Dissertation

EARLY DETECTION OF DEVELOPMENTAL DISORDERS: THE ROLE OF COMMUNICATIVE DEVELOPMENT

submitted by

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Statutory declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the “Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz“.

Graz, 30 October 2018 eh. Katrin Daniela Bartl-Pokorny

Disclosures

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Table of contents

Abbreviations and definitions

ABC	Autism Behavior Checklist
AD(H)D	Attention Deficit (Hyperactivity) Disorder
ADOS	Autistic Diagnostic Observation Schedule
ASD	Autism spectrum disorder
ASS	Autismus-Spektrum-Störung
CARS	Childhood Autism Rating Scale
CDI	MacArthur-Bates Communicative Development Inventories
CDKL5	Cyclin-dependent kinase-like 5 gene
CGG	Cysteine-guanine-guanine
CV	Consonant-vowel
DD	Developmental delay
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion tensor imaging
EEG	Electroencephalogram
ERP	Event-related potential
F	Female
FMRP	Fragile X mental retardation protein
FMR1	Fragile X Mental Retardation-1 gene
fNIRS	Functional near-infrared spectroscopy
FOXG1	Forkhead box G1 gene
FXPOI	Fragile X-associated primary ovarian insufficiency
FXS	Fragile X syndrome/Fragiles-X-Syndrom
FXTAS	Fragile X-associated tremor/ataxia syndrome
GUARDIAN	Graz University Audiovisual Research Database for the Interdisciplinary Analysis of Neurodevelopment
IBM	International Business Machines
ICD	International Statistical Classification of Diseases and Related Health Problems
iDN	Interdisciplinary Developmental Neuroscience
IJA	Initiating joint attention
IL	Illinois
IPCA	Inventory of Potential Communicative Acts
IQ	Intelligence quotient
L	(Pre-)linguistic vocalisation
L_{prop}	Proportion of communicative functions the behaviour type L was used for
LRDD	Late recognised developmental disorder

LTD	Long-term depression
LTP	Long-term potentiation
m	Male
MECP2	Methyl-CpG-binding protein 2 gene
MeCP2	Methyl-CpG-binding protein 2
mGluR-LTD	Group 1 metabotropic glutamate receptor dependent long-term depression
min	Minutes
mo	Months
MRI	Magnetic resonance imaging
mRNAs	Messenger ribonucleic acids
N/A	Data for the respective age band were not analysed for the respective study/not available
NDD	Neurodevelopmental disorder
NHS	Natural History Study
NL	Non-linguistic vocalisation
NL_{prop}	Proportion of communicative functions the behaviour type NL was used for
NLGN	Neuroligin
NRXN	Neurexin
NV	Non-verbal behaviour
NV_{prop}	Proportion of communicative functions the behaviour type NV was used for
OMIM	Online Mendelian Inheritance in Man
PSV	Preserved speech variant
PTCHD1	Patched domain containing 1
r_s	Spearman rank-order correlation coefficient
RettBASE	Rett Syndrome Database
RTT	Rett syndrome/Rett-Syndrom
RJA	Responding to joint attention
RQ	Research question
RVA	Retrospective video analysis
SHANK	Shank
SPSS	Statistical Package for the Social Sciences
TD	Typically developing/typical development
UK	United Kingdom
USA	United States of America

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Abstract in German

Einige Entwicklungsstörungen werden unmittelbar nach der Geburt oder bereits intrauterin erkannt, wohingegen die Diagnose anderer Entwicklungsstörungen für gewöhnlich erst im Kleinkindalter oder sogar später erfolgt. Bei zweiteren entstehen Zweifel an einer unauffälligen Entwicklung, wenn Meilensteine der Entwicklung nicht oder verspätet erreicht werden, Verhaltensauffälligkeiten eine gewisse Schwelle überschreiten und/oder gegebenenfalls physische Besonderheiten evident werden. Defizite im sozio-kommunikativen Bereich zählen zu den Kernsymptomen vieler dieser Entwicklungsstörungen, jedoch ist bisher wenig über die prädiagnostische sozio-kommunikative Entwicklung der Kinder bekannt. Ziel dieser Dissertation war es, den Wissensstand über die frühe sozio-kommunikative Entwicklung von Kindern mit spät erkannten Entwicklungsstörungen zu erweitern. Dazu erfolgte (a) die umfassende Analyse sozio-kommunikativer Fähigkeiten von Kindern mit Rett-Syndrom (RTT), Fragilem-X-Syndrom (FXS) oder Autismus-Spektrum-Störung (ASS), (b) der Vergleich der sozio-kommunikativen Fähigkeiten dieser Kinder mit einer Kontrollgruppe von sich normal entwickelnden Kindern und (c) eine erste Beschreibung möglicher spezifischer Entwicklungsprofile für die einzelnen Störungsbilder.

Als Grundlage der Untersuchungen dienten retrospektive Audio-Videoaufnahmen, die die Eltern von Kindern mit RTT (typisches RTT oder Preserved Speech Variante; n = 7), FXS (n = 9), ASS (n = 10) oder typischer Entwicklung (n = 10) aufgenommen hatten, als ihre Kinder zwischen 9 und 24 Monaten alt waren. Die Analyse der sozio-kommunikativen Formen und Funktionen erfolgte mit Hilfe des *Inventory of Potential Communicative Acts* (IPCA; Sigafoos, Arthur-Kelly und Butterfield, 2006).

Bereits gegen Ende des ersten Lebensjahres zeigten sich bei den untersuchten Kindern mit RTT, FXS oder ASS Auffälligkeiten im sozio-kommunikativen Bereich. Bei Kindern mit Entwicklungsstörungen wurden insbesondere limitierte Repertoires an Gesten, (vor-)sprachlichen Vokalisationen und sozio-kommunikativen Funktionen (v.a. das Fragen nach Gegenständen/Handlungen/Informationen) beobachtet. Die sozio-kommunikativen Fähigkeiten der FXS-Gruppe und der Kontrollgruppe nahmen mit dem Alter zu, wobei sie in der FXS-Gruppe über den gesamten Beobachtungszeitraum geringer waren. Die sozio-kommunikativen Fähigkeiten der ASS-Gruppe nahmen zunächst zu, jedoch zeigte sich ab der Mitte des zweiten Lebensjahres eine gewisse Abnahme, was auf eine mögliche Regressionsphase der untersuchten Kinder hindeutet.

Die vorliegende Dissertation konnte (a) frühe Auffälligkeiten hinsichtlich der sozio-kommunikativen Entwicklung von Kindern mit RTT, FXS oder ASS beschreiben und (b)

erste Hinweise auf spezifische Entwicklungsprofile hinsichtlich der sozio-kommunikativen Fähigkeiten liefern. Die aus dieser Arbeit gewonnenen Erkenntnisse könnten einen Beitrag zur früheren Erkennung dieser Entwicklungsstörungen leisten.

Abstract in English

A number of developmental disorders are usually detected in toddlerhood or beyond, when certain physical features become apparent, developmental milestones are not met (in time), and/or behavioural/neurofunctional deviances reach a certain threshold to allow clinical diagnosis. Deficits in the socio-communicative domain are among the core symptoms of a great proportion of these late recognised developmental disorders. However, the current knowledge on the pre-diagnostic socio-communicative development of children with such developmental disorders is still limited. This thesis aimed to shed light into the early socio-communicative development of children with late recognised developmental disorders by (i) comprehensively analysing the socio-communicative capacities of children with Rett syndrome (RTT), fragile X syndrome (FXS), or autism spectrum disorder (ASD) in their first 2 years of life, (ii) comparing these results with those of a control group of typically developing children, and (iii) providing cross-syndrome comparisons.

The analysis was based on retrospective audio-video recordings made by the parents of children with RTT (typical or preserved speech variant; n = 7), FXS (n = 9), ASD (n = 10), or typical development (TD; n = 10) when their children were between 9 and 24 months of age. The Inventory of Potential Communicative Acts (IPCA; Sigafoos, Arthur-Kelly and Butterfield, 2006) was applied to identify communicative forms and functions.

Developmental peculiarities in the socio-communicative domain of the participants with RTT, FXS, or ASD were found from the end of the first year of life onwards. In particular, participants later diagnosed with a developmental disorder had reduced gestural and (pre-)linguistic vocalisation repertoires and a limited range of communicative functions especially in terms of 'requesting an object/action/information' compared to the participants with TD. Socio-communicative capacities increased in the participants with FXS or TD throughout the observation period although those of the FXS group were lower compared to those of the TD group. Socio-communicative capacities of the participants with ASD initially increased and then seemed to decrease indicating a potential regression of communicative abilities.

The evidence of (a) early socio-communicative deviances in children with RTT, FXS, or ASD, and (b) specific socio-communicative profiles for different developmental disorders is conceptually appealing, but needs further research taking into account certain methodological difficulties. Still, our data advance the understanding of the pre-diagnostic socio-communicative development of children with RTT, FXS, or ASD, and might prove useful with respect to the earlier detection of children with late recognised developmental disorders.

1 Introduction

1.1 Developmental disorders with a late clinical manifestation

This thesis focuses on disorders manifesting in infancy, toddlerhood or (pre-)school age and are characterised by impairments in different developmental domains (e.g., speech and language, social-communication, motor, cognition; Table 1). These disorders are hereafter subsumed under the umbrella term *developmental disorders*[1]. Some of these disorders can be detected at or even prior to birth (e.g., infants with Down syndrome have a characteristic physical appearance and specific morphological characteristics leading to clinical diagnosis which is consecutively confirmed through genetic testing). There are however a number of developmental disorders that are usually detected later in development, when certain physical features become apparent, developmental milestones or border stones are not met (in time), or behavioural/neurofunctional deviances reach a certain threshold to allow clinical diagnosis. Such developmental disorders with a late clinical manifestation are for example autism spectrum disorder (ASD) or Rett syndrome (RTT; e.g., Marschik, et al., 2016; 2017). My thesis focuses on early or prodromal neurofunctional characteristics of individuals with late recognised developmental disorders (LRDDs). Besides different aetiologies, there are huge differences concerning the prevalence of these disorders ranging from 5-12/100 live births for developmental dyslexia to around 1-9/100,000 live births for rare/orphan developmental disorders such as RTT or even <1/1,000,000 live births for Pitt-Hopkins syndrome (see Table 1). Phenotypical characteristics of LRDDs range from rather specific limitations (e.g., specific learning disorder) usually allowing independent living in adulthood to severe global impairments resulting in the need of lifelong care and support (e.g., individuals with RTT). Furthermore, comorbidities of two or more developmental disorders are frequent (e.g., fragile X syndrome, FXS, and ASD; Abbeduto, McDuffie and Thurman, 2014) and single disorders are often characterised by a great phenotypical variability. There are, for example, individuals with a relatively mild phenotype of RTT who are able to speak a few words (including word combinations) and to walk independently, whereas others only have minimal communication capacities and are neither able to walk freely nor with support (e.g., Neul, et al., 2010). The differentiation between developmental disorders is often difficult as developmental disorders of different aetiologies share similar neurofunctional abnormalities. For example, a great proportion of individuals with RTT or FXS show autistic

[1] The actual versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013) and the International Statistical Classification of Diseases and Related Health Problems (ICD-10 2016; World Health Organization, 2016) partly differ in their classifications and/or inclusion criteria of these disorders. Details are provided in Chapters 1.1.1–1.1.3.

features, although sometimes only observed in certain developmental periods (Niu, et al., 2017). These overlapping abnormalities and comorbidities together with the great phenotypical variability and varying onsets of certain neurofunctional peculiarities hamper an early and reliable diagnosis of these developmental disorders.

Table 1: Selected developmental disorders with a late clinical manifestation.

Developmental disorder	**Prevalence**[1,2,3,4]	**Inheritance**[1,2]	**OMIM**
Angelman syndrome	1-9/100,000	Sporadic	105830
AD(H)D	11/100	Multigenic/multifactorial	143465*
ASD	1/68	Multigenic/multifactorial	209850*
(Mild) Canavan disease	<1/1,000,000	Autosomal recessive	271900
Coffin-Lowry syndrome	1-9/100,000	X-linked dominant	303600
Cohen syndrome	<1/1,000,000	Autosomal recessive	216550
Developmental dyslexia[5]	5-12/100	Multigenic/multifactorial	127700*
Fragile X syndrome	1-5/10,000	X-linked dominant	300624
Monosomy 22q13	<1/1,000,000	Sporadic	606232
Mowat-Wilson syndrome	<1/1,000,000	Autosomal dominant	235730
Noonan syndrome	5-10/10,000	Autosomal dominant	163950*
Pitt-Hopkins syndrome	<1/1,000,000	Autosomal dominant	610954
Prader-Willi syndrome	1-9/100,000	Sporadic	176270
Rett syndrome	1-9/100,000	X-linked dominant	312750
Smith-Magenis syndrome	1-9/100,000	Sporadic	182290
Specific language impairment/ communication disorder[5]	5-8/100	Multigenic/multifactorial	606711*
Tourette syndrome	1/360	Multigenic/multifactorial	137580
Tuberous sclerosis	1-5/10,000	Autosomal dominant	191100*

Abbreviations: AD(H)D = Attention Deficit (Hyperactivity) Disorder; ASD = autism spectrum disorder; OMIM = Online Mendelian Inheritance in Man.

[1]Orphanet – The Portal for Rare Diseases and Orphan Drugs; http://www.orpha.net/ (retrieved 30 January 2018)
[2]The Phenomizer – Clinical Diagnostics with Similarity Searches in Ontologies; http://compbio.charite.de/phenomizer/ (retrieved 30 January 2018)
[3]Centers for Disease Control and Prevention; https://www.cdc.gov/ (retrieved 30 January 2018)
[4]Genetics Home Reference; https://ghr.nlm.nih.gov/ (retrieved 30 January 2018)
[5]Bearing in mind the actual DSM-5 criteria (American Psychiatric Association, 2013)
*Multiple OMIM entries

With this thesis, I aim to contribute to an earlier detection of certain developmental disorders by describing socio-communicative capacities and potential deviances from typical socio-communicative development in the first 2 years of life of children later diagnosed with a developmental disorder. It is methodologically challenging to study the early development of children with LRDDs as these disorders are usually diagnosed in or beyond toddlerhood implying that prospective studies on the first 2 years of life are almost

impossible. However, the longitudinal investigation of younger siblings of individuals with a hereditary developmental disorder allows the prospective collection of data from individuals later diagnosed with a LRDD. So-called high-risk studies are popular in ASD research, but are problematic for investigating those developmental disorders with familial inheritance that have low prevalence rates (see Table 1). Moreover, many LRDDs have no or rare familial inheritance. For this reason, a prospective approach could not be chosen for this thesis that aimed to compare different LRDDs. A great proportion of the literature on LRDDs stems from studies applying retrospective questionnaires or interviews with parents of children with a LRDD. Although the concurrent validity of parental reports with standardised assessments was repeatedly reported to be high (e.g., Fenson, et al., 1994; Marschik, et al., 2007), the agreement between retrospective reports and prospective data was found to be relatively low (e.g., Henry, et al., 1994). Retrospective reports have certain limitations such as (1) memory bias, (2) parental awareness of the clinical diagnosis at the time of the interview/questionnaire, (3) parents are not trained to notice subtle atypicalities, (4) documentation of frequency of certain behaviours/atypicalities is impossible, (5) determining the exact onset of certain behaviours/atypicalities is difficult, (6) specific developmental aspects such as phonological development cannot be studied (e.g., Palomo, Belinchón and Ozonoff, 2006; Ozonoff, et al., 2011b; Marschik, 2014; Zhang, et al., 2017). A frequently used method that allows overcoming some of these limitations (especially parental recall and potential bias) is the retrospective analysis of family videos. Retrospective video analysis allows gathering detailed information about different developmental aspects long before a developmental disorder was formally diagnosed. Still, there are some limitations inherent in this methodological approach such as (1) unbalanced video material concerning content, audio and video quality, duration, age of individuals, etc., (2) parents may tend to turn off the camera in certain situations, e.g., when the child is crying, (3) absence of opportunities for certain behaviours, (4) behaviours may be present at a certain age but filmed only at a later age or not at all, (5) varying details on symptom severity and differing diagnostic reports (e.g., Palomo, Belinchón and Ozonoff, 2006; Marschik and Einspieler, 2011; Ozonoff, et al., 2011b). Despite its limitations, retrospective video analysis is certainly the ‘method of choice’ for this thesis as it proved to be a powerful approach for the detailed description of behavioural features, developmental trajectories of individuals with LRDDs as well as the improvement or regression of certain functions (e.g., Saint-Georges, et al., 2010; Marschik and Einspieler, 2011).

Since 2010, I have been a member of the Research Unit iDN (interdisciplinary Developmental Neuroscience; www.idn-research.org). Our research database, the ‘Graz University Audiovisual Research Database for the Interdisciplinary Analysis of

Neurodevelopment' (GUARDIAN; Pokorny, et al., 2016; see Chapter 2), has been built up over the last two decades and contains home videos of the first 2 years of life of individuals with various LRDDs. Due to sufficient quantity and quality of data for the analysis of the early socio-communicative development between 9 and 24 months of age, my thesis focuses on children with RTT, FXS, or ASD, and their typically developing (TD) peers as control group.

1.1.1 Rett syndrome

Rett syndrome (RTT; OMIM 312750) is one of the most common known causes of profound intellectual disability in females (e.g., Verpelli and Sala, 2012). In the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994), RTT was classified as a neurodevelopmental disorder (NDD) assigned to the autism spectrum (i.e., Rett's Disorder, 299.80). The current fifth version of the DSM (DSM-5; American Psychiatric Association, 2013) excludes RTT and other genetic disorders from its classification scheme. Despite the exclusion of genetic disorders from the DSM-5, the classification system provides clinicians with the opportunity to attribute mental disorders to several aspects such as genetic conditions or specify the severity of the disorder or age of onset. For example, the specifier *'associated with Rett syndrome'* (American Psychiatric Association, 2013, p.51) is chosen to describe an individual's medical condition in more detail by providing a factor that may have played a role in the aetiology of a certain mental disorder such as ASD. However, an individual with RTT who does not meet criteria of ASD or any other DSM-5-disorder will not receive a DSM-5 diagnosis. The current version of the ICD (ICD-10; World Health Organization, 2016) classifies RTT (i.e., Rett's syndrome, F84.2) as a pervasive developmental disorder (F84).

Rett syndrome has a prevalence of approximately 1 in 10,000 live female births (Hagberg, 1985; Laurvick, et al., 2006). Although RTT affects almost exclusively females, there were a few male cases reported in the literature (Christen and Hanefeld, 1995; Budden, Dorsey and Steiner, 2005; Tokaji, et al., 2018). Familial recurrence in RTT is very rare, comprising only around 1% of all reported cases (Miyamoto, et al., 1997; Schanen, et al., 1997). The clinical picture of RTT was first described in 1966 by the Austrian paediatrician Andreas Rett in the Austrian Journal *Wiener Medizinische Wochenschrift* (Rett, 1966). Seventeen years after Rett's report on 22 patients, Bengt Hagberg, et al. (1983) described 35 females who were characterised by the loss of speech and purposeful hand use together with hand stereotypies, followed by a phase of stabilisation. In their article, Hagberg, et al. referred to the work of Andreas Rett and introduced the term *Rett's*

syndrome[2]. More recent descriptions of the clinical profile of RTT still comprise a period of regression (i.e., loss of already acquired functions), which sets in between 6 and 18 months of age, followed by a phase of stabilisation or partial recovery of lost functions (Neul, et al., 2010; 2014). In the earlier descriptions of RTT, the pre-regressional phase was assumed to be apparently normal (e.g., Burd and Gascon, 1988). By now, however, there are strong doubts about an inconspicuous early developmental phase as evidence for atypicalities/deviances in different developmental domains already in the first months of life increased in the last two decades (e.g., Tams-Little and Holdgrafer, 1996; Leonard and Bower, 1998; Burford, Kerr and Macleod, 2003; Marschik, et al., 2013a; Einspieler, Freilinger and Marschik, 2016). For example, although individuals with RTT were reported to achieve certain motor and language milestones within the normal age bands or just slightly delayed, various deviances and peculiarities were observed when retrospectively analysing video material taken prior to regression (e.g., Marschik, et al., 2014a; Einspieler, Freilinger and Marschik, 2016). Concerning the motor domain, for example, endogenously generated spontaneous movements (i.e., general movements) in the first months of life were observed to be abnormal and behavioural abnormalities such as postural stiffness, tremor, tongue protrusion, hand stereotypies, and abnormal blinking were reported for a number of individuals with RTT already in the pre-regressional period (e.g., Einspieler, Kerr and Prechtl, 2005a; 2005b; Marschik, et al., 2009). Details on the early speech-language and socio-communicative development of individuals later diagnosed with RTT are outlined in Chapter 1.3.1.

