stimuli presentation. Looking at the percentages of repetitions performed for each stimuli, it does not emerge a preference for a particular visual stimuli, which could have hypothetically scored systematically better, eliciting more repetitions than others. From the graphs does not seem to emerge a particular moment in which the children stopped following some repetitions. Indeed, the participant's mothers tried to redirect the children's attention towards the screen while they felt the babies were looking elsewhere. Their intervention helped in collecting further eye recordings and possibly further repetitions, but in absence of video recordings it prevents to pinpoint the exact moments in which the children lost interest at first. However, it was evident in during the experimentation that the partnership with the mothers was fundamental both in making the children feel more at ease and also to collect more eye movement data.

Regarding the research questions 3.b and 3.c, a possible further step for refining the framework is to shorten the stimuli and the interstimulus materials, and to reduce a bit the number of repetitions for each stimuli. This operation should increase the number of repetitions performed and therefore also the tracking ratio over all the experiment duration. While the performance metrics (related to 3.a, 3.b and 3.c) highlight the need of further refinement of timing and conciseness of the stimuli and interstimulus materials, probably the most interesting results of this experimentation are related to the research question 3.d (*Do the diagrams of the eye tracking data show qualitatively the gaze patterns which the methods were aimed to elicit?*). Regardless of the amount of eye tracking data or repetitions, in the charts of 9 out of 10 total performed trials (2 are missing) it is possible to detect the correct gaze patterns under investigation. Even in the records of P3, which overall show few segments of the trials, the gaze patterns recorded were actually quite similar to the expected ones. These results suggest that the design of the visual stimuli is appropriate for eliciting the eye parameters of interest, at least in children between 9 and 24 months of age with no vision problems or any clinical diagnosis. They were interesting enough to elicit at least some visual tracking, and with some external reinforcement coming from the caregiver, the children did actually perform the expected gaze patterns. Therefore, as a further step in the research it is probably the procedure which needs to be refined more than the visual stimuli.

Summarizing, answering the research question 3, the outlined procedure seems to be applicable to children in the target age group 12-24 months, and with some major improvements probably even on younger children too. The timing and the duration of the stimuli and interstimulus materials seems to be the crucial point to fix, but the stimuli seem to elicit the correct eye movements.

## 6.2 Considerations about the data recordings, stimuli and process

During the experiments some further interesting elements emerged, which need to be taken into consideration for further developments of the framework.

In the pilot test trials it is quite evident that the left eye of the subject followed the targets with greater stabilization, and perhaps more accuracy, suggesting its dominance over the right eye. Therefore it would be probably more useful to analyze only the left eye records in order to compute performance metrics and having clearer results. In the charts from the experimental group, the children's eyes do not show this pattern as clear as PT, and therefore it would be necessary compute the records of both the eyes or determining each time what it seems to be the dominant eye record. Basing on the plotted charts, it is possible that at the young age of the experimental group the eye dominance mechanism is still not evident as much as in adults.

The "staircase" profile firstly shown by P1 (P1_T1, Fig. 23; P1_T2, Fig. 29) could be due to the fact that the velocity of the target smooth movement was too quick, therefore it required the P1's saccadic system to intervene during the target tracking. P2 did not show this staircase profile (P2_T1, Fig. 25; P2_T2, Fig. 31), while P3 did (P3_T1, Fig. 27; P3_T2, Fig. 33). These data suggest that, perhaps, the autonomy of the smooth pursuit system develops after 15 months of age towards the 24 months. Before 15 months of age, the smooth pursuit system does still not perform in complete autonomy, and it still interacts with the saccadic system noticeably, or maybe it works more precisely and autonomously at slower target velocities than the ones tested. Indeed, Falck-Ytter et al. (2013) report that vertical and two-dimensional tracking matures over the first years of life.

Regardless the physiological explanation of the behavior, it is probably necessary to generate smooth pursuit sinusoidal and triangular visual stimuli with slower target velocities, at least for the younger age ranges in the target group. This should allow the children's smooth pursuit systems to attune better to the target and to prevent the saccadic systems to intervene and to add noise to smooth pursuit data. P1 and P3 data also show the staircase profile during the Step-Ramp visual stimuli (P1_T3, Fig. 35; P3_T3, Fig. 38), but only in some parts of the chart and with less intensity. This might be due to the fact that the motion in this stimuli happens only on the horizontal axis. Therefore it is probably less complex for the children to attune their eye movement to such stimuli, comparing to the sinusoidal or triangular target motions.

From the data collected for P1_T4 (Fig. 40), it should be technically possible to compute the standard deviation of the saccade gain with an appropriate calculation module. Regardless the data noise shown during the fixations, which is not of interest for the framework, the visually guided saccades appear to have clean and well isolated velocity profiles in the record. In the future, isolating systematically these eye velocity profiles and comparing them with the velocity should be doable, and it would be definitely less challenging than computing smooth pursuit metrics.

Some practical issues emerged during this first series of experiments. If the location in which the experiment takes place is too bright, calibrating the eye tracker reveals to be challenging. In order to avoid to change locations multiple times in an home environment, it is beneficial to ask upfront directly to the caregivers or the owners of the facility about which location could be the most suitable one, and if they are available.

Instructing the caregivers about what they can do to support the experiments (e.g. redirect the children's attention toward the screen if they start to focus elsewhere) and what is their level of freedom (e.g. feel free to talk, move and play with the child during the interstimulus material presentation) is of utmost importance. They should feel to be research partners and stakeholders in the process. Their collaboration directly impacts on the amount of recorded data, and therefore the overall efficiency and effectiveness of the procedure.

Even if during the experiments the researchers tried to place themselves out of the participants' sight and to control remotely the computer, their presence was still a big distraction for the participants. Being strangers in an home environment surely catches everyone's attention. Even if the procedure is carried out at a clinical facility, it should be expected that the children would be at least a bit curious toward the people around them. In the future, it will be important to set up a series of remote controlling devices, connected via wireless (either Wi-Fi or even better local Bluetooth) to the experiment computer, which allows to see a streaming of the children's behavior and to control the experiment software from an another remote device, which could be even a tablet or a smartphone for example. This would allow the researchers to sit at a fair distance from the experiment location, preventing to add unnecessary distractions, and at the same time control when the child seems not interested anymore in the stimuli, and therefore move forward with the experiment. If the researchers can setup a dedicated location for the experiments, having more control over the layout and furnishing, an alternative option could be the one proposed by Sasson and Elison (2012), that is placing a partition between the eye-tracking station and the computer operated by the experimenters, with a camera showing a view of the participant. This kind of arrangement is very near to the one illustrated by Anderson et al. (2006)(Fig. 42).

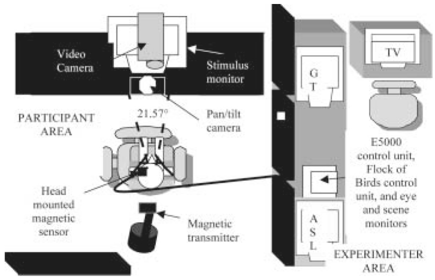


Figure 42: Experimental setup with a partition between participants and experimenters. Scheme taken from Anderson et al. (2006)

# 7 Conclusion and suggestions for further research

The developed eye tracking framework and procedure seems to elicit the expected gaze patterns in children between 12 and 24 months of age. Currently, no computational analysis on the raw data has been performed due to the researcher's lack of domain knowledge. The next step in this research would be to contact and team up with mathematicians and software engineers, in order to refine and complete the framework in its data analysis part. As already described in Section 3.5, the studies from Giordano et al. (2017); Jansson and Medvedev (2013); Larsson et al. (2015) already push the research forward in this direction, showing the interest of the software engineering community for the data analysis of complex eye movements.

If in the future it will be possible to compute precisely the eye parameters of interest from the eye tracking recordings, then it will be possible to collect data from broader samples of children in the target age. This would allow to assess systematically the construct and content validity of oculomotor performance as early ASD indicator.

If some of the parameters tested by the framework would reveal to systematically predict ASD diagnosis, a common point of developmental divergence could be found within the wide variety of symptoms and conditions of ASD. Then, investigating further the neurological basis of the oculomotor impairment comparing also the results with neuroimaging studies, would be then the natural next step for the research. It would provide a clearer picture of what are the fundamental neurological pathways involved in ASD and possibly develop treatment to overcome the divergent development.