As mentioned in Chapter 1, there is a great variability in manifestations and clinical severity in RTT. RTT can be divided in two main clinical presentations: typical and atypical RTT, or the so-called RTT variants (Neul, et al., 2010; details on differential diagnosis are provided below). A recent study by Tarquinio, et al. (2015) revealed a mean age of diagnosis of 2.7 years (interquartile range 2.0–4.1) for typical RTT (919 individuals included in the study) and 3.8 years (interquartile range 2.3–6.9) for atypical RTT (166 individuals included in the study). The clinical diagnosis of typical and atypical RTT is based on a number of consensus criteria (current criteria: Neul, et al., 2010).

For the clinical diagnosis of typical RTT the four main clinical consensus criteria need to be met (Neul, et al., 2010): (1) partial or complete loss of already acquired purposeful hand skills, (2) partial or complete loss of already acquired spoken language, (3) gait abnormalities (dyspraxic or absence of gait), and (4) stereotypic hand movements

[2] The scientific community does not use the term Rett's disorder or syndrome anymore; also, previously used abbreviations such as RS are outdated. The international consensus suggests using Rett syndrome and RTT as abbreviation.

(repetitive hand washing-like movements, clapping movements, hand-to-mouth stereotypies). Exclusion criteria for typical RTT are peri- or postnatal brain injury, neurometabolic diseases, severe infections that cause neurological deficits, and severe developmental deviations/deficits in the first 6 months of life. There are a number of supportive criteria that are commonly observed in individuals with typical RTT, but that are not required for diagnosis: (1) breathing disturbances and (2) bruxism when awake, (3) sleep problems, (4) abnormal muscle tone, (5) vasomotor changes (blue hands and feet), (6) scoliosis/kyphosis, (7) growth retardation, (8) small cold hands and feet, (9) inappropriate laughing/screaming spells, (10) reduced response to pain, and (11) intense eye communication (Neul, et al., 2010).

For the diagnosis of atypical RTT, two of the four main criteria need to be met. In addition, the diagnosis of atypical RTT requires the presence of – at least – five out of the eleven above-mentioned supportive criteria (Neul, et al., 2010). The three atypical RTT variants – the preserved speech variant (PSV), the early seizure variant, and the congenital variant – differ according to their age of symptom manifestation and clinical severity (Neul, et al., 2010; Pini, et al., 2016). The PSV (also referred to as Zappella variant; Zappella, 1992; Renieri, et al., 2009) is a relatively mild variant of RTT associated with 'some speech-language capacities' (i.e., use of a number of single words or even word combinations/phrases), relatively better functional hand use, milder intellectual disability, relatively milder scoliosis and kyphosis, and usually normal head circumferences, height and weight; epilepsy is rarely seen in this variant. In contrast, the early seizure variant (also referred to as Hanefeld variant; Hanefeld, 1985; Artuso, et al., 2010) is a relatively severe atypical RTT variant that is characterised by a seizure onset already in the first 5 months of age and before regression accompanied by severe hypotonia. The congenital variant (also referred to as Rolando variant; Rolando, 1985) is characterised by a severe early abnormal development already in the first 6 months of life, severe postnatal microcephaly before 4 months of age, an earlier regression, and breathing abnormalities when awake to name but a few.

Despite the often severe clinical profile, it is quite common for individuals with typical or atypical RTT to survive into middle age (Kirby, et al., 2010). Tarquinio, et al. (2015) recently described that more than 70% of the 1189 individuals with RTT included in their study reached age 45. Nielsen, Ravn and Schwartz (2001) reported about a 77-year-old woman with RTT.

From the first description of RTT it took more than 30 years to detect the main genetic cause of RTT, mutations in the *MECP2* gene on the long arm of the X chromosome

(Xq28) encoding methyl-CpG-binding protein 2 (Amir, et al., 1999). These mutations usually arise de novo in the paternal germline and can be found in around 97% of individuals with typical RTT and in around 86% of individuals with atypical RTT (e.g., Zoghbi, 2005; Williamson and Christodoulou, 2006; Neul, et al., 2010; 2014; Leonard, Cobb and Downs, 2017). The protein MeCP2 is expressed in tissues throughout the body and to a great extent in the brain (Gonzales and LaSalle, 2017). MeCP2 selectively binds to methylated CpG dinucleotides in deoxyribonucleic acid (DNA) promotors and is thereby involved in the regulation of transcription (Amir, et al., 1999; Chahrour and Zoghbi, 2007). Mutations in the *MECP2* gene are assumed to cause partial or complete functional loss of MeCP2 which affects brain development, starting already in embryonic development (Amir, et al., 1999; Shahbazian, et al., 2002; Jung, et al., 2003; Johnston, Blue and Naidu, 2005; Kaufmann, Johnston and Blue, 2005; Gonzales and LaSalle, 2010; 2017). The effects of a lack of MeCP2 become evident for instance in that the brains of individuals with RTT are typically undersized and underweighted when compared to the brains of typically developing controls (Kaufmann, et al., 2017a). Generalised volumetric grey matter reductions in children with RTT with *MECP2* mutations were revealed by structural magnetic resonance imaging (MRI; Kaufmann, Pearlson and Naidu, 1998) when compared to controls. Carter, et al. (2008) found the most significant reduction of grey matter in their participants with RTT in the following brain regions: “right cingulate and middle occipital gyri (Brodmann areas 32 and 19/39, respectively), bilateral posterior dorsal parietal lobe (Brodmann area 7), left middle frontal gyrus (Brodmann area 10), and bilateral pre- and post-central gyri (Brodmann areas 4/6 and 5/7, respectively)“ (Carter, et al., 2008, p.6). The authors stated that in their study population a clinically more severe phenotype of RTT was associated with more pronounced grey matter volume reductions in all four lobes (although only to a small extent in the occipital lobe). They moreover found relatively mild, diffuse reductions in cortical white matter in females with RTT when compared to typically developing controls (Carter, et al., 2008). Also in adult MeCP2-deficient mice, neuronal abnormalities were found: Different brain regions such as the hippocampus, the substantia nigra, and the locus coeruleus were found to contain atypically small neurons displaying increased packing density (e.g., Zhang, et al., 2010a; Panayotis, et al., 2011). In addition to decreases in neuronal soma, abnormalities/reductions in dendritic arborisation (Kishi and Macklis, 2004; Armstrong, 2005; Ballas, et al., 2009; Belichenko, et al., 2009) and spine density (Belichenko, et al., 1994; 2009) were observed. Interestingly, and in line with the assumption that the loss of MeCP2 function hinders normal neuronal maturation (Kaufmann, et al., 2017a), a relative over-representation of juvenile neurons has been found in different brain regions in MeCP2-deficient mice (e.g., Zhang, et al., 2010a; Panayotis, et al., 2011) and patients with RTT (Ronnett, et al., 2003). The above-described neuronal abnormalities in MeCP2-deficient

mice and individuals with RTT highlight the importance of MeCP2 in synaptic development (e.g., Kaufmann, et al., 2017a). Two forms of synaptic plasticity that are important for learning, namely long-term potentiation (LTP) and long-term depression (LTD; Bear and Malenka, 1994), were found to be deficient in MeCP2-deficient mice who show a RTT-like phenotype (Moretti, et al., 2006; Lonetti, et al., 2010). These deficits were already observed when the very first functional impairments started to manifest (Moretti, et al., 2006; Lonetti, et al., 2010). A lack of MeCP2 was also found to impact neural network activity (e.g., Zhang, et al., 2008). Neural networks of MeCP2-deficient mice were found to be hyperexcitable, resulting in atypical activities in the electroencephalogram (EEG) including epileptiform-like discharge activities in the hippocampus and somatosensory cortex (Zhang, et al., 2008; D'Cruz, et al., 2010). A longitudinal study on female MeCP2-deficient mice recently found that epileptiform discharge activities were increased in frequency and duration with increasing age (Wither, et al., 2018). Also epileptiform activity in patients with RTT was observed to increase during the regression phase (Glaze, 2005).

More than 800 different *MECP2* mutations (i.e., missense, nonsense, frameshift, in-frame insertions, in-frame deletions, large deletions encompassing whole exons or even the entire gene) have been identified so far (Rett Syndrome Database, RettBASE; Christodoulou, et al., 2003). The eight most common mutations in *MECP2* are the four missense mutations[3] R106W, R133C, T158M and R306C and the four nonsense mutations[4] R168X, R255X, R270X, R294X (Neul, et al., 2008). Type and location of the mutations as well as the X inactivation pattern are discussed to influence the RTT phenotype (Huppke, et al., 2002). Individuals with R133C, R306C, or R294X mutations were often found to have better functional abilities (Leonard, et al., 2003; Colvin, et al., 2004; Charman, et al., 2005; Schanen, et al., 2004; Bebbington, et al., 2008; Neul, et al., 2014), whereas individuals with T158M, R168X, R270X, or R255X mutations generally present with a more severe phenotype (Schanen, et al., 2004; Charman, et al., 2005; Bebbington, et al., 2008; Neul, et al., 2008). A significantly reduced life expectancy was reported for individuals with the nonsense mutation R270X compared to individuals with any of the other seven most frequent mutations (Jian, et al., 2005).

Although *MECP2* mutations were found in the vast majority of individuals with RTT, some individuals with a RTT diagnosis – especially those diagnosed with a RTT variant – were found to have different mutations (e.g., Sajan, et al., 2017). For example, some of the individuals with the early seizure variant of RTT have mutations in the Cyclin-dependent

[3] Missense mutations are point mutations leading to the substitution of a single amino acid in a protein.
[4] Nonsense mutations are point mutations changing a codon encoding an amino acid to a stop codon.

kinase-like 5 gene *(CDKL5*; Scala, et al., 2005; Bahi-Buisson, et al., 2008; Artuso, et al., 2010) and individuals with the congenital variant of RTT were found to have mutations in the forkhead box G1 gene (*FOXG1*; Ariani, et al., 2008). Moreover, there are individuals with *MECP2* mutations without clinical signs (Suter, et al., 2014). Due to this genetic heterogeneity, RTT is still a clinical diagnosis relying on characteristic functional abnormalities in different developmental domains that usually become evident in toddlerhood.

1.1.2 Fragile X syndrome

Fragile X syndrome (FXS; also known as Martin-Bell syndrome; OMIM 300624) is the second most common cause of intellectual disability, the leading cause of inherited intellectual disability, and the most common monogenic cause of ASD (e.g., Hagerman and Hagerman, 2002; Bagni, et al., 2012; Hunter, et al., 2014; Rajaratnam, et al., 2017). Similar to RTT, FXS is not included in the DSM-5 given its widely recognised genetic origin (American Psychiatric Association, 2013). However, a great proportion of individuals with FXS has comorbidities with other developmental disorders that are listed in the DSM-5. These individuals receive DSM-5 diagnoses[5] such as ASD (around 50% of males and 20% of females with FXS have comorbid ASD; Kaufmann, et al., 2017b), anxiety disorders (around 86% of males and 77% of females with FXS; Cordeiro, et al., 2011), or Attention Deficit (Hyperactivity) Disorder (AD(H)D; 54-59%[6] of children with FXS; Sullivan, et al., 2006). In the ICD-10 (World Health Organization, 2016), fragile X syndrome (i.e., Q99.2) belongs to the category 'other chromosome abnormalities, not elsewhere classified' (Q99).

FXS was recently estimated to occur in 1 of 5,000 males and in 1 of 4,000 to 8,000 females in the general population (Hagerman, et al., 2017), but prevalence values vary considerably in the literature. For example, Hunter, et al. (2014) found relatively lower prevalence rates of 1 in 7,143 males and 1 in 11,111 females in their meta-analysis and O'Byrne, et al. (2017) provided prevalence values of approximately 1 in 10,600 males and 1 in 43,000 females for the island of Ireland (i.e., Republic of Ireland and Northern Ireland combined).

In their study of 1992, Partington, et al. found that individuals of their FXS population (348 males and 433 females) died on average 12 years earlier than the general population. Life expectancy in FXS is however not shortened in each individual with FXS; Sabaratnam

[5] For details on the specifier system introduced in the DSM-5 please see Chapter 1.1.
[6] It should be noted that a more recent study reported much lower rates of 9–12% for comorbid AD(H)D in a smaller sample and at a younger age (Grefer, et al., 2016).

(2000), for example, reported about an 87-year-old male with FXS. A more recent study followed 34 males with FXS for 20 years (Arvio, 2016). During the follow-up period, 10 males of the initial cohort died; three were younger than 40 years at death and the oldest individual died with 77 years (Arvio, 2016).

A large proportion of individuals with FXS has characteristic physical features such as a long narrow face, a broad forehead, a prominent jaw, reduced facial depth, large ears, hyperextensible joints, macrocephaly, and macroorchidism in males (Hagerman and Hagerman, 2002; Heulens, et al., 2013). These features are typically very subtle in infancy and toddlerhood, but become more distinctive in older children and adolescents (e.g., Lachiewicz, Dawson and Spiridigliozzi, 2000). Therefore, a developmental disorder is typically not suspected until certain developmental atypicalities become evident. A great proportion of individuals with FXS has mild to severe intellectual disability. In addition, individuals with FXS often show atypical neurobehavioural features including autistic-like features such as avoidance of eye contact and unease when cuddled, attention deficits, hyperactivity, sensory hypersensitivity, hand biting, tendency to aggressive behaviour, self-injurious behaviours, repetitive behaviours including hand stereotypies, poor motor control, and perseverative speech (Bailey, Hatton and Skinner, 1998; Hagerman, 2002; Hessl, et al., 2006; Boyle and Kaufmann, 2010; Hardiman and McGill, 2018).

One of the first alarming signs for parents and clinicians, sometimes reported already for the first year of life, is a delay in different developmental domains (e.g., motor development, speech-language acquisition; Bailey, Hatton and Skinner, 1998; Kau, Meyer and Kaufmann, 2002; Mirrett, et al., 2004; Baranek, et al., 2005; Finestack, Richmond and Abbeduto, 2009; Roberts, et al., 2009; Zingerevich, et al., 2009; Hinton, et al., 2013; Kover, et al., 2015; Zhang, et al., 2017). Other behavioural peculiarities observed already from the end of the first year of life onwards are hypo- or hyperresponsiveness (Baranek, et al., 2008), atypical visual attention (Scerif, et al., 2005; Farzin, Rivera and Whitney, 2011; Roberts, et al., 2012), hypotonia (Baranek, et al., 2005), repetitive use of objects, repetitive movements such as hand flapping or body rocking, and unusual (finger) posturing (Baranek, et al., 2005; Roberts, et al., 2016; Hogan, et al., 2017; Zhang, et al., 2018a). Details on the speech-language and socio-communicative development in the first 2 years of life of individuals later diagnosed with FXS are outlined in Chapter 1.3.2. Given that these peculiarities are often rather subtle in early development and are not unique to individuals with FXS, an early diagnosis of FXS is hampered. Indeed, FXS is diagnosed in males on average with 35 to 37 months and in females with 41.6 months of age (Bailey, et al., 2009). A recent study by Gabis, et al. (2018) investigated 117 children and adults with FXS (25 females) and found a mean age of diagnosis of 31.9 months for those participants born

since 2007 and a mean age of diagnosis of 69.5 months for those born earlier. They furthermore reported that less than 20% of the families received a diagnosis of FXS within one year after seeking medical attention (Gabis et al. 2018).

James Purdon Martin and Julia Bell first described FXS in 1943 as an inherited form of intellectual disability that they believed to be linked to the X chromosome. Martin and Bell (1943) reported about a family including eleven males of two generations with intellectual disability born to mothers with normal intelligence. Twenty-six years later Herbert Lubs (1969) found a characteristic fragile site on the long arm of the X chromosome. Richards, Sylvester and Brooker (1981) re-examined some members of the family described by Martin and Bell and confirmed a fragile X chromosome in five of them. In 1991, Verkerk, et al. identified and sequenced the *Fragile X Mental Retardation-1* (*FMR1*) gene on the long arm of the X chromosome and associated it with the clinical picture of FXS. Most individuals diagnosed with FXS have an expansion of a CGG (cysteine-guanine-guanine) trinucleotide repeat (>200 CGG repeats) in the first exon of the *FMR1* gene (Verkerk, et al., 1991; Ciaccio, et al., 2017; Rajaratnam, et al., 2017; Mila, et al., 2018). Typically developing individuals have 5–40 CGG repeats whereas in *FMR1* premutation carriers[7] around 55–200 CGG repeats are identified (Ciaccio, et al., 2017; Rajaratnam, et al., 2017). A CGG expansion is passed on either from a carrier mother or from a carrier father (e.g., Kaufmann, 2010). If the mother is the carrier, half of her offspring will inherit the mutation (she either passes on her affected or her unaffected X chromosome). If the father is the carrier, all his female children, but none of his male children will inherit the mutation (his X chromosome is affected, his Y chromosome is intact). The characteristic CGG expansion in individuals with FXS leads to an atypical methylation in the *FMR1* gene and as a consequence to an absent or greatly diminished expression of the fragile X mental retardation protein (FMRP; e.g., Sears and Broadie, 2018). Full mutations rarely occur without DNA methylation; the respective individuals were observed to have normal intelligence (Smeets, et al., 1995). Interestingly, during the first few weeks of gestation the DNA of an embryo with full mutation is unmethylated and gene expression is active (Eiges, et al., 2007). Methylation and gene silencing typically occur at around 11 weeks of gestation (Willemsen, et al., 2002). Other mutational mechanisms such as deletions of *FMR1* gene (ranging from a single nucleotide to several Mb), however, also result in a lower expression of FMRP and can therefore cause FXS (Coffee, et al., 2008).

Several studies found a correlation between the magnitude of FMRP deficit and the severity of the physical phenotype of FXS and the degree of intellectual disability (Kaufmann

[7]A premutation occurs in 1 of 855 males and 1 of 291 females (Hunter, et al., 2014).

and Reiss, 1999; Tassone, et al., 1999; Loesch, Huggins and Hagerman, 2004). Females with FXS have an additional unaffected X chromosome that is able to produce FMRP; their phenotype is usually milder, characterised by milder cognitive and behavioural problems compared to their male peers (e.g., Hagerman, et al., 2009). Learning disabilities are quite common for females with FXS, but only 25% of females with FXS have an intelligence quotient (IQ) below 70 (de Vries, et al., 1996).

The majority of premutation carriers has FMRP levels within the normal ranges, but some premutation carriers – especially those with a higher number of CGG repeats – were found to have a reduced expression of FMRP compared to individuals with a normal CGG repeat length (Tassone, et al., 2000a; Tassone and Hagerman, 2003; Ludwig, et al., 2014). More important, a premutation results in an enhanced production of *FMR1* messenger ribonucleic acids (mRNAs; Tassone, et al., 2000b; Kenneson, et al., 2001; Tassone, et al., 2007) which may cause neuronal toxicity. These changes manifest in specific clinical features for premutation carriers such as fragile X-associated tremor/ataxia syndrome (FXTAS; occurring in around 40% of males and 16% of females with the premutation; Jacquemont, et al., 2004; Rodriguez-Revenga, et al., 2009) or fragile X-associated primary ovarian insufficiency (FXPOI; occurring in around 20% of females with the premutation; Sullivan, et al., 2005). Premutation carriers were moreover found to have mild deficits in executive functions, working memory, visuospatial processing, mathematical reasoning as well as a higher probability for depression or anxiety (e.g., Hippolyte, et al., 2014; Shelton, et al., 2016; Jiraanont, et al., 2017; Shelton, Cornish and Fielding, 2017).