Contextually to the search for adequate algorithms for the analysis of the recorded eye movements, the experimental procedure needs to be refined and improved. Finding a good balance between number of repetitions necessary for having reliable results, and length of the procedure will be a priority key point to fix. Shortening and refining both stimuli and interstimulus materials is the first step.The procedure seems to elicit and measure correct gaze patterns also for children younger than the target group. However, even further refinement of the procedure is needed if it should be applied it to younger children, given their shorter attention span and the difficulty to sit still for long times

While doing more experiments on larger samples, it is also possible that less eye parameters than the ones currently implemented the framework will reveal to be more sensitive. It is also possible that multiple paradigms provide similar results and become redundant. Therefore, the number of stimuli could decrease in future developments of the framework, shortening the time needed for the whole eye tracking session and at the same time leaving more space for the most reliable paradigms.

Finding and teaming up with clinical teams and structures to conduct experiments is vital for the development of the current research. The input of these professionals will be fundamental to define and perform possible longitudinal experimental designs. These could provide insights on the children's developmental trajectories and the sensitiveness of the eye tracking methodology over the time. Sharing and discussing the eye tracking measurements with these experts is also of extreme importance, either them being neuropsychiatrists, logopedist, etc. Eye movement patterns could be related to behavioral manifestations apparently distant as domain.

There are a number of features in the experiment procedure and stimuli which probably need to be researched in spin-off studies and then integrated in the general framework. Indeed, the framework should act as a catalyst for further research on each micro-experimental variable.
The velocity of the targets should be the priority parameter to fix, since it allows to calculate the gain of the eye movement, which in literature seems to be a key divergent parameter characterizing ASDg and therefore it needs to be measured accurately.
Another example could be that the color of the targets in the developed stimuli is currently arbitrary. Franklin et al. (2008) report less accurate color perception in children with ASD of around 11 years of age, but not when it comes to discern category of colors. If the visual variable color could impact on attention or oculomotor performance is not known at the moment. This and other micro-variables might influence the outcomes of the measurement.

The experimental stimuli have been developed to be replicable and modifiable enough to be used also in different types of eye tracking research, perhaps on subjects with other neurodevelopmental disorders as well as TDg. It is conceivable that even if the stimuli will be used for other purposes, but on children belonging to the target age group, the insights coming from other studies could help to improve the stimuli parameters for this research as well.

In conclusion, there is still a long way to go before the framework will be functional to early ASD diagnosis, both in terms of refining the procedure and harmonizing it with the current clinical practice. Literature shows noticeable interest in the subject and eye tracking is a sensible tool for investigating divergent neurodevelopmental disorders. Interaction designers can keep on contributing to the scientific debate acting as mediators, facilitators and possibly leaders within this complex multidisciplinary research field. The ultimate goal of preventing small children to develop lifelong impairments provides enough motivation itself. The key point is to make more objective and precise instruments available to clinicians, both from practical and economical points of view.

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# A Informed consent form [Norsk]

The following appendix includes the informed consent form for the study in Norwegian language.

NTNU

# Eye-tracking (blikksporing) som støtteverktøy for tidlig diagnostisering av Autisme-spekter lidelse

## FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

Vi er en gruppe forskere innen interaksjonsdesign fra NTNU i Gjøvik. Med denne forespørselen ber vi om din deltakelse i et forskningsstudie som har som mål å evaluere anvendelighet av en metode i blikksporing på 12-24 måneder gamle barn. Metoden har som formål å identifisere visse øyebevegelser som kan indikere tidlige tegn på autismespekterforstyrrelse. I dette eksperimentet vil det imidlertid ikke bli gjort noen bedømmelse av barnas prestasjonsevne. Formålet med eksperimentet er å evaluere hvor passende metoden er på en representativ bruker.

## HVA INNEBÆRER PROSJEKTET?

Ditt barn vil bli bedt om å se på en rekke bilder og/eller videoer på en skjerm. Ved starten av eksperimentet vil det gjøres en kalibreringstest sammen med barnet, og fra det øyeblikket vil blikksporeren samle inn data om barnets øyebevegelser. Blikksporeren fremtrer som en svart boks festet under dataskjermen. Den produserer ikke lyd eller bevegelse, og den skader ikke barnets øyner på noen slags måte.