Although FMRP is present in almost all cell types, it is particularly strongly expressed in neurons (Feng, et al., 1997). FMRP is an RNA-binding protein that is important for the activity-dependent transportation of mRNAs to dendrites and for the regulation of activity-dependent translation of a large number of mRNAs (Bassell and Warren, 2008; Napoli, et al., 2008; Pfeiffer and Huber, 2009; Sidorov, Auerbach and Bear, 2013). These mRNAs encode proteins that play a role in synaptic plasticity and dendritic maturation (e.g., Kindler and Kreienkamp, 2012). An FMRP loss was found to lead to a deficit in activity-dependent mRNA transport in neurons of *FMR1* knockout mice (Dictenberg, et al., 2008; Kao, et al., 2010) and an overexpression[8] of numerous proteins, which was suggested to alter neuronal structure and function (e.g., Bassell and Warren, 2008; Darnell, et al., 2011; Khayachi, et al., 2018). *FMR1* knockout mice, *FMR1* knockout flies, and individuals with FXS were found to have abnormalities in dendritic spine morphology (e.g., they were longer, thinner, more tortuous compared to those of controls; they appeared immature; dendritic spine density

[8] It has to be noted, however, that increased protein synthesis levels were not found in all individuals with FXS (Jacquemont, et al., 2018).

was different; Irwin, Galvez and Greenough, 2000; Kaufmann and Moser, 2000; Irwin, et al., 2001; Bassell and Warren, 2008; He and Portera-Cailliau, 2013; Berman, et al., 2014). Deficits in synaptic plasticity were observed to coincide with these morphological abnormalities: In *FMR1* knockout mice group 1 metabotropic glutamate receptor dependent long-term depression (mGluR-LTD) is enhanced in the hippocampus (Huber, et al., 2002; Till, et al., 2015), whereas hippocampal LTP is discussed controversially: Some studies found a reduction of LTP in the hippocampus (e.g., Hu, et al., 2008; Tian, et al., 2017), whereas others did not (e.g., Godfraind, et al., 1996; Li, et al., 2002). Altered LTD/LTP were also found in other brain areas including the anterior cingulate cortex (Koga, et al., 2015), the amygdala (Suvrathan and Chattarji, 2011), and the cerebellum (Koekkoek, et al., 2005). Neuroimaging studies revealed increased grey matter volumes in caudate nucleus, fusiform gyrus and thalamus as well as decreased grey matter volumes in cerebellum, amygdala, hypothalamus, superior temporal gyrus, prefrontal cortices, and insula in individuals with FXS (e.g., Lee, et al., 2007; Gothelf, et al., 2008; Hoeft, et al., 2008; Lightbody and Reiss, 2009; Bray, et al., 2011; Cohen, et al., 2011). There are heterogeneous findings concerning the hippocampal volumes in individuals with FXS (Lightbody and Reiss, 2009). Interestingly, longitudinal and cross-sectional studies on individuals with FXS revealed different volumes for some brain regions throughout development (e.g., Hazlett, et al., 2012) whereas for other brain regions such as the orbital gyri, prefrontal cortex gyri, amygdala or thalamus differences emerge at some point in development (Hoeft, et al., 2008; 2010; Bray et al. 2011). Aberrant white matter volumes in individuals with FXS were found in prefrontal and temporal brain regions (Hoeft, et al., 2008; Hazlett, et al., 2012). Individuals with FXS have altered white matter microstructure in fronto-striatal pathways, in parietal sensory-motor tracts (Barnea-Goraly, et al., 2003) as well as in the left cingulum hippocampus and in the inferior longitudinal, inferior fronto-occipital and uncinate fasciculi (Barnea-Goraly, et al., 2003; Green, et al., 2015; Hall, Dougherty and Reiss, 2016). A recent longitudinal diffusion tensor imaging (DTI) study (Swanson, et al., 2018) revealed alterations in white matter fibre pathways in infants with FXS already from 6 months of age onwards.

Individuals with FXS were not only found to have structural peculiarities in the brain, but also atypical activation patterns in response to different tasks. For example, individuals with FXS differed from controls concerning their activation in different brain regions (e.g., fusiform gyrus, superior temporal sulcus) during face and gaze processing tasks (e.g., Garrett, et al., 2004; Watson, et al., 2008; Bruno, et al., 2014). Furthermore, Menon, et al. (2000) revealed a correlation between FMRP levels and activation in the right inferior and middle frontal gyrus, left middle frontal gyrus, and right supramarginal gyrus when performing a working memory task. Similar findings were achieved by Kwon, et al. (2001).

Individuals with FXS also showed different activation patterns in attention tasks (e.g., Cornish, et al., 2004; Van der Molen, et al., 2012). For example, Cornish, et al. (2004) revealed significantly greater activation in the cingulate cortex as well as in the left and right ventral prefrontal areas in females with FXS compared to controls.

1.1.3 Autism spectrum disorder

Autism spectrum disorder (ASD; OMIM 209850) is characterised through persistent socio-communicative deficits and restricted, repetitive patterns of behaviour, interests, or activities (American Psychiatric Association, 2013). The DSM-5 (American Psychiatric Association, 2013) classifies ASD (i.e., 299.00) as a neurodevelopmental disorder. The ICD-10 (World Health Organization, 2016) assigns ASD to the category of pervasive developmental disorders (F84; F84.0: Autistic disorder; F84.5: Asperger's syndrome; F84.9: Pervasive developmental disorder, unspecified/Atypical autism).

A number of comorbidities were identified in individuals with ASD, such as anxiety disorder (e.g., Zaboski and Storch, 2018: in around 40% of individuals with ASD), ADHD (e.g., Gordon-Lipkin, et al., 2018: comorbidity rate of 45%), developmental coordination disorder (e.g., Kopp, Beckung and Gillberg, 2010: in 80% of females with ASD in preschool age and in 25% of females with ASD in school age), or depressive disorders (e.g., Hudson, Hall and Harkness, 2018: affecting around 14%). As already mentioned in Chapters 1.1.1 and 1.1.2, ASD is also diagnosed in a great proportion of individuals with genetic disorders such as RTT and FXS (cf. specifier *'associated with Rett syndrome'*; American Psychiatric Association, 2013, p.51).

Prevalence rates for ASD vary considerably throughout the literature and have considerably increased from the earliest reports from the 1960s and 1970s until now (Fombonne, 2005; Elsabbagh, et al., 2012a; Lai, Lombardo and Baron-Cohen, 2014; Fombonne, 2018). For the USA, Baio, et al. (2018) recently reported an average prevalence of 16.8 per 1,000 children aged 8 years, ranging from 13.1 per 1,000 children in Arkansas to 29.3 per 1,000 children in New Jersey. The authors found that ASD was more common in boys (26.6 per 1,000) than in girls (6.6 per 1,000). A lower prevalence rate of 0.9 per 1,000 children was found for India (Raina, et al., 2015). Taylor, Jick and Maclaughlin (2013) reported ASD prevalence rates of 3.8 per 1,000 boys and 0.8 per 1,000 girls for the UK. Compared to prevalence rates of up to 3% in the general population, younger siblings of children with ASD have an increased risk for ASD. The recurrence risk for siblings born after a child diagnosed with ASD was found to range between 6.9% and 18.7% (e.g.,

Ozonoff, et al., 2011a; Grønborg, Schendel and Parner, 2013; Risch, et al., 2014; Sandin, et al., 2014).

A population-based cohort study revealed a shorter life expectancy in individuals with ASD compared to the general population; individuals with ASD were found to die on average 16 years earlier than individuals in the control group (Hirvikoski, et al., 2016). The authors found that individuals in the high-functioning ASD group had an increased risk to commit suicide. A similar trend for ASD in general was also proposed by several other studies (e.g., Chen, et al., 2017; Zahid and Upthegrove, 2017).

Pioneer work on ASD was done by the Austro-Hungarian psychiatrist Leo Kanner (1943) who migrated to the USA in the 1920s and by the Austrian paediatrician Hans Asperger (1944). Recently Van Drenth (2018) identified another pioneer, the Dutch researcher Ida Frye, who described a case with the clinical picture of ASD already in the late 1930s[9]. Perhaps the first description of the clinical picture of (high-functioning) ASD, however, stems from the Soviet researcher Grunya Efimovna Sukhareva in the year 1926 (Ssucharewa and Wolff, 1996; Posar and Visconti, 2017). The first systematic descriptions of a number of cases with ASD (Kanner, 1943; Asperger, 1944) outlined deficits in interaction with caregivers, avoidance of eye contact, deviances/delays in speech-language acquisition, learning difficulties, deficits in attention, being afraid of daily noises such as vacuum cleaners, repetitive movements and vocalisations, insistence on sameness, clumsiness in gait, and gross motor performances. Seventy-five years later these behavioural and developmental peculiarities are still among the most frequently described features of ASD and have been intensively studied in children, adolescents, and adults on the spectrum (e.g., Bölte, 2009; American Psychiatric Association, 2013; Lai, Lombardo and Baron-Cohen, 2014; Fakhoury, 2015; Lim, et al., 2017; Masi, et al., 2017).

In the last two decades the number of studies focusing on infants, toddlers, and preschool children (later diagnosed) with ASD considerably increased (e.g., Bölte, et al., 2016). Especially high-risk studies (i.e., prospective studies focusing on the younger siblings of children diagnosed with ASD) and studies applying retrospective video analyses searched for peculiarities in various developmental domains already in the first 2 years of life (for overviews please see Zwaigenbaum, Bryson and Garon, 2013; Sacrey, Bennett and Zwaigenbaum, 2015a). For example, motor abnormalities (i.e., abnormal general movements and/or lower optimality scores in general movement assessment) in the first 5 months of life were found in a considerable proportion of individuals later diagnosed with

[9] The documentation of this case is to be found in the Annual Reports on the years 1937–1938 and 1939–1940 of the Paedological Institute in Nijmegen as well as in Frye's dissertation (1968).

ASD (Phagava, et al., 2008; Einspieler, et al., 2014a; Zappella, et al., 2015). Individuals with ASD were found to have delays in motor development (e.g., Bryson, et al., 2007; Ozonoff, et al., 2008a; Bhat, Galloway and Landa, 2012; Arabameri and Sotoodeh, 2015). Moreover, a number of prospective studies reported significantly more repetitive behaviours such as repetitive arm waving in infants and toddlers with ASD than in control groups (e.g., Loh, et al., 2007; Watt, et al., 2008; Matson, Dempsey and Fodstad, 2009; Elison, et al., 2014; Stronach and Wetherby, 2014; Wolff, et al., 2014; Schertz, et al., 2016). However, other studies – based on retrospective video analyses – did not find differences in terms of repetitive behaviours between infants with ASD and typically developing infants (Werner, et al., 2000; Werner and Dawson, 2005), or between infants with ASD and infants with developmental delay (Baranek, 1999; Osterling, Dawson and Munson, 2002). Some studies described unusual/asymmetric posturing (e.g., head lag) for infants and toddlers with ASD (e.g., Adrien, et al., 1993; Teitelbaum, et al., 1998; Baranek, 1999; Esposito, et al., 2009; Flanagan, et al., 2012). Furthermore, stereotypic or atypical use of objects/object play was observed from the end of the first year of life onwards (e.g., Bryson, et al., 2007; Poon, et al., 2012). Bryson, et al. (2007) revealed a severe decrease in the IQ between 12 and 24 or 36 months of age in a subgroup of individuals with ASD: Some individuals with an average/near average IQ at 12 months were found to have severe cognitive impairment 1 or 2 years later. Furthermore, already young toddlers with ASD were found to have atypical eye movement behaviours and deficits in visual attention (for an overview please see Little, 2018). For example, studies investigating the disengagement from a central stimulus in order to fixate a peripheral one revealed longer disengagement latencies in children later diagnosed with ASD from 9 months of age onwards (Elsabbagh, et al., 2009; 2013). Hendry, et al. (2018) recently suggested prolonged attention to visual stimuli to be a potential early marker for ASD. Another recent study by Nyström, et al. (2018) revealed an enhanced pupillary light reflex in 9–10 months old infants later diagnosed with ASD.

A pattern not mentioned in the earliest descriptions of ASD is regression (i.e., loss) of previously acquired skills that occurs in a number of children with ASD (for early reports on regression in ASD please see Kurita, 1985; Hoshino, et al., 1987). Parr, et al. (2011) reported a regression before 36 months of age in 23.9% of their participants with ASD. Barger, Campbell and McDonough (2013) revealed in their meta-analysis an overall prevalence rate for regression of 32.1%. Ozonoff, et al. (2018) recently suggested that regression might even occur in the majority of individuals with ASD. Regression especially affects the speech-language and socio-communicative domains (e.g., Lord, Shulman and DiLavore, 2004; Luyster, et al., 2005; Ozonoff, et al., 2008b; Brignell, et al., 2017). Details

on the speech-language and socio-communicative development in the first 2 years of life of individuals later diagnosed with ASD are outlined in Chapter 1.3.3.

Due to the above-mentioned early deviances/delays, it may not be surprising that many parents express first concerns about their child's development already in the first or second year of life (e.g., Baghdadli, et al., 2003; Chawarska, et al., 2007; Sacrey, et al., 2015b; Karp, et al., 2017). Still, ASD is typically diagnosed much later (for overviews and discussions please see Rogers, 2000; Zwaigenbaum and Penner, 2018). For example, Baio, et al. (2018) recently stated that in their study population the median age of earliest known ASD diagnosis was 52 months (ranging from 40 months in North Carolina to 59 months in Arkansas). A recent parent survey study (Sicherman, et al., 2018) found a median age of ASD diagnosis of 33 months (mean age was 40 months). Both studies found relatively higher diagnosis ages for Asperger's syndrome (Baio, et al., 2018; Sicherman, et al., 2018).

In the last decades, a number of studies revealed a relatively greater appearance of (minor) morphological deviances in children with ASD than in typically developing children (e.g., Hammond, et al., 2008; Ozgen, et al., 2010; 2011; 2013). Ozgen, et al. (2013) found that asymmetry of the face, multiple hair whorls, and a prominent forehead significantly differentiated children with ASD from the control group. It has been indicated that certain genes potentially play a role in craniofacial development and that mutations in these genes could result in morphological deviances in respective individuals (e.g., LaMantia, 1999; Machado and Eames, 2017; Wilderman, et al., 2018). Interestingly, genetic factors are also regarded to play a crucial role in the aetiology of ASD (for a recent review please see Woodbury-Smith and Scherer, 2018). Ozgen, et al. (2013) suggested that the genes that are important for craniofacial morphology might overlap with candidate genes for ASD[10]. The Human Gene Module (https://gene.sfari.org/database/human-gene/) currently lists 1,007 potential candidate genes for ASD. Some of the most recurrently reported candidate genes for ASD are neurexin (*NRXN*) family genes (e.g., Dabell, et al., 2013; Wang, et al., 2018), patched domain containing 1 (*PTCHD1)* (e.g., Noor, et al., 2010; Torrico, et al, 2015), neuroligin (*NLGN*) family genes (e.g., Jamain, et al., 2003; Nakanishi, et al., 2017) and Shank (*SHANK*) family genes (e.g., Mashayekhi, et al., 2016; Sungur, Schwarting and Wöhr, 2016). Duplications or deletions of several DNA loci have repeatedly been found in individuals with ASD, including for example 16p11.2 (e.g., Weiss, et al., 2008; Green

[10] Interestingly, for example mutations in the gene *EBF3* have recently been identified to be associated with facial dysmorphism (e.g., Harms, et al., 2017) as well as with ASD (Tanaka, et al., 2017). Furthermore, there is limited evidence that mutations in the gene *NFIA* are associated with facial dysmorphism (Bayat, et al., 2017) as well as with ASD (Iossifov, et al., 2012).

Snyder, et al., 2016), 15q11-q13 (e.g., Shao, et al., 2003; Hogart, et al., 2010; Urraca, et al., 2013), and 22q11 (e.g., Hiroi, et al., 2013; Clements, et al., 2017). It needs to be mentioned that mutations in ASD candidate genes and loci can also be present in the general population or in individuals with other developmental disorders (Woodbury-Smith and Scherer, 2018). In addition to genetic causes, a number of environmental factors have been associated with ASD (for an overview please see Karimi, et al., 2017). A few examples are infections during pregnancy (e.g., rubella: Chess, Fernandez and Korn, 1978; fever: Hornig, et al., 2018; cytomegalovirus: Garofoli, et al., 2017), low maternal melatonin level (Braam, et al., 2018), maternal underweight or obesity before pregnancy (Andersen, et al., 2018), maternal medication use during pregnancy (e.g., paracetamol: Masarwa, et al., 2018; valproic acid: Nicolini and Fahnestock, 2018), prenatal pesticide exposure (Philippat, et al., 2018), environmental pollutants (Bjørklund, et al., 2018), advanced parental age (Wu, et al., 2017), and birth at gestational age <35 or >42 weeks (Zhang, et al., 2010b).

Given the complex aetiology of ASD made up by genetic and environmental factors, the heterogenous clinical picture of this developmental disorder is not surprising. In order to shed light into the structural and functional brain development in ASD, neuroimaging studies on children with ASD at different ages – recently already in prenatal at risk cohorts – have been increasingly applied in the last 2 decades (for overviews please see Bölte, et al., 2016[11]; Wolff, Jacob and Elison, 2018). Among other early deviances, a relatively large head circumference and brain overgrowth in infants and toddlers have repeatedly been associated with ASD (e.g., Courchesne, et al., 2007; Courchesne, Campbell and Solso, 2011; Sacco, Gabriele and Persico, 2015; Hazlett, et al., 2017). For example, the meta-analysis of Sacco, Gabriele and Persico (2015) revealed macrocephaly in 15.7% and brain overgrowth in 9.1% of the individuals with ASD. It has to be noted, however, that this meta-analysis included studies partly comprising wide age bands from infancy to adulthood; macrocephaly and brain overgrowth were found to be more pronounced in early childhood (Sacco, Gabriele and Persico, 2015). Interestingly, a recent prenatal cohort study by Blanken, et al. (2018) did not find a significant relation between foetal head growth and ASD diagnosis. The MRI study by Hazlett, et al. (2017) showed that hyper-expansion of the cortical surface area[12] between 6 and 12 months of age preceded brain overgrowth found between 12 and 24 months of age in children who received an ASD diagnosis.

[11] I am second author of this article focusing on methodological trends of technology use in research on young children with ASD between 1965 and 2013. I was mainly concerned with the selection and analysis of relevant papers.

[12] Hyper-expansion was observed in cortical areas linked to processing sensory information such as left middle occipital cortex (Hazlett, et al., 2017).

A number of studies found cerebellar abnormalities in individuals with ASD; the meta-analysis by Stoodley (2014) revealed grey matter volume decreases in the inferior cerebellar vermis (lobule IX), the right Crus I, and the left lobule VIIIB. Increases in cerebellar white matter were for example shown by Bloss and Courchesne (2007) and by Akshoomoff, et al. (2004). Other studies, however, found no differences in cerebellar volume between individuals with ASD and controls (e.g., Hazlett, et al., 2005; 2011). Post-mortem studies repeatedly found a reduced number and/or size of Purkinje cells in the cerebellum (e.g., Fatemi, et al., 2002; Skefos, et al., 2014; Wegiel, et al., 2014). Jeong, et al. (2014) used diffusion MRI tractography to in vivo compare the Purkinje cells of children with ASD and children with typical development. The authors found diffusion differences in the cerebellum between the two groups indicating a Purkinje cell pathology of individuals with ASD (Jeong, et al., 2014). Furthermore, an increased volume of the amygdala was a consistent finding in children with ASD (e.g., Mosconi, et al., 2009; Schumann, et al., 2009), but the volume was found to normalise in late childhood and adolescence (e.g., Barnea-Goraly, et al., 2014). Interestingly, several studies revealed an association between amygdala volume and clinical severity (Munson, et al., 2006; Schumann, et al., 2009; Barnea-Goraly, et al., 2014).

A recent review by Hansel (2018) summarised findings on LTD deregulation and syndromic ASD (referred to individuals with genetic disorders such as RTT and FXS) or non-syndromic ASD (referred to individuals without known genetic disorders). In the subchapters about RTT and FXS, I already mentioned synaptic plasticity deficits in these developmental disorders. Interestingly, LTD deregulation was also observed in mouse models of non-syndromic ASD (for example in neuroligin3 knockout mice; e.g., Baudouin, et al., 2012), albeit LTD was observed to be normal in other studies on non-syndromic ASD (e.g., Zhang, et al., 2015; Ha, et al., 2016). Furthermore, 6-month-old infants who were later diagnosed with ASD were found to have deficits in brain connectivity in regions involved in low-level sensory processing (Lewis, et al., 2017). A recent functional connectivity magnetic resonance imaging study was performed on 6-month-old infants at low or high risk for ASD and implemented a machine-learning algorithm that could correctly predict an ASD diagnosis at 24 months of age in nine of eleven children. All 48 infants who were not diagnosed with ASD at 24 months of age were correctly identified at 6 months of age (Emerson, et al., 2017).

Social stimuli were observed to result in different brain activation patterns in infants later diagnosed with ASD compared to typically developing infants. For example, when viewing facial stimuli with dynamic eye gaze, infants with and without familial risk for ASD differed in their event-related potentials (ERPs) (Elsabbagh, et al., 2012b). A functional

near-infrared spectroscopy (fNIRS) study found that already at an age of 4–6 months, infants who were later diagnosed with ASD showed reduced activation in inferior frontal and posterior temporal cortical regions in response to visual social stimuli compared to low-risk infants (Lloyd-Fox, et al., 2018). Moreover, those infants later diagnosed with ASD had reduced activation in left lateralised temporal regions in response to vocal sounds compared to low-risk infants or high-risk infants without ASD (Lloyd-Fox, et al., 2018). Similarly, Blasi, et al. (2015) revealed atypical neural responses to human voice with and without emotional valence in 4–7-month-old infants later diagnosed with ASD. Interestingly, activity in language-sensitive superior temporal cortices in toddlers with ASD in response to speech was found to be predictive of language outcomes; hypoactivity in these brain areas was related to lower language skills (Lombardo, et al., 2015).

1.2 Typical socio-communicative development in the first 2 years of life

Communication is an essential human capacity needed in daily life and is defined as a basic right for all individuals (United Nations, 2008; Murphy, et al., 2018). There are a number of different models and theories on communication (cf. de Saussure, 1916; Bühler, 1934; Shannon and Weaver, 1949); they share the essence of communication being a process involving at least two communication partners, the communicator or sender of a message and the recipient of the message. The communicator conveys his intentions through mutually understood communicative forms to the recipient who draws conclusions from the message (e.g., Tomasello, 2008). In the human society, people usually communicate via speech and gestures, i.e. "with socially learned, intersubjectively shared symbols of a type not used by other animal species" (Tomasello, Carpenter and Liszkowski, 2007, p.705). However, there are additional or alternative ways to communicate. Already in 1957, Skinner provided a definition of communication that goes beyond speech and gestures. According to his definition, all behaviours that are effective to reach a certain goal via a communication partner are communicative behaviours (in his terminology 'verbal behaviour'[13]; Skinner, 1957). Examples for (potentially) effective forms of communication are facial expressions, non-linguistic vocalisations, body movements, or aided augmentative and alternative communication (e.g., Sigafoos, Arthur-Kelly and Butterfield, 2006). This definition implies that individuals with speech-language related disorders as well as infants who have a limited set of gestures and only pre-linguistic verbal behaviours have the potential to successfully and intentionally communicate with their environment using alternative communication strategies (e.g., Hertenstein, et al., 2006; Sigafoos, Arthur-Kelly and Butterfield, 2006).

Infants need to learn certain principles and rules of communication to successfully interact with others. For example, already at the end of the first half year of life infants acquire turn-taking capacities in interactive settings with their caregivers, i.e., they learn to vocalise in an alternating pattern with their caregivers. Harder, et al. (2015) studied the coordination in mother-infant vocalisations between 4 and 10 months of age. They found that 4-month-old infants predominantly co-vocalised with their mothers whereas with 7 months, co-vocalisations had significantly decreased and turn-taking behaviour became predominant (Harder, et al., 2015). Contrary, Gratier, et al. (2015) found no differences in turn-taking behaviour between 2 and 5 months of age, but noted that infants were active

[13] As 'verbal behaviour' in the sense of Skinner (1957) focuses more on the function than on the structure of the behaviour, it is not restricted to speech or vocal behaviours; other potential 'verbal behaviours' are gestures, sign language, picture exchange systems, crying, and touching a person, to name but a few.

participants in turn-taking already from 2 months of age onwards. Hedenbro and Rydelius (2014) found that the ability to initiate turn-taking sequences at 9 months of age correlated with social competence at 48 months of age.

The earliest forms of communication are dyadic interactions between an adult/caregiver and the infant, for example via eye contact and responsive smiling (e.g., Bruinsma, Koegel and Koegel, 2004). The onset of joint attention brings a third entity into play, namely an object, a third person, or an event (e.g., Bates, 1979; for a recent overview on joint attention please see Mundy, 2018). Joint attention enables communication partners to commonly focus on and communicate about an object/person/event (Bruinsma, Koegel and Koegel, 2004; Mundy and Jarrold, 2010). Communicator and recipient share common knowledge and each communication partner knows that the other communication partner understands the larger context in which their communicative acts take place (Tomasello, Carpenter and Liszkowski, 2007). An exemplary situation for joint attention is the joint book reading of an infant and his/her caregiver. Caregiver and infant communicate together about the book via communicative forms, such as eye gaze alternation between communication partner and book, or index finger pointing.

Joint attention development begins already in the first 6 months of life (e.g., Mundy, 2018). Joint attention behaviours can be divided in two categories, namely responding to joint attention (RJA) and initiating joint attention (IJA; Mundy and Jarrold, 2010; Mundy, 2018). RJA means that infants follow the gaze or the pointing of other persons to share common interests. RJA begins to develop earlier than IJA; gaze following was observed to emerge between 2 and 4 months and to stabilise between 6 and 8 months of age (Gredebäck, Fikke and Melinder, 2010). IJA refers to infants' attempts to direct other persons' attention to objects or to events by communicative forms. This form of joint attention begins to develop around the 9th month of age (Mundy, 2018). IJA requires an infant to realise that his/her behaviours can cause events and that he/she can actively contact others to achieve wants and needs (e.g., Bates, Camaioni and Volterra, 1975; Harding and Golinkoff, 1979; Bruinsma, Koegel and Koegel, 2004). By IJA, an infant intentionally communicates with others, a capability that is commonly assumed to emerge around 9 months of age (Bates, 1979). Physiologically, the development of intentionality goes hand in hand with the development/activation of frontal cortical areas (e.g., Chugani, 1998; 1999; Leisman, et al., 2012).

Based on the speech-act theory by Austin (1962), Bates, Camaioni and Volterra (1975) divided the typical communicative development in three phases: the perlocutionary phase, the illocutionary phase and the locutionary phase. In the perlocutionary phase

infants' behaviours have effects on the environment without the infants' intention to communicate with other persons. For example, an infant tries to get a ball by reaching for the ball and potentially by producing vocalisations, but no eye contact, words or other communicative forms directed towards a present caregiver take place. Despite the lack of caregiver-directed communicative forms, the caregiver might still hand the object over to the infant. At this stage, caregivers often overinterpret the children's behaviours as if they were intentional (von Tetzchner, 1997). An infant in the illocutionary phase notices that other persons can help him/her to achieve his/her wants and needs and, therefore, the infant actively and intentionally communicates with them. Certain characteristics indicate intentionality: e.g., gaze alternation between an object and the communication partner or continuing with a behaviour until a response from the communication partner is received (Wetherby and Prizant, 1989; Stephenson and Linfoot, 1996). In the former example, the infant would additionally seek eye contact with a present caregiver while reaching for the ball and vocalising. Conventional speech-language realisations are not necessary at this point of communication development (e.g., Harding and Golinkoff, 1979). The locutionary phase includes the use of linguistic forms that are consistently used to, for example, name specific objects. In addition to reaching and eye contact, the infant produces for example the word 'ball'.

Infants and toddlers intentionally use communicative forms to fulfil certain communicative functions. These functions can be of either a responsive or an initiative type. Wetherby, et al. (1988) found more initiating than responding communicative acts in typically developing infants and toddlers. Bates (1976) divided early communicative functions into the two main classes proto-imperatives and proto-declaratives, emerging from 8 months of age onwards (Chapman, 2000; Paul, 2007). Proto-imperatives include an infant's request for objects or actions as well as rejections or protests in communicative settings. Carpenter, Mastergeorge and Coggins (1983) found that rejecting was the first communicative function to emerge (~8 months), followed by requesting (~9 months). Kutsuki, et al. (2009) longitudinally investigated requesting behaviours between 11 and 15 months. They found that with increasing age greater combinations of co-occurring behaviour modes (defined as use of hands, eye gaze, facial expression, and vocalisation) were used to express requests (Kutsuki, et al., 2009). According to Bates (1976), proto-declaratives include attempts to establish interaction and/or joint attention with a caregiver; e.g., by demonstrating objects. The most frequently observed proto-declarative function in typically developing infants and toddlers is commenting. This function emerges between 9.5 and 10.5 months of age (Carpenter, Mastergeorge and Coggins, 1983; Paul 2007). Between 16 and 24 months of age, typically developing children also use more advanced

communicative functions such as requests for information (e.g., by requesting the name of an object), acknowledgements (i.e., showing the communication partner that his/her utterance was noticed; e.g., via imitating parts of the utterance), and responding to questions (Chapman, 2000; Paul, 2007). These communicative functions refer to previous speech acts and not – as the earlier emerging functions – to objects or events in the environment (Paul 2007).

1.2.1 Socio-communicative forms

A number of behaviours (hereafter referred to as communicative forms) that are potentially used to fulfil certain communicative functions were already mentioned above. In the following, potential communicative forms will be described in more detail. It will be outlined when forms first appear in typically developing children and when they finally become functional, representing a typical communicative repertoire.

The first potentially intentional communicative forms are non-conventional non-verbal behaviours (e.g., eye contact including gaze alternation, body movements such as reaching, touching a person, or moving closer), non-linguistic verbal behaviours (e.g., crying, unspecific vocalisations, pleasure vocalisations), and gestures (e.g., pointing, passing objects; e.g., Bruner, 1975; Harding and Golinkoff, 1979; Watt, Wetherby and Shumway, 2006; Määttä, et al., 2016). Several studies demonstrated a relationship between some of these early pre-linguistic communicative forms and later language outcomes (e.g., McCathren, Warren and Yoder, 1996; Watt, Wetherby and Shumway, 2006; Bopp and Mirenda, 2011; Määttä, et al., 2016). As described above, intentionality gradually develops throughout the first year of life (Bates, 1979). However, already infants' behaviours in the first weeks of life might be interpreted by their parents to express emotional states and needs and elicit parental responses (e.g., Oller, 2000). Moreover, it is difficult to define the transition between non-intentional and intentional communication; towards the end of the first year of life infants use different behaviour types partly with and partly without a communicative intention (e.g., babbling occurs both in caregiver-infant settings and in infant-alone settings). Therefore, Chapters 1.2.1.1 and 1.2.1.2 contain a description of non-verbal and verbal communicative forms from a child's very beginning of development until 2 years of age, of course keeping in mind that the earliest nonverbal and verbal behaviours are not 'real' communicative forms at the age they emerge.

1.2.1.1 Nonverbal communicative forms

The human face and especially the eye region and the mouth region play a central role in social communication (e.g., Emery, 2000). Interestingly, already newborns were observed to prefer looking at faces compared to other visual stimuli (e.g., Valenza, et al., 1996; Wilkinson, et al., 2014). A recent study even postulated the preference of face-like visual stimuli in the foetus in the third trimester of pregnancy (Reid, et al., 2017). By 2 months of age, infants were described to focus on the eye region in a face (Maurer and Salapatek, 1976; Haith, Bergman and Moore, 1977); 3-month-old infants were found to prefer human eyes over nonhuman eyes (Dupierrix, et al., 2014). The motor pattern of smiling is to be observed in full-term newborns, in preterm infants, and with ultrasound in utero (Kurjak, et al., 2005; Einspieler, Marschik and Prechtl, 2008; Einspieler, Prayer and Prechtl, 2012). Endogenous smiling in newborns is often observed when infants are sleeping, especially in active sleep (state II; Wolff, 1987). Although the movement pattern of smiling is present early, it only becomes functional at around 6–8 weeks postterm age when smiling emerges in interactive face-to-face settings (Anisfeld, 1982; Einspieler, et al., 2004; Over, 2016). This socially elicited responsive smiling is probably the first intentional smiling (e.g., Oller, 2000). A few weeks later, between 12 and 15 weeks postterm age, infants start to reach for objects (Hopkins and Prechtl, 1984; Von Hofsten, 1984). At this early age, joint attention has not yet developed and reaching is not used for communicative purposes. A few months later, however, the motor pattern reaching has not only developed further (Marschik, et al., 2008; Guimarães, et al., 2013), but now becomes a potential communicative form to request an object from another person (e.g., Bates, 1979; Ramenzoni and Liszkowski, 2016): The communicative intention of reaching is for example noticeable by its combination with eye gaze alternation between caregiver and desired object.

Around 10 months of age, the first gestures emerge (e.g., Bates, Camaioni and Volterra, 1975). Gestures are the first communicative forms with symbolic character that provide children the possibility to express information before they have appropriate words to do so (Iverson and Goldin-Meadow, 2005). There are different types of gestures, emerging at different ages. The first gestures begin to be used prior to the onset of spoken language and are referred to as deictic (or performative) gestures (Capone and McGregor, 2004). Demonstrating and passing objects as well as index finger pointing belong to this gestural type (Bates, Camaioni and Volterra, 1975; Bates, 1979). Demonstrating and passing objects, occurring around 10 or 11 months of age, were found to be precursors of the pointing gesture, appearing between 12 and 13 months of age (e.g., Bates, Camaioni and Volterra, 1975; Boundy, Cameron-Faulkner and Theakston, 2016). Around the first birthday, infants engage in first play schemes (Capone and McGregor, 2004), i.e., they

manipulate objects and depict them in terms of their function (e.g., pretend to eat with a doll's china set, pretend to phone with a toy phone). Representational (or symbolic or referential) gestures emerge before the 25-word-milestone (Acredolo and Goodwyn, 1988; Capone and McGregor, 2004). They differ from play schemes in that no manipulation of objects take place. Instead, movements of the hands are used to symbolise a referent, e.g., pretending to phone by holding the hand towards the ear. A subtype of representational gestures are conventional gestures which are culture-specific signs (e.g., nodding the head to indicate yes, waving bye-bye; Iverson, Capirci and Caselli, 1994).

1.2.1.2 Verbal communicative forms

Among the first sounds that are produced by infants are vegetative sounds (e.g., sneezing, hiccup, burping, coughing, yawning; Oller, 1980; Nathani, Ertmer and Stark, 2006). They result from autonomous bodily processes and are not intended to fulfil communicative purposes. Though, parents tend to interpret them, for example by patting the infant's back when they hear the infant coughing (Oller, 2000).

Additional sounds that are already produced from birth onwards are fussing and crying vocalisations. Crying changes in character throughout the first 2 years of life (e.g., changes in the fundamental frequency; Rothgänger, 2003; Esposito and Venuti, 2010). Crying in newborns is a response to physical needs such as pain or hunger and appears to lack intentions towards a caregiver (e.g., Oller, 2000). At that age, it has indexical communicative function as parents react to crying by trying to meet their infant's needs (e.g., Acebo and Thoman, 1995). Towards the end of the first year of life, infants begin to combine crying/fussing vocalisations with gestures (e.g., extending arms seeking comfort; e.g., Oller, 2000). Another vocal pattern present already in the first weeks of life are vowel-like sounds. They have a determinable pitch, but no distinct melodic contour and they do not excite the vocal tract's full resonance (Oller, 1980; Papoušek, 1994). In the second or third month of life, cooing vocalisations emerge (Oller, 1980; Stark, 1980). These are consonant-like sounds that can be combined with vowel-like sounds (Nathani, Ertmer and Stark, 2006) and have a distinct melodic contour (Papoušek, 1994). Cooing is the first vocal pattern with syllable character (Oller, 1980; Locke, 1995; Nathani, Ertmer and Stark, 2006) requiring discernible tongue movements that are necessary for later emerging target-language phonation (Oller, 2000). Interestingly, cooing develops around the same age as social smiling and often co-occurs with smiling in interactive settings. Between 2 and 4 months, laughing and pleasure vocalisations emerge (Sroufe and Waters, 1976; Stark, 1980; van Wulfften-Palthe and Hopkins, 1984; Oller, 2000). Similar to crying and fussing,

laughing becomes more and more intentional throughout the first year of life, often to initiate interactions (Papoušek and Papoušek, 1984; Nwokah, et al., 1994). At around 4 or 5 months of age, explorative sounds, such as raspberry vocalisations, humming or squealing, emerge (Papoušek, 1994). Around that age, also marginal babbling sets in. Marginal babbling is characterised by a series of consonant-like and vowel-like segments with prolonged formant transitions (Nathani, Ertmer and Stark, 2006). Over the next months, consonant-like and vowel-like syllables shift to well-formed syllables with faster formant transitions, resulting in consonant-vowel (CV) syllables, referred to as canonical syllables (Papoušek, 1994; Oller, et al., 1999). By 8 months of age, infants combine CV syllables, i.e., canonical or reduplicated babbling emerges (e.g., /baba/; Oller, 1980; Stark, 1980; Oller, et al., 1999; Paul 2007). At around 10 months of age, variegated babbling consisting of different CV-syllables (e.g., /daguba/) emerges (Oller, 1980; Stark, 1980; Paul, 2007).

The transition to word production is a gradual process from performative routines to referential word use (Bates, O'Connell and Shore, 1987). Performative routines, also referred to as proto-words, emerge towards the end of the first year of life, have a phonetically consistent form, but are not yet conform to the target language in terms of phonological form, semantics, or context-independent use (e.g., Kauschke, 2000). The first referential words are produced on average at 13 months of age (Bloom, Margulis and Tinker, 1993). Referential words have a conventional lexical form, refer to specific semantic entities and are used as independent and flexible signs in different contexts (Kauschke, 2000). By 18 to 19 months of age, the majority of toddlers have acquired a productive vocabulary of 50 words (Menyuk, Liebergott and Schultz, 1995). It should be noted that there is a huge variability in terms of vocabulary growth in toddlerhood (e.g., Bates, et al., 1994). Around the middle of the second year of life, the so-called vocabulary spurt was described to set in where children very quickly learn new words; according to Bloom, Margulis and Tinker (1993) infants in the vocabulary spurt acquire at least three new words per week or twelve new words per month. However, the universal presence of this vocabulary spurt has been discussed controversially (e.g., Clark, 1993; Anisfield, et al., 1998; Kauschke, 2000; Ganger and Brent, 2004), as for example Ganger and Brent (2004) found such a spurt-like expansion of words only in one of five children. First two-word combinations typically occur around the same age (Rudolph and Leonard, 2016). At 24 months of age, children were found to have an average productive vocabulary of approximately 300 words (Fenson, et al., 1994; Eriksson, et al., 2012). A child that has not acquired a productive vocabulary of at least 50 words and produces no word combinations at 24 months of age is defined as 'late talker' (Rescorla, 1989). Although a considerable amount of late talkers has a language outcome within the normal ranges, late talkers have

an increased risk for persisting language-related deficits (e.g., specific language impairment[14]) and developmental disorders in general (e.g., Rescorla, 1989; 2005; Marschik, et al., 2007; Preston, et al., 2010; Bartl-Pokorny, et al., 2013a; Capone Singleton, 2018; Franchini, et al., 2018).

1.2.1.3 The role of gestures in speech-language acquisition

A cross-cultural widespread gesture that is especially important for language development is index finger pointing (Butterworth, 2003; Rohlfing, Grimminger and Lüke, 2017). The occurrence of a pointing gesture does not necessarily mean that the message that should be transferred with the pointing gesture is understood by the recipient. It is important for the recipient to know to what exactly the communicator points to and why he does so. The communication partners need to have common ground (Clark, 1996; Tomasello, Carpenter and Liszkowski, 2007), i.e., they need to share common knowledge about a larger context. Other communicative forms such as an excited facial expression might also help the recipient to understand why the communicator points to an object (Tomasello, Carpenter and Liszkowski, 2007).