## MULIGE FORDELER OG ULEMPER

Denne studien vil samle inn informasjon om hvor bærekraftig metoden er på små barn. Dersom eksperimentet en dag skulle vise seg å være passende på små barn, vil det være mulig å gjennomføre en slik test på små barn som har høy risiko for å utvikle autismespekterforstyrrelse (ASD). Jo tidligere det er mulig å avsløre potensielle indikasjoner på ASD, som spesielle øyebevegelser, desto raskere er det mulig å gjøre inngripen med egnet terapi, og derfor øke mulighetene for rehabilitering. I dette tilfelle vil det imidlertid ikke gjøres noen vurdering av barnets øyebevegelser.
I over to tiår har blikksporingsteknologi hatt en utstrakt bruk i eksperimentell forskning for å samle inn informasjon om hva deltakerne i studiene ser på og hva de tildeler oppmerksomhet. Ingen skader har blitt påvist ved bruken av slike innretninger. Ingen stressende eller ubehagelige situasjoner er involvert i dette eksperimentet.

## FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst trekke ditt samtykke, uten å oppgi noen grunn. Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.
Forskerne Giampiero Dalai og Frode Volden vil være tilstede I eksperimentets lokaler
Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte Giampiero Dalai (giampied@stud.ntnu.no, +47 47731016) eller Frode Volden, (frodv@ntnu.no, +47 93227262).

## HVA SKJER MED INFORMASJONEN OM DEG?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i *Hva innebærer prosjektet?*.
Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert.
Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. Dataene vil bli fullstending anonymisert fra det øyeblikket deltakerne forlater eksperimentets lokaler.
Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om deg blir

behandlet på en sikker måte.  Informasjon om deg vil bli anonymisert eller slettet senest fem år etter prosjektslutt.
Basert på det som står skrevet I forrige avsnitt vil det ikke være mulig å identifisere barnet ditt i resultatene av studiet når de publiseres.

## GODKJENNING

Prosjektet er meldt inn til Regional komite for medisinsk og helsefaglig forskningsetikk. Hensikten med prosjektet oppgis å være at man skal undersøke en prosedyre for blikksporing hos små barn. Fokus vil utelukkende være på selve prosedyren for blikksporing på små barn (12-24 måneder). Siden dette prosjektet ikke har som formål å generere statistiske resultater, anser komiteen at det ikke omfattes av helseforskningslovens virkeområde.

## SAMTYKKE TIL DELTAKELSE I PROSJEKTET

Som foresatte til ________________________________ (Fullt navn) samtykker vi til at hun/han kan delta i prosjektet

Sted og dato

Foresattes signatur

Foresattes navn med trykte bokstaver

Sted og dato

Foresattes signatur

Foresattes navn med trykte bokstaver

# B Informed consent form [English]

The following appendix includes the informed consent form for the study in English language.

NTNU

# "Eye tracking as a supporting diagnostic tool for Autism Spectrum Disorders"

## REQUEST FOR PARTICIPATION IN THE RESEARCH PROJECT

We are a group of researchers in interaction design from NTNU Gjøvik. With this request, we ask you to participate in a research study that intends to evaluate the applicability of a procedure of eye tracking on 12-24 months old children. The procedure is aimed to highlight some eye movements which can be used as an early sign of Autism Spectrum Disorders. However, in this experiment no judgements will be done on the children's performance. The aim of the experiment is to assess only the feasibility of the procedure on a representative user.

## WHAT DOES THE STUDY ENTAIL?

Your child will be asked to watch a series of images and/or videos on a screen. At the beginning of the experiment, a calibration exercise will be done with the child, and from that moment on the eye tracker will start to collect data about the child's eye movements. The eye tracker appears as a black box attached underneath the computer screen. It does not produce any sound or movement, and it does not hurt in anyway the child's eyes.

## POTENTIAL ADVANTAGES AND DISADVANTAGES

The study will provide information about the suitability of the procedure on small children. One day, if the experiment will prove to be feasible on small children, it will be possible that this kind of test could be carried out on small children with high risk of developing Autism Spectrum Disorders (ASD). The earlier it is possible to detect potential markers of ASD, like particular eye movements, the quicker is possible to intervene with appropriate therapies, and therefore increase the opportunities of rehabilitation. However, in this case no judgement will be done on the child's eye movement.
Eye tracking technology has been already used extensively in experimental research for more than two decades, in order to collect information about what the study participants look at and what they pay attention to. No damaging consequences are known for this type of equipment. No particular stressing or discomforting situations are involved in the experiment.