The motor pattern of an extended index finger was already observed in dynamic magnetic resonance imaging (MRI) at 27 weeks of gestation and also shortly after birth (Marschik, et al., 2013b). However, at around 11 or 12 months of age it becomes a functional communicative form to share attention and interest with other people to events or objects (e.g., Leung and Rheingold, 1981; Carpenter, Nagell and Tomasello, 1998; Liszkowski, et al., 2004). There are two major types of pointing in early childhood: proto-declarative and proto-imperative pointing (Tomasello, Carpenter and Liszkowski, 2007). With the classical proto-declarative pointing, the child tries to get an adult's attention by directing the adult's attention to an object. With the classical proto-imperative pointing, the child aims to motivate the adult to pass an object to him/her. However, already infants and toddlers point for a variety of reasons exceeding the classical proto-declarative and proto-imperative pointing (Tomasello, Carpenter and Liszkowski, 2007; Rohlfing, Grimminger and Lüke, 2017). For example, a child sees a bike, points to it and says 'dad' (dad usually drives to work with the bike), a child points to request actions (e.g., 15-month-old girl points to her shoes to indicate that she wants help to put on the shoes), to answer questions (e.g., 14-month-old girl points to the mobile when mum asks where the mobile is), to choose between two objects (e.g., 13-month-old boy chooses to drink from a glass and not from the bottle),

[14] i.e., communication disorders according to the actual version of the DSM-5 (American Psychiatric Association, 2013).

or to request information about the name of an object (e.g., 30-month-old boy points to an insect and asks for the name of this animal).

As shown in the examples above, gestures are often used in combination with (single) words, which increases the communicative information that can be transferred (e.g., Capirci, et al., 1996; Iverson and Goldin-Meadow, 2005). Iverson and Goldin-Meadow (2005) demonstrated that the onset of such gesture-word combinations predicted the onset of two-word-combinations. A number of other studies also demonstrated a relationship between early gesture use and language acquisition, supporting the hypothesis that gestures can help to facilitate the transition to spoken language (e.g., Acredolo and Goodwyn, 1988; Capirci, et al., 1996; Capone and McGregor, 2004; Iverson and Goldin-Meadow, 2005; Özçalışkan, Adamson and Dimitrova, 2016; Cadime, et al., 2017; Lüke, et al., 2017).

1.3 Early socio-communicative development in late recognised developmental disorders

On 30 May 2018, I conducted a literature search in PubMed to find relevant articles on the early socio-communicative development of children with RTT, FXS, or ASD. The following search terms were used:

> (communicat* OR language OR speech OR gestur* OR linguist* OR verbal* OR non-verbal*) AND (“Rett syndrome” OR Rett);
>
> (communicat* OR language OR speech OR gestur* OR linguist* OR verbal* OR non-verbal*) AND ("fragile X*" OR "Martin Bell*");
>
> (communicat* OR language OR speech OR gestur* OR linguist* OR verbal* OR non-verbal*) AND autis*.

The search, limited to the first 2 years of life, revealed 90 articles on RTT, 60 articles on FXS, and 1,327 articles on ASD. On the first glimpse, these numbers seem quite high, but in-depth analyses of these articles revealed that research and empirical evidence on the pre-diagnostic socio-communicative development in RTT, FXS, and ASD is still sparse: A great proportion of the found studies included wide age bands starting from the end of the second year of life onwards (i.e., in most cases after diagnosis; e.g., Franchini, et al., 2017), dealt with intervention evaluation (e.g., Bradshaw, Koegel and Koegel, 2017) or did not explicitly focus on the infants’ communicative repertoires but rather on parental experience with services and treatments (e.g., Becerra, et al., 2017), parental responses to infants’ communicative acts (e.g., Leezenbaum, et al., 2014), or brain functional connectivity findings in very young at risk infants that might predict ASD diagnosis at a later age (e.g., Emerson, et al., 2017). Moreover, most studies focused on one or more specific aspects of communicative development (e.g., gestures, vocabulary at a specific age, imitation) and did not comprehensively describe the communicative repertoires of individuals later diagnosed with a developmental disorder.

In the next subchapters, a brief overview on what we currently know about the socio-communicative development in the first 2 years of life of children with RTT, FXS, or ASD will be provided. More details on existing studies and a comparison with my own findings in the framework of my thesis are to be found in the Discussion Section below. In this literature overview, the following articles I published as (co-)first author will be excluded: Bartl-Pokorny, et al., 2013b; Marschik, et al., 2014b; 2014c. These three studies will be described in detail in the Methods and Results Sections of my thesis.

1.3.1 Early socio-communicative development in Rett syndrome

As already mentioned above, the pre-regressional period of RTT is no longer regarded as inconspicuous (e.g., Tams-Little and Holdgrafer, 1996; Leonard and Bower, 1998; Burford, Kerr and Macleod, 2003; Marschik, et al., 2013a; Einspieler, Freilinger and Marschik, 2016), even though peculiarities are often subtle at first.

Retrospective parental interviews in the framework of the RTT Natural History Study (NHS) revealed the occurrence of social smiling in almost all infants with RTT (Neul, et al., 2014). However, studies applying retrospective video analysis described the smiling of infants later diagnosed with RTT as frozen, bizarre, strange, or inadequate (Burford, 2005; Einspieler, Kerr and Prechtl, 2005b; Einspieler, et al., 2014b). Infants and toddlers were found to show reduced reactions to their own name when being called (Townend, et al., 2015; Zhang, et al., 2018b) and deficits in joint attention (Trevarthen and Daniel, 2005). They were moreover described to have limited gestural repertoires, especially in terms of symbolic gestures (Tams-Little and Holdgrafer, 1996; Marschik, et al., 2009; 2012a; 2012b). Marschik, et al. (2012b) proposed a reduced pragmatic functionality of gestures between 9 and 18 months of age as they were only used to gain attention to self, request an object, request an action, or occurred as imitations. Most infants with RTT were reported to produce cooing and babbling vocalisations; toddlers with RTT were described to have a relatively small vocabulary already prior to regression and only a minority of them ever acquire word combinations; early speech-language capacities were also suggested to be related to mutation types (e.g., Tams-Little and Holdgrafer, 1996; Uchino, et al., 2001; Neul, et al., 2014; Urbanowicz, et al., 2015). Most studies on early speech-language development relied on retrospective parental or clinician's questionnaires/interviews. To provide new insights into the early speech-language development of individuals with RTT, our research unit (including me as a co-author) analysed the occurrence of cooing, babbling, (proto-)words and word combinations in the first 2 years of life of girls later diagnosed with RTT or PSV[15] based on retrospective video analysis (Marschik, et al., 2013a). We found a clearly deviating speech-language development in RTT and PSV that was more pronounced in the individuals with RTT. Seven out of ten individuals with RTT and all individuals with PSV reached the cooing milestone, whereas babbling was observed only in half of the infants with RTT and four of five infants with PSV. Only three of ten individuals with RTT and three of five individuals with PSV were observed to produce (proto-)words. Word combinations were observed only in one female with PSV (Marschik, et al., 2013a). We moreover reported that the early speech-language development was characterised by an interspersed

[15] Typical Rett syndrome is referred to as RTT hereafter. The preserved speech variant of Rett syndrome is referred to as PSV hereafter.

character of apparently normal and abnormal vocalisations (including cooing and babbling) such as repetitive vocalisations, pressed vocalisations, high-pitched crying-like vocalisations, and vocalisations on ingressive airstream (e.g., Marschik, Einspieler and Sigafoos, 2012c; Marschik, et al., 2013; 2014a; Pokorny, et al., 2018; for an overview please see Roche, et al., 2018). Moreover, volubility was found to be reduced (Marschik, et al., 2012d). In 2012, Marschik, et al. (2012a; including me as co-author and second coder) for the first time comprehensively analysed the potential socio-communicative repertoires of females with the relatively milder PSV of RTT in the second year of life. This study – a pilot study for my thesis – for the first time retrospectively applied the Inventory of Potential Communicative Acts (IPCA; Sigafoos, Arthur-Kelly and Butterfield, 2006; for details on the method please see Chapter 2.3) on children with a developmental disorder before they were formally diagnosed. We found a reduced set of socio-communicative forms and functions in our participants with an overall preference of non-verbal communicative forms in the second year of life. Based on our promising findings, we suggested that the IPCA in combination with retrospective video analysis might be a powerful tool to delineate early socio-communicative capacities and atypical developmental pathways of individuals later diagnosed with (other) developmental disorders (Marschik, et al., 2012a).

1.3.2 Early socio-communicative development in fragile X syndrome

Individuals with FXS were described to show hyporesponsiveness to sensory stimuli in infancy, a pattern that often seems to be reversed in toddlerhood or preschool age (Baranek, et al., 2008). One important aspect of responsiveness in the social context is response to one's own name when being called. To date, response to name in the first 2 years of life of individuals with FXS has only been investigated by Baranek, et al. (2005) and by our group (Zhang, et al., 2018b; data annotation for this study was largely performed by myself). Baranek, et al. (2005) detected a significant difference among participants with FXS, ASD, developmental delay (DD), or TD in response to name (assessed by the number of adult name prompts necessary to elicit an infant's response). The authors, however, did not report specific statistical comparisons between any two groups. We descriptively compared response to name (assessed by response rate) in participants with FXS, ASD, RTT, PSV, or TD in the first 2 years of life (Zhang, et al., 2018b). Data for participants with TD were only available for the age band 9–12 months; descriptive analysis revealed a considerably lower response rate for individuals with FXS than for individuals with TD (35.29% vs. 65.85%; Zhang, et al., 2018b). The cross-syndrome comparison is discussed in Chapter 4.2.3.

The gestural repertoires of individuals with FXS were described to be reduced already from the end of the first year of life onwards (Roberts, et al., 2002; Hahn, et al., 2017; Rague, et al., 2018). Recently, Rague, et al. (2018) applied the Words and Gestures form of the parental questionnaire MacArthur-Bates Communicative Development Inventories (CDI; Fenson, et al., 2007) to study the gestural development between 9 and 24 months of age of individuals with FXS, individuals at high risk for ASD, and individuals with low familial risk for developmental disorders. The authors found that individuals with FXS had the smallest gestural repertoires throughout the observation period, followed by the high-risk and low-risk individuals.

Knowledge on early vocalisations in FXS is very limited. Belardi, et al. (2017) recently revealed by means of retrospective video analysis that infants later diagnosed with FXS had lower volubility and lower canonical babbling ratios between 9 and 12 months of age than infants with TD. Infants and toddlers with FXS were found to have a delayed speech-language development and delays were more pronounced in the expressive than in the receptive domain (Prouty, et al., 1988; Roberts, et al., 2001; 2002; Mirrett, et al., 2004; Brady, et al., 2006; Abbeduto, Brady and Kover, 2007; Finestack, Richmond and Abbeduto, 2009; Roberts, et al., 2009; Luyster, et al., 2011; Kover, et al., 2015). Hinton, et al. (2013) found a delayed onset of first words in individuals with FXS that was more pronounced in participants with comorbid ASD. Studies providing a comprehensive description of the early communicative repertoires in individuals with FXS are missing[16].

1.3.3 Early socio-communicative development in autism spectrum disorder

Compared to RTT and FXS, there is a broader body of knowledge on the early development of individuals with ASD. The earliest descriptions of the socio-communicative development of individuals with ASD prior to diagnosis stems from parental reports (e.g., Ornitz, Guthrie and Farley, 1977; Hoshino, et al., 1987). From the 1990s onwards, retrospective video analysis has been applied to delineate the early socio-communicative development of individuals with ASD (for an overview please see Zwaigenbaum, Bryson and Garon, 2013). In the last 20 years, prospective studies on infants at heightened familial risk for ASD (high risk studies) considerably added to the body of knowledge on the early development of children with ASD (please see Bölte, et al., 2016 for a methodological overview). Various

[16] Please note that the study of Marschik, et al. (2014c) is part of the empirical part of my thesis and therefore excluded here.

studies, applying different research methods, described atypicalities in the socio-communicative domain already for the first year of life, but in most studies peculiarities became more evident after the first birthday (e.g., Werner and Dawson, 2005; Zwaigenbaum, et al., 2005; Bryson, et al., 2007; Clifford and Dissanayake, 2008; Ozonoff, et al., 2010; 2011b).

Infants and toddlers later diagnosed with ASD were repeatedly found to have reduced eye contact, gaze avoidance, were less frequently looking at other people, had reduced affective expressions, inadequate facial expressions, deficits in joint attention, and deficits in social smiling (e.g., Adrien, et al., 1993; Maestro, et al., 2002; Werner and Dawson, 2005; Zwaigenbaum, et al., 2005; Clifford, Young and Williamson, 2007; Clifford and Dissanayake, 2008; Shumway and Wetherby, 2009; Ozonoff, et al., 2010; Poon, et al., 2012; Filliter, et al., 2015; Lee, et al., 2018). The findings on social smiling are inconsistent; Clifford, Young and Williamson (2007) and Clifford and Dissanayake (2008) found no deficits in social smiling based on frequency counts. Individuals with ASD were observed to show reduced social interest including peer interest and a preference to be alone (Adrien, et al., 1993; Clifford, Young and Williamson, 2007). They were moreover repeatedly reported to have deficits in imitation in the first 2 years of life (e.g., Mars, Mauk and Dowrick, 1998; Zwaigenbaum, et al., 2005; Young, et al., 2011; Poon, et al., 2012). A number of studies revealed reduced response to name when being called in the first 2 years of life (e.g., Osterling and Dawson, 1994; Osterling, Dawson and Munson, 2002; Wetherby, et al., 2004; Clifford, Young and Williamson, 2007; Gammer, et al., 2015; Miller, et al., 2017; Zhang, et al., 2018b). Winder, et al. (2013) revealed deficits in the spontaneous initiation of communicative acts in individuals at high risk for ASD compared to individuals at low risk for ASD when they were 13 and 18 months old. A reduced gestural repertoire and/or a limited frequency of gesture use was found in individuals with ASD compared to individuals with TD from 9–12 months of age onwards (Osterling, Dawson and Munson, 2002; Colgan, et al., 2006; Stone, et al., 2007; Shumway and Wetherby, 2009; Veness, et al., 2012; Watson, et al., 2013; Chawarska, et al., 2014; Gordon and Watson, 2015; Özçalışkan, Adamson and Dimitrova, 2016).

In the study by Zappella, et al. (2015), cooing was not observed in three of ten participants later diagnosed with ASD in their first half year of life; instead, the observed vocalisations were unspecific and hardly modulated. Iverson and Wozniak (2007) reported a delayed onset of canonical babbling in infants later diagnosed with ASD. Patten, et al. (2014) found that individuals later diagnosed with ASD produced lower rates of canonical babbling and had lower volubility at 9–12 months and 15–18 months compared to individuals with TD. Chericoni, et al. (2016) and Chenausky, Nelson and Tager-Flusberg

(2017) similarly reported lower volubility for individuals later diagnosed with ASD compared to individuals with TD. In comparison to controls, infants and toddlers later diagnosed with ASD produced fewer vocalisations directed towards other people (e.g., Dawson, et al., 2000; Maestro, et al., 2002; 2005; Bryson, et al., 2007; Ozonoff, et al., 2010). Language delays were reported to be among the first signs that raised parental concerns (e.g., De Giacomo and Fombonne, 1998). Prospective at risk studies found lower expressive and receptive language scores in infants and toddlers later diagnosed with ASD compared to high risk and low risk infants not diagnosed with ASD (e.g., Zwaigenbaum, et al., 2005; Landa and Garrett-Mayer, 2006; Barbaro and Dissanayake, 2012; Lazenby, et al., 2016).

1.4 Research questions

The aim of this thesis was to describe the socio-communicative capacities and potential deviances from typical socio-communicative development in the first 2 years of life of children later diagnosed with RTT, FXS, or ASD. I aimed to answer the following research questions (RQs) related to three research topics (i-iii).

i) RQ1 – topic: Communicative forms

RQ1a: Which communicative forms can be observed in the first 2 years of life in individuals with a late recognised developmental disorder (LRDD)?

RQ1b: Do children with a LRDD differ from children with TD in terms of acquisition and usage of communicative forms? (LRDD-TD comparison)

RQ1c: Do children with RTT, FXS, or ASD differ in terms of acquisition and usage of communicative forms? (Cross-syndrome comparison)

ii) RQ2 – topic: Communicative functions

RQ2a: Which communicative functions are present in the communicative repertoires of individuals with a LRDD in their first 2 years of life?

RQ2b: Do children with a LRDD differ from children with TD in terms of their communicative functions? (LRDD-TD comparison)

RQ2c: Do children with RTT, FXS, or ASD differ in terms of their communicative functions? (Cross-syndrome comparison)

iii) RQ3 – topic: Verbal and non-verbal communication

RQ3a: Do individuals with a LRDD prefer non-verbal behaviours, non-linguistic vocalisations, or (pre-)linguistic vocalisations for specific communicative functions in their first 2 years of life?

RQ3b: Do children with a LRDD differ from children with TD in terms of their use of non-verbal behaviours, non-linguistic vocalisations, and (pre-)linguistic vocalisations? (LRDD-TD comparison)

RQ3c: Do children with RTT, FXS, or ASD differ in terms of their use of non-verbal behaviours, non-linguistic vocalisations, and (pre-)linguistic vocalisations? (Cross-syndrome comparison)

To answer the above-mentioned research questions, six studies, hereafter referred to as Studies A–F, were conducted. As most of these studies focused on a single LRDD (see below), the research questions concerning cross-syndrome comparisons (i.e., RQ1c, RQ2c, RQ3c) will mainly be addressed in the subchapters 4.1.3, 4.2.3, and 4.3.3 of the discussion.

Study A focused on individuals with RTT between 9 and 12 months of life; Study B compared individuals with RTT with individuals with TD between 9 and 12 months of life; Study C compared an individual with RTT, an individual with PSV, and an individual with TD throughout the first 2 years of life; Study D focused on individuals with FXS throughout the first 2 years of life; Study E focused on individuals with ASD throughout the first 2 years of life; and Study F focused on individuals with TD throughout the first 2 years of life. For details on the participants, please see Chapter 2.1.

Studies A, D, and E addressed RQ1a, RQ2a, and RQ3a. Study B addressed RQ1a, RQ1b, RQ2a, RQ2b, RQ3a, and RQ3b. Study C addressed all nine research questions (i.e., RQ1a–RQ3c). Study F is related to RQ1b, RQ2b, and RQ3b.

Aspects of the reported research were not published before the submission of my thesis (i.e., Studies E–F). I published parts of the analyses for Studies A–D as first author or shared first author.

Study A:

Bartl-Pokorny, K.D., Marschik, P.B., Sigafoos, J., Tager-Flusberg, H., Kaufmann, W.E., Grossmann, T. and Einspieler, C., 2013b. Early socio-communicative forms and functions in typical Rett syndrome. *Research in Developmental Disabilities*, 34(10), pp.3133-8.

Bartl-Pokorny, K.D., Marschik, P.B., Sigafoos, J., Einspieler, C., 2013. Potential communicative acts and early pragmatic functions in typical Rett syndrome. 3rd

European Rett Syndrome Conference; OCT 17-19, 2013; Maastricht, THE NETHERLANDS. [Poster].[17]

Study B:

Bartl-Pokorny, K.D., Pokorny, F.B., Sigafoos, J., Krieber, M., Marschik, P.B. and Einspieler, C., 2016. The socio-communicative domain: Can we observe peculiarities in individuals with typical Rett syndrome already in the first year of life? *Wiener Medizinische Wochenschrift*, 166(11-12), p.387. Rett Syndrome – RTT50.1; SEPT 15-17, 2016; Vienna, AUSTRIA. [Poster]

Study C:

Marschik, P.B., **Bartl-Pokorny, K.D.***, Tager-Flusberg, H., Kaufmann, W.E., Pokorny, F., Grossmann, T., Windpassinger, C., Petek, E. and Einspieler, C., 2014b. Three different profiles: Early socio-communicative capacities in typical Rett syndrome, the preserved speech variant and normal development. *Developmental Neurorehabilitation*, 17(1), pp.34-8.

Study D:

Marschik, P.B., **Bartl-Pokorny, K.D.***, Sigafoos, J., Urlesberger, L., Pokorny, F., Didden, R., Einspieler, C. and Kaufmann, W.E., 2014c. Development of socio-communicative skills in 9- to 12-month-old individuals with fragile X syndrome. *Research in Developmental Disabilities*, 35(3), pp.597-602.

(*shared first authorship)

[17] In the following, I will not explicitly refer to this poster as its content was included in Bartl-Pokorny, et al. (2013b).