## VOLUNTARY PARTICIPATION

Participation in the study is voluntary. If you wish to participate, sign the declaration of consent on the final page. You can withdraw your consent to participate in the study at any time and without stating any particular reason. If you withdraw from the study, you are entitled to demand that the collected data are deleted, unless the data have already been incorporated in analyses or used in scientific publications. The researchers who are present in the experimental facility are Giampiero Dalai and Frode Volden. If you later on wish to withdraw your consent or have questions concerning the study, you may contact Giampiero Dalai (giampied@stud.ntnu.no, +47 47731016) or Frode Volden, (frodv@ntnu.no, +47 93227262).

## WHAT WILL HAPPEN TO THE INFORMATION ABOUT YOU?

The data that are registered about you will only be used in accordance with the purpose of the study as described in *WHAT DOES THE STUDY ENTAIL?*. You are entitled to have access to what information is registered about you and you are further entitled to correct any mistakes in the information we have registered. All the data will be processed without name, ID number or other directly recognisable type of information. The data will be fully anonymized from the moment the participants leave the experimental facility.

The Project Leader is responsible for the day-to-day running of the research project and that information about you is treated in a safe manner. Information about you will be anonymized or deleted no later than five years after the end of the project.
Based on what stated in the previous paragraph it will not be possible to identify you or your child in the results of the study when these are published.

## APPROVAL

The project proposal has been submitted to the Regional Committees For Medical and Health Research Ethics. The purpose of the project is to investigate a procedure for eye detection in small children. Given that the focus of the project will be exclusively on eye detection on young children (12-24 months), and does not intend to generate statistical results, the committee believes that this project is not covered by the scope of the Health Research Act.

## CONSENT FOR PARTICIPATION IN THE STUDY

As legal representative of ________________________________ (Full Name) we agree that he / she can participate in the project

| | |
|---|---|
| Place and date | Signature of the legal representative |
| | Legal representative's name in printed letters |

| | |
|---|---|
| Place and date | Signature of the legal representative |
| | Legal representative's name in printed letters |

# C Research protocol, detailed

The following appendix includes the detailed research protocol for the study.

NTNU
Norwegian University of Science and Technology



Giampiero Dalai


# RESEARCH PROTOCOL (v. 2.1 - final)

## ENVIRONMENT AND EQUIPMENT

The experimental facility is the home of the family of one of the participants in the session. Rather low control over the environment is expected, flexibility is required.

A laptop computer is equipped with a SMI RED250mobile eye tracker. Set the sampling rate of 250 Hz (maximum). Try to keep the light in the room a bit dim, in order to encourage the child to focus on the screen. A chair is positioned in front of the screen at an adequate distance for the eye tracker to capture the child's eye. The caregiver will sit on the chair and the child will sit on the caregiver's lap throughout all the experiment. The researchers position themselves out of the child's field of sight.

Equipment checklist:
- ▢ Scripts and forms
- ▢ Identification
- ▢ Computer remote or portable keyboard + extension cord
- ▢ Pens and notebooks
- ▢ Eye tracker case:
    - ▢ Laptop
    - ▢ Eye tracker + authentication USB key + magnets

Make sure the test is running correctly and it is fully charged before departing for the participants' home.

## LIST OF EXPERIMENT STIMULI AND INTERSTIMULUS MATERIALS

The items are enlisted by order of appearance in the experiment.

| Index | Code | Material |
|---|---|---|
| 1 | v1 | Introduction video - Frederick, by Leo Lionni. No data recording. |
| 2 | c1 | Calibration routine - Ladybug target, 5 points. |
| 3 | s1 | Sinusoidal motion visual stimuli - Ladybug target. Eye tracking recording. |
| 4 | i1 | Interstimulus video - The Very Hungry Caterpillar, by Eric Carle. No data recording. |
| 5 | c2 | Calibration routine - Bee target, 5 points. |
| 6 | s2 | Triangular motion visual stimuli - Bee target. Eye tracking recording. |
| 7 | i2 | Interstimulus video - The Mixed-Up Chameleon, by Eric Carle. No data recording. |

| | | |
|---|---|---|
| 8 | c3 | Calibration routine - Snail target, 5 points. |
| 9 | s3 | Step-Ramp pursuit visual stimuli - Snail target. Eye tracking recording. |
| 10 | i3 | Interstimulus video - I See A Song, by Eric Carle. No data recording. |
| 11 | c4 | Calibration routine - Butterfly target, 5 points. |
| 12 | s4 | Visually guided saccades visual stimuli - Butterfly target. Eye tracking recording. |