2 Material and methods

For this thesis, the socio-communicative development in the first 2 years of life of individuals with RTT, PSV, FXS, ASD, or TD was investigated based on retrospective audio-video material provided by the individuals' parents (i.e., home videos). Retrospective video analysis (RVA) allows delineating certain neurofunctions long before a developmental disorder is formally diagnosed (for details on the methods used please see Chapters 2.2 and 2.3). The applied RVA was approved by the ethics committee of the Medical University of Graz (27-388 ex 14/15). All parents gave their informed consent for analysis of their data for research purposes and for publication of the results. The video material analysed for this thesis was part of iDN's research database GUARDIAN (Pokorny, et al., 2016). The recruitment of video material was supported by Dr. Alison Kerr (University of Glasgow, UK), Professor Michele Zappella (Foundation for Autism Research, New York, USA, and Tuscany Rett Centre Versilia Hospital, Lido di Camaiore, Italy), and Dr. Jörg Richstein (Interessensgemeinschaft Fragiles-X e.V., Germany).

Studies A–F partly covered different age bands in the first 2 years of life (i.e., 9–12 months/13–18 months/19–24 months). In Chapter 2.1, the participants of each study will be described in detail. Some participants were included in two or more studies; this will be specified in Table 2b and Chapter 2.1. For consistency with the published articles/conference presentations, I decided to keep the participants' denominations from the respective publications (e.g., Child 1, Participant A, RTT 1, TD 1). Tables 2a and 2b provide a brief overview of the participants and the duration of the video material that was analysed for Studies A–F.[18]

[18] It should be noted that the wording in the next sub-chapters is partly similar to articles published on Studies A, C, and D (please see Chapter 1.4), as well as to other articles applying retrospective video analyses published by the Research Unit iDN and including me as co-author.

Table 2a: Participants and home video material available for Studies A–F.

	Number of participants (m/f)			
Study ID	**9–12 months**	**13–18 months**	**19–24 months**	**Footage (min)**
Study A	6 individuals (0/6) with RTT	N/A	N/A	459
Study B	5 individuals (0/5) with RTT, 5 individuals (0/5) with TD	N/A	N/A	759
Study C	1 individual (0/1) with RTT, 1 individual (0/1) with PSV, 1 individual (0/1) with TD	1 individual (0/1) with RTT, 1 individual (0/1) with PSV, 1 individual (0/1) with TD	1 individual (0/1) with RTT, 1 individual (0/1) with PSV, 1 individual (0/1) with TD	1275
Study D	7 individuals (5/2) with FXS	7 individuals (5/2) with FXS	3 individuals (1/2) with FXS	721
Study E	6 individuals (6/0) with ASD	4 individuals (4/0) with ASD	5 individuals (5/0) with ASD	355
Study F	8 individuals (3/5) with TD	10 individuals (4/6) with TD	8 individuals (3/5) with TD	1357

Abbreviations (in alphabetical order): ASD = autism spectrum disorder; f = female; FXS = fragile X syndrome; m = male; min = minutes; N/A = data for the respective age band were not analysed in the respective study/not available; PSV = preserved speech variant; RTT = Rett syndrome; TD = typical development.

Table 2b: Participants and home video material available for each age band.

Condition	**Participant ID**	**Footage available**			**Study ID**
		9–12 months	**13–18 months**	**19–24 months**	
RTT	Child 1 / RTT 1	✓	N/A	N/A	Study A, Study B
	Child 2	✓	N/A	N/A	Study A
	Child 3 / RTT 2 / Participant A	✓	✓	✓	Study A, Study B, Study C
	Child 4 / RTT 3	✓	N/A	N/A	Study A, Study B
	Child 5 / RTT 4	✓	N/A	N/A	Study A, Study B
	Child 6 / RTT 5	✓	N/A	N/A	Study A, Study B

TD	TD 1	✓	✓	✓	Study B, Study F
	TD 2 / Participant C	✓	✓	✓	Study B, Study C, Study F
	TD 3	✓	✓	N/A	Study B, Study F
	TD 4	✓	✓	✓	Study B, Study F
	TD 5	✓	✓	✓	Study B, Study F
	TD 6	N/A	✓	✓	Study F
	TD 7	✓	✓	✓	Study F
	TD 8	N/A	✓	✓	Study F
	TD 9	✓	✓	✓	Study F
	TD 10	✓	✓	N/A	Study F
PSV	Participant B	✓	✓	✓	Study C
FXS	Child 1	✓	N/A	N/A	Study D
	Child 2	✓	✓	N/A	Study D
	Child 3	✓	✓	N/A	Study D
	Child 4	✓	✓	N/A	Study D
	Child 5	✓	✓	✓	Study D
	Child 6	✓	✓	✓	Study D
	Child 7	✓	N/A	✓	Study D
	Child 8	N/A	✓	N/A	Study D
	Child 9	N/A	✓	N/A	Study D
ASD	ASD 1	✓	✓	N/A	Study E
	ASD 2	✓	✓	✓	Study E
	ASD 3	✓	N/A	N/A	Study E
	ASD 4	✓	N/A	✓	Study E
	ASD 5	✓	N/A	N/A	Study E
	ASD 6	✓	✓	N/A	Study E
	ASD 7	N/A	✓	N/A	Study E
	ASD 8	N/A	N/A	✓	Study E
	ASD 9	N/A	N/A	✓	Study E
	ASD 10	N/A	N/A	✓	Study E

Abbreviations (in alphabetical order): ASD = autism spectrum disorder; FXS = fragile X syndrome; N/A = data were not available for the respective age band; PSV = preserved speech variant; RTT = Rett syndrome; TD = typical development; ✓ = data were available and analysed for the respective age band.

2.1 Participants

2.1.1 Participants of Study A

The participants of Study A (Bartl-Pokorny, et al., 2013b) were six females with RTT (Child 1–Child 6). All participants had confirmed mutations in the *MECP2* gene. Three females were raised in monolingual German-speaking families (Child 3, Child 4, Child 6) and three came from monolingual English-speaking families (Child 1, Child 2, Child 5). All were singletons, pregnancies and deliveries were uneventful, and the children were born at term. Birth lengths, birth weights, head circumferences, and Apgar scores were within the normal ranges. For each participant, we had home video material available from 9–12 months of age.

2.1.2 Participants of Study B

The participants of Study B (Bartl-Pokorny, et al., 2016) were five females with RTT (RTT 1–RTT 5[19]) and five females with TD (TD 1–TD 5). All participants with RTT had confirmed mutations in the *MECP2* gene. Three of the females with RTT came from monolingual German-speaking families (RTT 2, RTT 3, RTT 5) and two were from monolingual English-speaking families (RTT 1, RTT 4). All participants with TD came from monolingual German-speaking families. All participants of Study B were singletons, pregnancies and deliveries were uneventful, and the children were born at term. Birth lengths, birth weights, head circumferences, and Apgar scores were within the normal ranges. For each participant, we had home video material available from 9–12 months of age.

2.1.3 Participants of Study C

Study C (Marschik, et al., 2014b) compared a female with RTT (Participant A), a female with PSV (Participant B), and a female with TD (Participant C)[20]. Genetic testing revealed the following *MECP2* mutations: p.Arg168* R168X for Participant A and c.378-43_964delinsG for Participant B. The three participants were all from monolingual German-speaking families. They were singletons and first borns to their mothers. Pregnancies and deliveries were uneventful and they were born at term. Birth lengths, birth weights, head

[19] All participants with RTT were also included in Study A: Child 1 in Study A = RTT 1 in Study B, Child 3 = RTT 2, Child 4 = RTT 3, Child 5 = RTT 4, Child 6 = RTT 5.
[20] Participant A was also included in Studies A and B: Child 3 in Study A = RTT 2 in Study B = Participant A in Study C. Participant C was also included in Study B: TD 2 in Study B = Participant C in Study C.

circumferences, and Apgar scores were within the normal ranges. For each participant, we had home video material available from 9–24 months of age.

2.1.4 Participants of Study D

Study D investigated the socio-communicative development throughout the first 2 years of life of individuals later diagnosed with FXS. Video material was assigned to the following three age bands: age band 9–12 months, age band 13–18 months, and age band 19–24 months. The results of age band 9–12 months were published in Marschik, et al. (2014c). For age band 9–12 months, we had available data of seven participants (Child 1–Child 5 were males; Child 6 and Child 7 were females). For age band 13–18 months, we had available data of seven participants (Child 2–Child 5 and Child 8 were males; Child 6 and Child 9 were females). For age band 19–24 months, we had audio-video material available for three participants (Child 5 was male; Child 6 and Child 7 were females).

Seven participants were singletons and grew up in monolingual German-speaking families (Child 1, Child 2, Child 5–Child 9). A twin pair (Child 3, Child 4) came from a bilingual German-Spanish speaking family. Pregnancies and deliveries were uneventful for all participants. Four of them were born at 36 weeks of gestation (Child 2–Child 4, Child 9); the other participants were born at term. Birth lengths, birth weights, head circumferences, and Apgar scores were within the normal ranges for gestational age. Age of FXS diagnosis ranged from 1;1–10;0 (years;months). The only participant who was diagnosed before 3 years of age was genetically tested early due to known familial FXS (Child 5). Clinical diagnosis revealed the following comorbidities: ASD for Child 2; anxiety disorder for Child 1, Child 2, and Child 6.

2.1.5 Participants of Study E

Study E investigated the socio-communicative development of individuals later diagnosed with ASD throughout the first 2 years of life. Video material was assigned to the following three age bands: age band 9–12 months, age band 13–18 months, and age band 19–24 months. For age band 9–12 months, we had available data of six participants (ASD 1–ASD 6; all males). For age band 13–18 months, home video material of four participants was available (ASD 1, ASD 2, ASD 6, ASD 7; all males). For age band 19–24 months, we analysed data of five participants (ASD 2, ASD 4, ASD 8–ASD 10; all males). All participants were singletons and born to monolingual Italian-speaking parents. All participants were born

at term after normal pregnancies with normal birth weight. For ASD 2, a prolonged delivery and mild neonatal asphyxia were reported. All parents reported that the development of their child seemed to be normal at least during the first year of life.

ASD diagnosis of all participants was performed by the child psychiatrist Professor Michele Zappella (affiliated with the Tuscany Rett Centre Versilia Hospital, Lido di Camaiore, Italy and the Foundation for Autism Research, New York, USA) based on clinical evaluation according to the ICD-10 criteria for ASD and/or the Autism Diagnostic Observation Schedule (ADOS; Lord, et al., 2001; applied for ASD 7, score = 28; ASD 8, score = 19; ASD 10, score = 18), the Autism Behavior Checklist (ABC; Krug, Arick and Almond, 1980; applied for ASD 1, score = 47), and/or the Childhood Autism Rating Scale (CARS; Schopler, Reichler and Rochen Renner, 1988; applied for ASD 1, score = 38; ASD 3, score = 36; ASD 6, score = 33; ASD 8, score = 44.6; ASD 10, score = 32.5). The following comorbidities were reported: Tourette syndrome for ASD 1 and ASD 3; ADHD for ASD 3 and ASD 10.

2.1.6 Participants of Study F

Study F investigated the typical socio-communicative development throughout the first 2 years of life. Video material was assigned to the following three age bands: age band 9–12 months, age band 13–18 months, and age band 19–24 months. Participants of Study F were partly also included in Studies B and C. For consistency with Study B, the participants' denomination in Study F was kept the same as in Study B (TD 1–TD 5; all females). For age band 9–12 months, we had available data of eight participants (TD 1–TD 5 were females; TD 7, TD 9 and TD 10 were males). For age band 13–18 months, home video material of ten participants was available (TD 1–TD 6 were females; TD 7–TD 10 were males). For age band 19–24 months, we analysed data of eight participants (TD 1, TD 2, TD 4–TD 6 were females; TD 7–TD 9 were males). All participants were singletons and born to monolingual German-speaking parents. Pregnancies and deliveries were uneventful. Birth lengths, birth weights, head circumferences, and Apgar scores were within the normal ranges. None of the participants was diagnosed with a developmental disorder.

2.2 Audio-video material

The extensive audio-video material analysed for Studies A–F was part of iDN's research database GUARDIAN (Pokorny, et al., 2016) that contains videos of the first years of life of individuals with various LRDDs and individuals with TD. The audio-video material used for Studies A–F (hereafter referred to as home videos) was recorded by the participants' parents when their children were between 9 and 24 months of age. At the time of recording, the parents were not aware of the medical condition (RTT, PSV, FXS, ASD) or the neurotypical outcome of their children. The audio-video recordings were made during different settings: typical family routines such as play situations, feeding, or bathing as well as special events such as family gatherings or birthday parties. All interactive scenes (i.e., all situations in which a communicative act between the participant and another person may be expected) were included in the final data set. Scenes in which the children were not seen or were out of hearing range from the camera's perspective were excluded. There is a certain inter-individual variability in types and number of different scenes as well as duration of the video material.

The home video material was first assigned to the respective months of age; for example, video material assigned to 12 months includes video material throughout the twelfth month of age. The first birthday is the last day included in the 12-month-video-file. In case of preterm birth, the video material was corrected for age (e.g., video material of a child who was born at 34 weeks of gestation that was taken 8 weeks after birth would have been assigned to the 1-month-video-file). For analyses of Studies A–F, the video material was further grouped into the relevant age bands: 9–12 months, 13–18 months, and 19–24 months. The home video material of all participants with the respective medical conditions or TD were included when at least 10 minutes of audio-video recordings for the respective age band was available in GUARDIAN. In some cases, parents documented age or date of their video material. For a proportion of home videos, we had no information available from the parents; in these cases, various hints such as birthday parties or the parents' voice saying the age of the child or the date of recording on the camera served as the basis for correct age assignments. Video scenes that were impossible to assign to a specific age were excluded. Subsequent to the age assignment, a research assistant blind to the purpose of the study checked the recordings for sufficient quality standards and prepared the recordings for coding with the Noldus Observer XT software (www.noldus.com).

2.2.1 Audio-video material of Study A

The footage of all six participants with RTT between 9 and 12 months of age comprised a total of 459 minutes[21] (Bartl-Pokorny, et al., 2013b). The footage per participant ranged from 12 to 236 minutes. The mean video duration was 77 minutes; the median video duration was 37 minutes.

2.2.2 Audio-video material of Study B

Study B (Bartl-Pokorny, et al., 2016) compared five individuals with RTT and five individuals with TD between 9 and 12 months of age. The total footage for both groups comprised 759 minutes.

The footage of RTT 1–RTT 5 was 414 minutes. The footage per participant with RTT ranged from 12 to 236 minutes. The mean video duration was 83 minutes; the median video duration was 28 minutes.

The footage of TD 1–TD 5 was 345 minutes. The footage per participant with TD ranged from 19 to 148 minutes. The mean video duration was 69 minutes; the median video duration was 59 minutes.

A Mann-Whitney U test showed that the RTT group (n = 5) and the TD group (n = 5) did not significantly differ in terms of video durations [U = 10.000, p = .602].

2.2.3 Audio-video material of Study C

Study C (Marschik, et al., 2014b) compared a female with RTT (Participant A), a female with PSV (Participant B), and a female with TD (Participant C) between 9 and 24 months of age. The footage of all three participants between 9 and 24 months of age comprised a total of 1275 minutes (Marschik, et al., 2014b). Participant A had a footage of 977 minutes, Participant B had 126 minutes, and Participant C had 172 minutes. The available home video material allowed for a splitting into three pre-defined age intervals: 9–12 months (total duration: 342 minutes), 13–18 months (total duration: 623 minutes), and 19–24 months of age (total duration: 310 minutes).

[21] Video durations in minutes were rounded to integer values.

2.2.4 Audio-video material of Study D

Study D analysed individuals with FXS between 9 and 24 months of age (parts of the results have been published in Marschik, et al., 2014c). The total footage between 9 and 24 months comprised 721 minutes.

The footage of the seven participants with FXS in age band 9–12 months comprised a total of 224 minutes (Marschik, et al., 2014c). The footage per participant ranged from 21 to 68 minutes. The mean video duration was 32 minutes; the median video duration was 27 minutes.

The footage of the seven participants with FXS in age band 13–18 months comprised a total of 361 minutes. The footage per participant ranged from 11 to 93 minutes. The mean video duration per participant was 52 minutes; the median video duration was 60 minutes.

The footage of the three participants with FXS in age band 19–24 months comprised a total of 136 minutes. The footage per participant ranged from 15 to 78 minutes. The mean video duration per participant was 45 minutes; the median video duration was 43 minutes.

A Kruskal-Wallis test showed that the video durations of the three distinct age bands ($n_{9–12}$, $n_{13–18}$, n19–24 did not significantly differ [$H(2) = 1.302$, $p = .522$].

2.2.5 Audio-video material of Study E

Study E analysed individuals with ASD between 9 and 24 months of age. The total footage between 9 and 24 months comprised 355 minutes.

The footage of the six participants with ASD in age band 9–12 months comprised a total of 126 minutes. The footage per participant ranged from 12 to 30 minutes. The mean video duration was 21 minutes; the median video duration was also 21 minutes.

The footage of the four participants with ASD in age band 13–18 months comprised a total of 102 minutes. The footage per participant ranged from 12 to 58 minutes. The mean video duration was 26 minutes; the median video duration was 17 minutes.

The footage of the five participants with ASD in age band 19–24 months comprised a total of 128 minutes. The footage per participant ranged from 10 to 44 minutes. The mean video duration was 26 minutes; the median video duration was 21 minutes.

A Kruskal-Wallis test showed that the video durations of the three distinct age bands did not significantly differ [$H(2) = 0.506$, $p = .776$].

2.2.6 Audio-video material of Study F

Study F analysed individuals with TD between 9 and 24 months of age. The total footage between 9 and 24 months comprised 1357 minutes.

The footage of the eight participants with TD in age band 9–12 months comprised a total of 413 minutes. The footage per participant ranged from 13 to 149 minutes. The mean video duration was 52 minutes; the median video duration was 38 minutes.

The footage of all ten participants with TD in age band 13–18 months comprised a total of 501 minutes. The footage per participant ranged from 14 to 149 minutes. The mean video duration was 50 minutes; the median video duration was 43 minutes.

The footage of the eight participants with TD in age band 19–24 months comprised a total of 443 minutes. The footage per participant ranged from 14 to 138 minutes. The mean video duration was 55 minutes; the median video duration was 44 minutes.

A Kruskal-Wallis test showed that the video durations of the three distinct age bands did not significantly differ [$H(2) = 0.244$, $p = .885$].

2.3 Inventory of Potential Communicative Acts

The coding for Studies A–F was based on the Inventory of Potential Communicative Acts (IPCA; Sigafoos, et al., 2000a; Sigafoos, Arthur-Kelly and Butterfield, 2006). The IPCA is an interview schedule originally developed to assist in assessment and intervention planning for individuals with developmental disabilities and severe communication impairments (Sigafoos, et al., 2000a). The original aim was to gather descriptive information on the potential communicative repertoires of individuals with developmental disabilities by means of interviews of therapists with caregivers/teachers of the respective individuals (Sigafoos, et al., 2000a; 2000b; Sigafoos, Arthur-Kelly and Butterfield, 2006; Didden, et al., 2010; Braddock, et al., 2015). To date there are no norm data available for the IPCA. The IPCA consists of more than 50 questions asking caregivers/teachers how an individual communicates ten different pragmatic functions (hereafter referred to as communicative functions; Sigafoos, et al., 2000a; Sigafoos, Arthur-Kelly and Butterfield, 2006). These ten communicative functions are: (i) social convention, (ii) attention to self, (iii) reject/protest, (iv) request an object (v) request an action, (vi) request information, (vii) comment, (viii) choice making, (ix) answer, and (x) imitation. Please see Table 3 for example questions.

Table 3: Example questions used in the Inventory of Potential Communicative Acts (IPCA; Sigafoos, et al., 2000a; Sigafoos, Arthur-Kelly and Butterfield, 2006) to delineate the potential communicative repertoires of individuals with developmental disabilities.

Communicative function	**Example questions**
(i) Social convention	How does the child greet? How does the child react to his/her own name?
(ii) Attention to self	How does the child try to get your attention? How does the child seek comfort?
(iii) Reject/protest	How does the child express that he/she does not like something? How does the child react when a favourite toy is taken away?
(iv) Request an object	How does the child request a toy? How does the child ask for more of something?
(v) Request an action	How does the child express that he/she needs help with dressing? How does the child let you know that he/she wants you to come closer?
(vi) Request information	How does the child ask for the name of an object? How does the child let you know that he/she does not understand what you said?
(vii) Comment	How does the child express when he/she is happy? How does the child express when he/she is tired?
(viii) Choice making	How does the child make a choice between two or more objects? How does the child make a choice between two or more activities?
(ix) Answer	How does the child indicate yes/no in response to a question? How does the child react when someone talks to him/her?
(x) Imitation	Does the child imitate speech? Does the child imitate pointing?