## ROLES AND RESPONSIBILITIES

Lead researcher (Giampiero Dalai), research assistant (Frode Volden).
Lead researcher: Responsible for the preparation of the equipment, setup of the experimental procedure and stimuli on the eye tracker laptop, administration of informed consent forms, setup of the equipment in the participant's home environment, conduction of the experiment routine, tracking of timing, quick note taking only on paper.
Research assistant: Logistic support for moving team and equipment. The assistant is not asked to take notes or carry out any operation. He will report orally his general impressions at the end of the experiment sessions. He can answer questions about the context around the experiment if asked by the participants' caregivers.

## PROCEDURE

The experiment will consist of four different phases:

### 1. Introduction and setup

The researchers introduce themselves at the moment of arrival to the experiment facility.
The researchers administer to the caregiver a recap of the experimental procedure and an informed consent form. The researchers will note down some basic information about the child (age in months, sex, any suspect of vision problems) in order to profile the child in an anonymous way. The researchers will answer any caregiver's question prior to the experiment start.

The researchers set up the equipment, placing the laptop computer on an appropriate surface, a chair in front of it. The researchers ask the caregiver to sit in a comfortable position with the child in his/her lap, in front of the display monitor and facing directly it. The researchers check if the eye tracker tracks the child's eyes correctly. The caregiver should not interfere with the child's vision of the screen.
In the meantime, a video (`v1`) will be streamed on the display monitor, in order to start to capture the child's attention.

### 2. Calibration

When the caregiver feels that he/she and the child are ready to start, an automated calibration routine (`c1`) is shown on the display monitor, consisting of a moving pointer accompanied by sounds, which the child should be attracted enough to follow it with his/her gaze. If the eye tracking algorithm considers the calibration adequate (<0.5 degrees of tracking slip) the experiment software will start streaming the sequence of visual stimuli.

After this first calibration routine, further calibration routines (c2, c3, c4) are executed before each visual stimuli.

### 3. Visualization

A series of videos is shown on the screen. Some of the images are actual stimuli materials (s1, s2, s3, s4), others are inter-stimulus materials with the aim of keeping the child entertained and during which the eye tracker does not record data (i1, i2, i3).

### 4. Conclusion

When the series of images/videos is over, a message is displayed on the display monitor and the test is ended. The researchers then wrap up the experiment, greet the caregiver and leave the experiment facility.

## TIMELINE

| Approximate duration | Procedure | | |
|---|---|---|---|
| 15 min | Introduction and setup | | |
| 12 - 13 min (It can vary and even last longer depending on the child's interest in the visual materials) | 1 min | c1 | Calibration |
| | 31 s | s1 | Sinusoidal motion |
| | 2 min | i1 | Interstimulus video |
| | 1 min | c2 | Calibration |
| | 31 s | s2 | Triangular motion |
| | 2 min | i2 | Interstimulus video |
| | 1 min | c3 | Calibration |
| | 20 to 40 s | s3 | Step-Ramp pursuit |
| | 2 min | i3 | Interstimulus video |
| | 1 min | c4 | Calibration |
| | 30 to 60 s | s4 | Visually guided saccades |

## DATA ANALYSIS

The sampling rate of 250 Hz of the SMI RED250mobile eye tracker allows to collect data of four eye parameters: fixations, saccades, blinks and pupil dilation. The data collected on the child participating in the study will be inspected visually in order to understand if the measurement worked throughout all the experiment and/or at which point the child lost interest, if there was data loss due to calibration issues or large head movements of the child. The analysis is aimed just to detect problems with the procedure and highlight possible improvements for it. The data will be compared between the participants, in order to understand if the data was consistent across experiments. No judgement will be made on the child's performance.

# D Experiment stimuli detailed descriptions

The following appendix includes the detailed description of the visual stimuli used in the study. These data are generated by Processing 3 codes during the compilation of the executive files, which render the visual stimuli.

# EXPERIMENT STIMULI DETAILED DESCRIPTIONS

## Sinusoidal motion visual stimuli [s1]

The screen width is 34.5 cm and the height is 19.5 cm. The horizontal resolution is 1920 px and the vertical resolution is 1080 px. The user's distance from the screen is set at 50.0 cm.
The display monitor refresh rate is 60 FPS, each frame lasts 16.66 ms.
The sine wave parameters are: Amplitude (A): 11.034209 deg; Frequency (f): 0.2 Hz; Period (T): 5.0 s; velocity (v): 2.6155162 deg/s; wavelength (λ): 13.07758 deg.
Each trial lasts 15.0 seconds. The wave completes 3.0 cycles in each trial (2 trials, 1 for each direction, 6 cycles in total). The initial focus-on-target routine lasts 1.0 s. The total length of the session is 31.0 s.
The target picture path is "/ladybug.svg"; The target size is 1.0 deg.

## Triangular motion visual stimuli [s2]

The screen width is 34.5 cm and the height is 19.5 cm. The horizontal resolution is 1920 px and the vertical resolution is 1080 px. The user's distance from the screen is set at 50.0 cm.
The display monitor refresh rate is 60 FPS, each frame lasts 16.66 ms.
The triangle wave parameters are: Amplitude (A): 11.034209 deg; Frequency (f): 0.2 Hz; Period (T): 5.0 s; velocity (v): 2.6155162 deg/s; wavelength (λ): 13.07758 deg.
Each trial lasts 15.0 seconds. The wave completes 3.0 cycles in each trial (2 trials, 1 for each direction, 6 cycles in total). The initial focus-on-target lasts 1.0 s. The total length of the session is 31.0 s.
The target picture path is "/bee.svg"; The target size is 1.0 deg.

## Step-Ramp pursuit visual stimuli [s3]

The screen width is 34.5 cm and the height is 19.5 cm. The horizontal resolution is 1920 px and the vertical resolution is 1080 px. The user's distance from the screen is set at 50.0 cm.
The display monitor refresh rate is 60 FPS, each frame lasts 16.66 ms.
The step is 3.0 deg; the pursuit limit is 15.0 deg
The array of velocity profiles of the target (in deg/s) for each randomized test are:

- Test Randomized_1: [ -8.0, 4.0, -4.0, 8.0, -8.0, 8.0, -4.0, 4.0 ]
- Test Randomized_2: [ 4.0, -4.0, 8.0, -4.0, 4.0, -8.0, -8.0, 8.0 ]
- Test Randomized_3: [ -4.0, 8.0, -4.0, -8.0, 4.0, 8.0, 4.0, -8.0 ]

The number of trials per velocity is 2, the number of velocities is 2, the number of directions is 2. The total number of trials in the experiment is 8.
The target is displayed at the center of the screen between 1000.0 ms and 2000.0 ms.
The total experiment duration ranges from 20.0 seconds to 40.0 seconds.
The target picture path is "/snail.svg"; The target size is 1.0 deg.

## Visually guided saccades visual stimuli [s4]

The screen width is 34.5 cm and the height is 19.5 cm. The horizontal resolution is 1920 px and the vertical resolution is 1080 px. The user's distance from the screen is set at 50.0 cm.
The display monitor refresh rate is 60 FPS, each frame lasts 16.66 ms.
The central target duration is between 1000.0 ms and 2000.0 ms.
The peripheral target duration is between 1000.0 ms and 2000.0 ms.

The total experiment duration ranges from 30.0 s to 60.0 s.
The distance of the peripheral target from the central target ranges between 5.0 deg to 15.0 deg.
The array of displacement profiles of the target (in deg) are:

- Test Randomized_1: [ 14.832732, -9.743024, 5.970555, -11.630829, 8.985348, -6.670554, 12.401097, -14.475862, 13.471872, 13.548758, -7.14576, -14.06731, -10.945073, 14.758865, 12.54543 ]
- Test Randomized_2: [ 11.19659, -11.230872, -7.2530355, -5.1153092, -8.695057, 5.495724, -10.51643, -8.251087, 6.223626, 9.082907, 10.843807, -14.971769, 13.415259, 11.896386, 12.722762 ]
- Test Randomized_3: [ -6.2812967, 14.379347, 7.3835897, 7.3666596, 10.319616, -11.062942, 9.729986, 6.780423, -11.380352, -8.600257, -5.5837626, 13.622085, -9.637011, -6.6532755, 7.743903 ]

The target picture path is "/butterfly.svg"; The target size is 1.0 deg.