For this thesis, the IPCA was applied to delineate the socio-communicative repertoires of the participants based on home videos. For this, all communicative forms that were observed in the home videos were noted. These were defined as all behaviours of infants and toddlers used for communicative purposes, i.e., the coder interprets a behaviour as being intentionally used to communicate with other people. A behaviour was annotated as intentional if the caregiver/interaction partner of the participant visible in the video reacted to the participant's behaviour, e.g., via joint gaze at an object, speech ('Ah, you want to eat an apple!'), if an object was passed to the participant after the participant reached for it, and so on. Communicative forms of the participants were either nonverbal or verbal behaviours. Nonverbal behaviours were further classified into one of three subcategories: body movements (e.g., moving towards a person, reaching for an object, touching a person), gestures (e.g., waving bye-bye, index finger pointing, passing an object to another person), or facial expressions (e.g., eye contact, social smiling). Verbal behaviours were further classified into one of two subcategories: non-linguistic vocalisations (e.g., crying, fussing, pleasure vocalisations), or (pre-)linguistic vocalisations (e.g., babbling, proto-words, word combinations).

In a next step, each behaviour was assigned to one of the above-mentioned ten communicative functions. An example: An infant reaches for an object and seeks eye contact with the parent while producing unspecified vocalisations. The parent interprets these behaviours as attempts to request the object and passes the object to the child. In this example, the coder would note the three communicative forms *reaching for an object* (subcategory body movements), *eye contact* (subcategory facial expressions), and *unspecified vocalisations* (subcategory non-linguistic vocalisations) as well as the communicative function *request an object*[22]. The final data set contains all different communicative forms/behaviours and all different communicative functions that were observed per participant and age band. It was not indicated how often a certain communicative form/behaviour or function was observed in the footage.

In order to answer RQ3, all body movements, gestures, and facial expressions were assigned to the category nonverbal behaviours (NV); vocalisations were assigned to one of the categories non-linguistic vocalisations (NL), or (pre-)linguistic vocalisations (L). For each behaviour type (NV, NL, L) the proportion of communicative functions the behaviour type was used for, was calculated (hereafter referred to as NV_{prop}, NL_{prop}, L_{prop}). An example: A child was observed to have six different communicative functions; NV were used for five different communicative functions, NL for four functions, and L were used for all six

[22] Certain types of communicative forms (e.g., eye contact, unspecified vocalisation) might be used for further communicative functions in other video sequences.

functions. This means that the child used NV for 83.33% of the observed communicative functions (NV_{prop} = 83.33%), NL for 66.67% of the observed communicative functions (NL_{prop} = 66.67%), and L for 100% of the observed communicative functions (L_{prop} = 100%).

As described in Chapter 1.2, intentional communication starts around 8–9 months of age. Therefore, we coded potential communicative forms and functions for Studies A–F not before the ninth month of age.

I analysed the data for each of the Studies A–F. A second coder[23] analysed (a) the whole data set of a study, (b) parts of the data set, or (c) discussed certain scenes with the first coder that were difficult to rate (e.g., due to linguistic background of the participating families, background noise in the home video, etc.). Inter-rater reliability was calculated via percentage of agreement, i.e., the ratio of behaviours the two coders agreed on to the total number of behaviours coded, similar to the approach suggested by Syed and Nelson (2015) and Bradley, et al. (2007). Disagreements occurred in between 7% and 13% of the ratings per study. The highest agreements were achieved for the communicative functions 'attention to self', 'request an object', 'comment', and 'imitation' as well as for the communicative forms reaching, crying, pleasure vocalisations, eye contact, and word combinations. A great proportion of initial disagreements between the two coders concerned the classification of intentionality of waving-like hand movements that were interpreted either as gestures or as stereotypies. Moreover, some disagreements on the intentionality of babbling vocalisations, on the differentiation of unspecified vocalisations and babbling (e.g., transition from cooing and marginal babbling to canonical babbling), and on the differentiation of babbling and single words (e.g., /mama/) occurred. All sequences with disagreements were discussed by the two coders and resolved through consensus resulting in a single agreed upon rating.

[23] The second coder was either Professor Peter B Marschik, the main supervisor of this thesis and director of the Research Unit iDN, or another postgraduate researcher of iDN experienced in the analysis of socio-communicative and speech-language development.

2.4 Statistics

Statistical analyses were performed using IBM SPSS Statistics 25 (SPSS Inc., Chicago, IL).[24] As the available samples in my studies were small and normal distributions could not be assumed in most cases, the data were processed with nonparametric procedures. Only if the cell size was greater than five, data were submitted to statistical comparison. Otherwise, descriptive statistics were presented only. Mann-Whitney U test was run to compare the difference of two independent groups. Spearman rank-order correlation coefficient (r_s) was applied to estimate the association between two variables. Kruskal-Wallis H test was run to compare three or more independent groups and Friedman test or Wilcoxon signed-rank test were applied for repeated measures of two or more retests. η^2 was chosen to report the effect size of U test and H test. Kendall's coefficient of concordance was reported for the effect size of Friedman test. Alpha was set to .05, two-tailed for all analyses.

[24] Statistics was advised by Professor Christa Einspieler, who is the second supervisor of my thesis, Dr Dajie Zhang, and Magdalena Krieber-Tomantschger of the Research Unit iDN. All inferential statistical calculations were performed in cooperation with Dr. Dajie Zhang and Magdalena Krieber-Tomantschger.

3 Results

3.1 Results of Study A

3.1.1 Study A: Communicative forms (related to RQ1a[25])

The participants with RTT of Study A (Bartl-Pokorny, et al., 2013b) were observed to use 15 different communicative forms in age band 9–12 months (range: 3–12, median: 6, mean: 7[26]). Overall, seven different body movements, two facial expressions/eye movements, five non-linguistic vocalisation types, and one gesture were observed (Table 4).

The correlation between video duration and number of different forms was significant [r_s = .886, p = .019, n = 6].

3.1.2 Study A: Communicative functions (related to RQ2a)

The total number of different communicative functions observed per participant ranged from three to seven (median: 6, mean: 5). All participants 'gained attention to self' and 'answered'. None of the participants 'requested information' or 'made choices'. Varying numbers of participants were observed to perform other communicative functions according to the IPCA including 'commenting', 'social convention', 'rejecting', or 'requesting an object'. Table 5 lists the observed communicative functions for each participant.

The correlation between video duration and number of different functions was significant [r_s = .812, p = .050, n = 6].

3.1.3 Study A: Verbal and non-verbal communication (related to RQ3a)

Table 5 lists the behaviour types (i.e., non-verbal behaviour, NV; non-linguistic vocalisation, NL; (pre-)linguistic vocalisation, L) that were used by each participant for each observed communicative function. None of the participants were observed to use L (such as babbling or proto-words) for communicative purposes. NV dominated over NL for seven of the eight observed communicative functions in the dataset. More children used NL than NV for the communicative function 'reject/protest'.

[25] For Research questions (RQ), please see Chapter 1.4.
[26] Median and mean results were rounded to integer values.

Table 4: Communicative forms observed in six participants with Rett syndrome from 9–12 months of age (Bartl-Pokorny, et al., 2013b).

Communicative forms	**Participants**					
	Child 1	**Child 2**	**Child 3**	**Child 4**	**Child 5**	**Child 6**
Body movements						
Reaching		✓	✓	✓		✓
Moving closer		✓	✓			
Moving/turning away			✓			
Touching/tweaking persons				✓	✓	
Patting			✓			
Retaining objects		✓				
(Imitation of) manual routine[1]		✓	✓		✓	
Facial expressions/eye movements						
Eye contact	✓	✓	✓	✓	✓	✓
Smiling	✓	✓	✓		✓	✓
Gestures						
Waving hello/bye-bye			✓			
Non-linguistic vocalisations						
Unspecified vocalisations	✓	✓	✓	✓		✓
Fussing		✓	✓			✓
Crying			✓	✓		
Pleasure vocalisation			✓			✓
Laughing						✓
Total number of different forms	**3**	**8**	**12**	**5**	**4**	**7**

Abbreviation: ✓ = form observed in the dataset.
[1] Examples for manual routine: Participant gives a toy to his father after the father asked for the toy; participant pretends to eat an apple after the father pretended to do so.

Table 5: Communicative functions (according to the Inventory of Potential Communicative Acts, IPCA; Sigafoos, et al., 2000a; Sigafoos, Arthur-Kelly and Butterfield, 2006) observed (●) or not observed ( ) for six participants between 9 and 12 months of age, later diagnosed with Rett syndrome. For each observed communicative function, the behaviour type (i.e., non-verbal behaviour, non-linguistic vocalisation, (pre-)linguistic vocalisation) is given (Bartl-Pokorny, et al., 2013b).[27]

	Social convention			**Attention to self**			**Reject/ protest**			**Request object**			**Request action**			**Request information**			**Comment**			**Choice making**			**Answer**			**Imitate**			**Total**		
	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L
Child 1					●															●						●					3		
				✓	✓														✓	✓					✓	✓					3	3	0
Child 2					●			●			●			●						●						●			●			7		
				✓	✓		✓	✓		✓	✓		✓						✓						✓	✓		✓			7	6	0
Child 3		●			●			●												●						●			●			6		
	✓			✓	✓		✓	✓											✓	✓					✓			✓			6	3	0
Child 4					●			●			●															●						4		
				✓	✓			✓		✓	✓															✓	✓					3	4	0
Child 5		●			●															●						●			●			5		
	✓			✓															✓						✓			✓			5	0	0
Child 6		●			●			●			●									●						●						6		
	✓	✓		✓				✓		✓									✓	✓					✓						5	3	0
Total		3			6			4			3			1			0			5			0			6			3				
	3	1	0	6	4	0	2	4	0	3	2	0	1	0	0	0	0	0	5	3	0	0	0	0	6	3	0	3	0	0			

Abbreviations: NV = non-verbal behaviour; NL = non-linguistic vocalisation; L = (pre-)linguistic vocalisation; ● = function observed in the dataset; ✓ = behaviour type observed in the dataset.

[27] Table 5 is based on information provided in Tables 2 and 3 of the original article published in Research in Developmental Disabilities (Bartl-Pokorny, et al., 2013b, p.3135; doi: 10.1016/j.ridd.2013.06.040) and adds further details on the behaviour types observed for each participant.

3.2 Results of Study B

3.2.1 Study B: Communicative forms (related to RQ1a, RQ1b)

For Study B (Bartl-Pokorny, et al., 2016), the total amount of socio-communicative forms per participant ranged from three to twelve in the RTT group (median: 5, mean: 6) and from seven to 17 in the TD group (median: 16, mean: 14). Participants with RTT did not use (pre-)linguistic vocalisations in communicative settings. The communicative milestones of babbling and (proto-)words were achieved by all participants with TD. One of five participants with RTT was observed to use a gesture. Four of five participants with TD had a repertoire of one or more gestures; index finger pointing was observed in one of them (TD 2). Details are provided in Table 6.

For the RTT group (n = 5), the correlation between video duration and number of different forms was significant [r_s = .900, p = .037]. For the TD group (n = 5), the correlation between video duration and number of different forms was not significant [r_s = .821, p = .089].

3.2.2 Study B: Communicative functions (related to RQ2a, RQ2b)

The total number of different communicative functions observed per participant ranged from three to six in the RTT group (median: 5, mean: 5) and from four to eight in the TD group (median: 7, mean: 6). All participants with RTT used at least one communicative form to ‘gain attention to self’ and to ‘answer’. In addition to ‘gaining attention to self’ and ‘answering’, all females with TD were observed to ‘reject/protest’ and to ‘comment’. One participant (i.e., TD 5) was observed to ‘request an action’. No participant was observed to ‘make choices’ or to ‘request information’. Table 7 lists the observed communicative functions for the participants RTT 1–RTT 5 and TD 1–TD 5.

For the RTT group (n = 5), the correlation between video duration and number of different functions was significant [r_s = .975, p = .005]. For the TD group (n = 5), the correlation between video duration and number of different forms was not significant [r_s = .821, p = .089].

3.2.3 Study B: Verbal and non-verbal communication (related to RQ3a, RQ3b)

Table 7 lists the behaviour types (i.e., NV, NL, L) that were used by each participant for each observed communicative function. None of the participants with RTT was observed to use L for communicative purposes. NV dominated over NL for six of the seven observed communicative functions in the RTT dataset. More participants with RTT used NL than NV for the communicative function 'reject/protest'. L were used for five of the eight observed communicative functions in the TD group. NV were observed to dominate over NL and L for three communicative functions (i.e., 'social convention', 'request an action', 'answer') in the TD group. NL dominated over the other behaviour types for two communicative functions (i.e., 'reject/protest', 'comment'). L dominated over the other behaviour types for 'imitating'. All participants with TD used all three behaviour types to 'gain attention to self'.

Table 6: Communicative forms observed in five participants with Rett syndrome and five participants with typical development from 9–12 months of age (Bartl-Pokorny, et al., 2013b).

Communicative forms	**Participants with RTT**					**Participants with TD**				
	RTT 1	**RTT 2**	**RTT 3**	**RTT 4**	**RTT 5**	**TD 1**	**TD 2**	**TD 3**	**TD 4**	**TD 5**
Body movements										
Reaching		✓	✓		✓	✓	✓	✓		✓
Moving closer		✓							✓	✓
Moving towards object										✓
Moving/turning away		✓								✓
Touching/tweaking persons			✓	✓		✓			✓	✓
Patting		✓								
Retaining objects							✓	✓		
Rejecting objects/moving objects away							✓	✓		
(Imitation of) manual routine[1]		✓		✓		✓	✓	✓		✓
Hand flapping								✓		
Clapping hands										✓
Facial expressions/eye movements										
Eye contact	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Smiling	✓	✓		✓	✓	✓	✓	✓	✓	✓
Gestures										
Waving hello/bye-bye		✓					✓			✓
Index finger pointing							✓			
Please/I want							✓			
Passing an object						✓		✓		✓
Demonstrating an object								✓		✓
Non-linguistic vocalisations										
Unspecified vocalisations	✓	✓	✓		✓	✓	✓	✓	✓	✓
Fussing		✓			✓	✓	✓	✓		✓
Crying		✓	✓			✓	✓	✓	✓	
Pleasure vocalisation		✓			✓	✓	✓	✓		✓
Laughing					✓		✓	✓		
(Pre-)linguistic vocalisations										
Babbling						✓	✓	✓		✓
(Proto-)words						✓	✓	✓	✓	✓
Total number of different forms	**3**	**12**	**5**	**4**	**7**	**12**	**16**	**16**	**7**	**17**

Abbreviations: RTT = Rett syndrome; TD = typical development; ✓ = form observed in the dataset.

[1] Examples for manual routine: Participant gives a toy to his father after the father asked for the toy; participant pretends to eat an apple after the father pretended to do so.

Table 7: Communicative functions (according to the Inventory of Potential Communicative Acts, IPCA; Sigafoos, et al., 2000a; Sigafoos, Arthur-Kelly and Butterfield, 2006) observed (●) or not observed ( ) for five participants with Rett syndrome and five participants with typical development from 9–12 months of age. For each observed communicative function, the behaviour type (i.e., non-verbal behaviour, non-linguistic vocalisation, (pre-)linguistic vocalisation) is given (Bartl-Pokorny, et al., 2016).

	Social convention			**Attention to self**			**Reject/ protest**			**Request object**			**Request action**			**Request information**			**Comment**			**Choice making**			**Answer**			**Imitate**			**Total**		
	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L
RTT 1					●															●						●						3	
				✓	✓														✓	✓					✓	✓					3	3	0
RTT 2		●			●			●												●						●			●			6	
	✓			✓	✓		✓	✓											✓	✓					✓			✓			6	3	0
RTT 3					●			●			●															●						4	
				✓	✓			✓		✓	✓															✓	✓					3	4	0
RTT 4		●			●															●						●			●			5	
	✓			✓															✓						✓			✓			5	0	0
RTT 5		●			●			●			●									●						●						6	
	✓	✓		✓				✓		✓									✓	✓					✓						5	3	0
Total RTT		3			5			3			2			0			0			4			0			5			2				
	3	1	0	5	3	0	1	3	0	2	1	0	0	0	0	0	0	0	4	3	0	0	0	0	5	2	0	2	0	0			
TD 1		●			●			●												●						●						5	
	✓			✓	✓	✓	✓	✓											✓	✓	✓				✓	✓					5	4	2
TD 2		●			●			●			●									●						●			●			7	
	✓	✓		✓	✓	✓	✓	✓		✓	✓								✓	✓					✓	✓	✓			✓	6	6	3
TD 3		●			●			●			●									●						●			●			7	
	✓			✓	✓	✓	✓	✓		✓	✓								✓	✓					✓	✓	✓		✓	✓	6	6	3
TD 4					●			●												●						●						4	
				✓	✓	✓		✓												✓					✓	✓						2	4	1
TD 5		●			●			●			●			●						●						●			●			8	
	✓			✓	✓	✓	✓	✓	✓	✓	✓		✓						✓	✓					✓		✓			✓	7	4	4
Total TD		4			5			5			3			1			0			5			0			5			3				
	4	1	0	5	5	5	4	5	1	3	3	0	1	0	0	0	0	0	4	5	1	0	0	0	5	4	3	0	1	3			

Abbreviations: NV = non-verbal behaviour; NL = non-linguistic vocalisation; L = (pre-)linguistic vocalisation; RTT = Rett syndrome; TD = typical development; ● = function observed in the dataset; ✓ = behaviour type observed in the dataset.

3.3 Results of Study C

3.3.1 Study C: Communicative forms (related to RQ1a, RQ1b, RQ1c)

In Study C (Marschik, et al., 2014b) we observed 27 different communicative forms between 9 and 24 months of age (Participant A, RTT: 15; Participant B, PSV: 18; Participant C, TD: 26). Participant A produced eleven different forms in age band 9–12 months, 13 different communicative forms in age band 13–18 months, and ten different communicative forms in age band 19–24 months (i.e., 11/13/10 communicative forms). Participant B produced 6/10/15 communicative functions and Participant C produced 16/19/20 communicative forms. Participant A did not use (pre-)linguistic verbal forms in communicative settings throughout the observation period, Participant B used (proto-)words from 9–12 months of age onwards, and Participant C had word combinations in age band 19–24 months. We observed three different gestures in the dataset of Participant A; Participant B had six different gestures and Participant C had seven different gestures. More details are provided in Table 8 below.

3.3.2 Study C: Communicative functions (related to RQ2a, RQ2b, RQ2c)

Participant A used the observed communicative forms for six communicative functions in age band 9–12 months, eight functions in age band 13–18 months, and six functions in age band 19–24 months (i.e., 6/8/6 communicative functions). Participant B had 3/6/8 communicative functions. Participant C had 7/9/9 communicative functions. ‘Requesting information’ was not observed in the participants with RTT; ‘choice making’ was not observed in all three participants. More details are provided in Table 9.

3.3.3 Study C: Verbal and non-verbal communication (related to RQ3a, RQ3b, RQ3c)

All participants used NL for communicative purposes during the whole observation period. Over time, the functional use of NL showed different patterns: NL decreased in Participant C, increased in Participant B and showed an increase-decrease pattern in Participant A. L were observed in Participants B and C; Participant C used L for more communicative functions in all age bands than Participant B. For details, please see Table 9.

Table 8: Communicative forms observed in a participant with Rett syndrome (A), a participant with the preserved speech variant of Rett syndrome (B), and a participant with typical development (C) from 9–24 months of age (Marschik, et al., 2014b, p.36).

	Communicative forms	**C**			**B**			**A**		
		9-12 mo	**13-18 mo**	**19-24 mo**	**9-12 mo**	**13-18 mo**	**19-24 mo**	**9-12 mo**	**13-18 mo**	**19-24 mo**
Body movements	Moving/turning away	□	●	□	□	□	●	●	□	●
	Moving closer	□	●	●	□	●	●	●	●	□
	Taking person somewhere (by hand)	□	□	●	□	□	□	□	□	□
	Touching (person)	□	●	●	●	□	●	□	□	●
	Reaching	●	●	●	□	●	●	●	●	●
	Moving object away	●	□	●	□	□	□	□	□	□
	Retaining object	●	□	□	□	□	□	□	□	□
	(Imitation of) manual routine	●	●	●	□	□	●	●	●	□
Facial expressions/ Eye movements	Eye contact	●	●	●	●	●	●	●	●	●
	Smiling	●	●	●	□	●	●	●	●	●
Gestures	Index finger pointing	●	●	●	●	●	●	□	□	□
	Waving indicating hello/bye bye	●	●	●	□	●	□	●	●	□
	Extending arms seeking comfort	□	●	●	□	□	●	□	●	□
	Demonstrating an object	□	●	□	●	●	□	□	□	□
	Shaking the head indicating no	□	□	●	□	□	●	□	□	□
	Passing an object	□	●	□	□	□	□	□	●	□
	Please/I want	●	●	●	□	□	□	□	□	□
	Sending kisses	□	□	□	□	□	●	□	□	□
Non-linguistic vocalizations	Fussing	●	●	●	□	□	●	●	●	●
	Crying	●	●	□	□	□	□	●	●	●
	Pleasure vocalizations	●	●	●	□	●	□	●	●	●
	Laughing	●	●	●	□	□	●	□	●	●
	Unspecified vocalizations	●	●	●	●	●	●	●	●	●
(Pre)linguistic vocalizations	Babbling (canonical and variegated)	●	□	□	□	□	□	□	□	□
	Onomatopoetics	□	□	●	□	□	□	□	□	□
	(Proto-)words	●	●	●	●	●	●	□	□	□
	Word combinations	□	□	●	□	□	□	□	□	□
	Total: Communicative forms per age period	16	19	20	6	10	15	11	13	10
	Total: Different communicative forms	26			18			15		

Abbreviations: mo = months; ● = form observed in the dataset; □ form absent in the dataset.

This table is reproduced from Marschik, et al. (2014b, p.36), i.e., Marschik, P.B., Bartl-Pokorny, K.D., Tager-Flusberg, H., Kaufmann, W.E., Pokorny, F., Grossmann, T., Windpassinger, C., Petek, E. and Einspieler, C., 2014b. Three different profiles: Early socio-communicative capacities in typical Rett syndrome, the preserved speech variant and normal development. *Developmental Neurorehabilitation*, 17(1), pp.34-8; doi:10.3109/17518423.2013.837537, with permission of the publisher Taylor & Francis (https://www.tandfonline.com). This is the version of the article Table 1 (p.36) prior to formatting by the publisher. American English spelling is kept from the original.

Table 9: Communicative functions (according to the Inventory of Potential Communicative Acts, IPCA; Sigafoos, et al., 2000a; Sigafoos, Arthur-Kelly and Butterfield, 2006) observed (●) or not observed ( ) for a participant with Rett syndrome (A), a participant with the preserved speech variant of Rett syndrome (B), and a participant with typical development (C) from 9–24 months of age (Marschik, et al., 2014b). For each observed communicative function, the behaviour type (i.e., non-verbal behaviour, non-linguistic vocalisation, (pre-)linguistic vocalisation) is given (Marschik, et al., 2014b).

	Social convention			**Attention to self**			**Reject/ protest**			**Request object**			**Request action**			**Request information**			**Comment**			**Choice making**			**Answer**			**Imitate**			**Total**		
	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L
C 9–12		●			●			●			●									●						●			●			7		
	✓	✓		✓	✓	✓	✓	✓		✓	✓								✓	✓					✓	✓	✓			✓	6	6	3
C 13–18		●			●			●			●			●			●			●						●			●			9		
	✓			✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓		✓	✓	✓	✓					✓	✓	✓	✓		✓	9	5	8
C 19–24		●			●			●			●			●			●			●						●			●			9		
	✓		✓	✓		✓	✓	✓		✓		✓	✓		✓	✓		✓	✓	✓	✓					✓		✓			✓	8	2	8
B 9–12		●			●															●						●						3		
	✓			✓	✓	✓																				✓	✓					3	2	1
B 13–18		●			●						●			●						●						●						6		
	✓	✓		✓	✓	✓				✓			✓	✓					✓	✓					✓						6	4	1
B 19–24		●			●			●			●			●						●						●			●			8		
	✓	✓	✓	✓	✓	✓	✓	✓		✓			✓	✓	✓				✓	✓	✓				✓	✓	✓	✓			8	6	5
A 9–12		●			●			●												●						●			●			6		
	✓			✓	✓		✓	✓											✓	✓					✓			✓			6	3	0
A 13–18		●			●			●			●			●						●						●			●			8		
	✓	✓		✓	✓			✓		✓	✓		✓						✓	✓					✓	✓		✓			7	6	0
A 19–24		●			●			●			●									●						●						6		
	✓			✓	✓		✓	✓		✓	✓								✓	✓					✓	✓					6	5	0

Abbreviations: NV = non-verbal behaviour; NL = non-linguistic vocalisation; L = (pre-)linguistic vocalisation; ● = function observed in the dataset; ✓ = behaviour type observed in the dataset.

3.4 Results of Study D

3.4.1 Study D: Communicative forms (related to RQ1a)

For Study D (parts of the results were published in Marschik, et al., 2014c), the total amount of socio-communicative forms per participant with FXS ranged from two to eleven in age band 9–12 months (median: 7, mean: 7), from three to 19 in age band 13–18 months (median: 5, mean: 8), and from nine to 16 in age band 19–24 months (median: 9, mean: 11). In age band 9–12 months, two of the seven participants used babbling for communicative purposes; (proto-)words were not observed. In age band 13–18 months, two of seven participants used (pre-)linguistic vocalisations for communicative purposes; all three participants in age band 19–24 months used (proto-)words for communicative purposes. Word combinations were not observed in the dataset. One of seven participants used a gesture (i.e., demonstrating an object) in age band 9–12 months; index finger pointing was observed in Child 6 and Child 2 in age band 13–18 months; Child 2 used two additional gestures. Gestures were not observed for the other five participants in this age band. Child 6 and Child 7 used three gestures each in age band 19–24 months; Child 5 used two gestures. For details, please see Tables 10a, 10b, and 10c.

For Study D, the correlation between video duration and number of different forms showed a trend in age band 9–12 months [$r_s = .750$, $p = .052$, n = 7] and was not significant in age band 13–18 months [$r_s = .245$, $p = .596$, n = 7]. Correlation was not calculated for age band 19–24 months due to limited cell size (n = 3).

3.4.2 Study D: Communicative functions (related to RQ2a)

The total number of different communicative functions observed per participant ranged from three to six in age band 9–12 months (median: 4, mean: 4), from three to seven in age band 13–18 months (median: 5, mean: 5) and from five to seven in age band 19–24 months (median: 6, mean: 6). In age band 9–12 months, all participants used at least one communicative form to ‘gain attention to self. ‘Requesting action’, ‘requesting information’, ‘choice making’, and ‘imitating’ were not observed. In age band 13–18 months, all participants used at least one communicative form to ‘answer’. ‘Request action’, ‘choice making’, and ‘request information’ were not observed in this age band. In age band 19–24 months, all three participants were observed to ‘gain attention to self’, ‘request action’, ‘comment’, and ‘answer’. ‘Choice making’ and ‘requesting information’ were not observed. For details, please see Tables 11a, 11b, and 11c.

For age band 9–12 months, the correlation between video duration and number of different functions was not significant [r_s = .505, p = .247, n = 7]. For age band 13–18 months, the correlation between video duration and number of different functions was not significant [r_s = .614, p = .143, n = 7]. Correlation was not calculated for age band 19–24 months due to limited cell size (n = 3).

3.4.3 Study D: Verbal and non-verbal communication (related to RQ3a)

Tables 11a, 11b, and 11c list the behaviour types (i.e., NV, NL, L) that were used by each participant for the observed communicative functions. In age band 9–12 months, NV dominated over NL for three of the six observed communicative functions. NV and NL were equally often observed for 'reject/protest' and 'request an object'. Only for 'commenting' NL dominated over NV. L were used by one participant respectively to 'gain attention to self', 'comment', and 'answer'. In age band 13–18 months, NV dominated over NL for five of the seven observed communicative functions. NV and NL were equally often observed for 'commenting'. Each behaviour type was used once for 'imitation' in age band 13–18 months. In age band 19–24 months, NV dominated over the other two behaviour types for five of eight observed communicative functions. NV and L were equally often observed for 'reject/protest', 'request object', and 'imitate'. NL were not observed to dominate over the other behaviour types for any communicative functions in age band 19–24 months.

In a next step, the proportions of communicative functions for which the participants used non-verbal behaviours, non-linguistic vocalisations, and (pre-)linguistic vocalisations (i.e., NV_{prop}, NL_{prop}, L_{prop}) were calculated for each age band (Figure 1). Values for median, minimum, and maximum proportions are provided in Appendix 6.1 (Table 16). Statistical calculation aimed to analyse differences between age band 9–12 months (n = 7) and age band 13–18 months (n = 7); age band 19–24 months was not included due to limited cell size (n = 3). A Wilcoxon signed-rank test revealed that NV_{prop}, NL_{prop}, and L_{prop} were not significantly different in the participants with FXS between the two age bands 9–12 months and 13–18 months [NV_{prop}: Z = -1.604, p = .109; NL_{prop}: Z = -1.069, p = .285; L_{prop}: Z = -.447, p = .655].

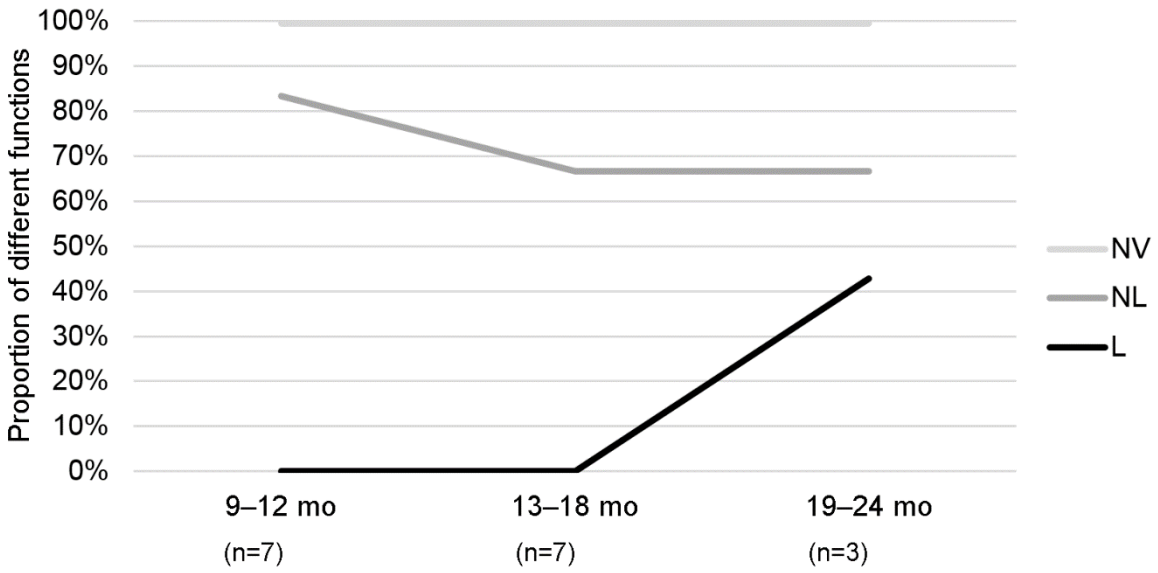

Figure 1: Median proportions of observed communicative functions for which the participants with fragile X syndrome used the behaviour types ‘nonverbal behaviour’ (NV), ‘non-linguistic vocalisation’ (NL), and ‘(pre-)linguistic vocalisation’ (L) in the three age bands 9–12 months (mo), 13–18 mo, and 19–24 mo.

Table 10a: Communicative forms observed in seven participants with fragile X syndrome from 9–12 months of age (Marschik, et al., 2014c).

Communicative forms	**Participants**						
	Child 1	**Child 2**	**Child 3**	**Child 4**	**Child 5**	**Child 6**	**Child 7**
Body movements							
Reaching	✓	✓			✓	✓	✓
Touching person				✓		✓	
Moving/turning away					✓		
Retaining objects					✓		
Hand flapping							✓
Manual routine[1]	✓						
Facial expressions/eye movements							
Eye contact	✓	✓	✓	✓	✓	✓	✓
Smiling	✓	✓	✓	✓	✓	✓	
Gestures							
Demonstrating an object							✓
Non-linguistic vocalisations							
Unspecified vocalisations	✓	✓			✓	✓	✓
Fussing	✓	✓		✓	✓	✓	
Crying	✓				✓	✓	
Pleasure vocalisations	✓	✓			✓	✓	
Laughing	✓	✓			✓	✓	
(Pre-)linguistic vocalisations							
Babbling	✓				✓		
Total number of different forms	**10**	**7**	**2**	**4**	**11**	**9**	**5**

Abbreviation: ✓ = form observed in the dataset.
[1] Examples for manual routine: Participant gives a toy to his father after the father asked for the toy; participant pretends to eat an apple after the father pretended to do so.

Table 10b: Communicative forms observed in seven participants with fragile X syndrome from 13–18 months of age.

Communicative forms	**Age band 13–18 months**						
	Child 2	**Child 3**	**Child 4**	**Child 5**	**Child 6**	**Child 8**	**Child 9**
Body movements							
Reaching	✓	✓	✓				✓
Touching person	✓						
Moving/turning away	✓			✓			
Retaining objects				✓			✓
Hand flapping	✓			✓			
Manual routine[1]	✓				✓		
Hugging person	✓						
Moving closer	✓				✓	✓	
Facial expressions/eye movements							
Eye contact	✓	✓	✓	✓	✓	✓	✓
Smiling	✓	✓	✓	✓	✓	✓	
Gestures							
Demonstrating an object	✓						
Index finger pointing	✓				✓		
Extending arms seeking comfort	✓						
Non-linguistic vocalisations							
Unspecified vocalisations	✓			✓	✓	✓	
Fussing	✓		✓	✓	✓		
Crying	✓				✓		
Pleasure vocalisations	✓			✓	✓		
Laughing	✓			✓	✓		
(Pre-)linguistic vocalisations							
Babbling						✓	
(Proto-)words	✓						
Onomatopoetics	✓						
Total number of different forms	**19**	**3**	**4**	**9**	**10**	**5**	**3**

Abbreviation: ✓ = form observed in the dataset.
[1] Example for manual routine: Participant gives a toy to his father after the father asked for the toy.

Table 10c: Communicative forms observed in three participants with fragile X syndrome from 19–24 months of age.

Communicative forms	**Age band 19–24 months**		
	Child 5	**Child 6**	**Child 7**
Body movements			
Reaching		✓	
Touching person		✓	✓
Moving/turning away		✓	
Hand flapping	✓		✓
(Imitation of) manual routine[1]	✓		
Moving closer		✓	
Rejecting objects		✓	
Turning towards person			✓
Facial expressions/eye movements			
Eye contact	✓	✓	✓
Smiling		✓	✓
Gestures			
Demonstrating an object	✓	✓	
Index finger pointing		✓	✓
Extending arms seeking comfort			✓
Waving hello/bye-bye		✓	
Passing an object	✓		
Please/I want			✓
Non-linguistic vocalisations			
Unspecified vocalisations	✓	✓	
Fussing		✓	
Pleasure vocalisations	✓	✓	
Laughing	✓	✓	
(Pre-)linguistic vocalisations			
Babbling		✓	
(Proto-)words	✓	✓	✓
Total number of different forms	**9**	**16**	**9**

Abbreviation: ✓ = form observed in the dataset.
[1] Examples for manual routine: Participant gives a toy to his father after the father asked for the toy; participant pretends to eat an apple after the father pretended to do so.

Table 11a: Communicative functions (according to the Inventory of Potential Communicative Acts, IPCA; Sigafoos, et al., 2000a; Sigafoos, Arthur-Kelly and Butterfield, 2006) observed (●) or not observed ( ) for seven participants between 9 and 12 months of age, later diagnosed with fragile X syndrome. For each observed communicative function, the behaviour type (i.e., non-verbal behaviour, non-linguistic vocalisation, (pre-)linguistic vocalisation) is given (Marschik, et al., 2014c).[28]

	Social convention			**Attention to self**			**Reject/ protest**			**Request object**			**Request action**			**Request information**			**Comment**			**Choice making**			**Answer**			**Imitate**			**Total**		
	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L
Child 1					●						●									●						●						4	
				✓	✓	✓				✓	✓								✓	✓					✓	✓					4	4	1
Child 2					●						●									●						●						4	
				✓	✓					✓	✓								✓	✓					✓	✓					4	4	0
Child 3		●			●																					●						3	
	✓			✓																					✓						3	0	0
Child 4		●			●															●						●						4	
	✓			✓	✓															✓					✓							3	2	0
Child 5		●			●			●			●									●						●						6	
	✓			✓	✓		✓	✓		✓	✓								✓	✓	✓				✓	✓	✓				6	5	2
Child 6		●			●						●									●						●						5	
	✓	✓		✓	✓					✓	✓								✓	✓					✓	✓					5	5	0
Child 7					●						●															●						3	
				✓	✓					✓	✓														✓						3	2	0
Total		4			7			1			5			0			0			5			0			7			0				
	4	1	0	7	6	1	1	1	0	5	5	0	0	0	0	0	0	0	4	5	1	0	0	0	7	4	1	0	0	0			

Abbreviations: NV = non-verbal behaviour; NL = non-linguistic vocalisation; L = (pre-)linguistic vocalisation; ● = function observed; ✓ = behaviour type observed.

[28] Table 11a is based on information provided in Tables 2 and 3 of the original article published in Research in Developmental Disabilities (Marschik, et al., 2014c, p.599; doi: 10.1016/j.ridd.2014.01.004) and adds further details on the behaviour types observed for each participant.

Table 11b: Communicative functions (according to the Inventory of Potential Communicative Acts, IPCA; Sigafoos, et al., 2000a; Sigafoos, Arthur-Kelly and Butterfield, 2006) observed (●) or not observed ( ) for seven participants between 13 and 18 months of age, later diagnosed with fragile X syndrome. For each observed communicative function, the behaviour type (i.e., non-verbal behaviour, non-linguistic vocalisation, (pre-)linguistic vocalisation) is given.

Age band 13–18 months																																	
	Social convention			**Attention to self**			**Reject/ protest**			**Request object**			**Request action**			**Request information**			**Comment**			**Choice making**			**Answer**			**Imitate**			**Total**		
	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L
Child 2		●			●			●			●									●						●				7		
	✓			✓	✓	✓	✓	✓		✓	✓	✓							✓	✓	✓				✓	✓	✓			✓	6	5	5
Child 3		●			●						●									●						●					5		
	✓			✓						✓									✓						✓						5	0	0
Child 4		●																		●						●					3		
	✓																			✓					✓	✓					2	2	0
Child 5		●			●			●												●						●			●			6		
	✓			✓	✓		✓	✓											✓	✓					✓	✓			✓		5	5	0
Child 6		●			●															●						●			●			5		
	✓	✓		✓	✓														✓	✓					✓	✓		✓			5	4	0
Child 8		●			●																					●					3		
	✓			✓	✓	✓																			✓						3	1	1
Child 9					●			●																		●					3		
				✓			✓																		✓						3	0	0
Total		6			6			3			2			0			0			5			0			7			3				
	6	1	0	6	4	2	3	2	0	2	1	1	0	0	0	0	0	0	4	4	1	0	0	0	7	4	1	1	1	1			

Abbreviations: NV = non-verbal behaviour; NL = non-linguistic vocalisation; L = (pre-)linguistic vocalisation; ● = function observed; ✓ = behaviour type observed.

Table 11c: Communicative functions (according to the Inventory of Potential Communicative Acts, IPCA; Sigafoos, et al., 2000a; Sigafoos, Arthur-Kelly and Butterfield, 2006) observed (●) or not observed ( ) for three participants between 19 and 24 months of age, later diagnosed with fragile X syndrome. For each observed communicative function, the behaviour type (i.e., non-verbal behaviour, non-linguistic vocalisation, (pre-)linguistic vocalisation) is given.

Age band 19–24 months																																	
	Social convention			**Attention to self**			**Reject/ protest**			**Request object**			**Request action**			**Request information**			**Comment**			**Choice making**			**Answer**			**Imitate**			**Total**		
	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L
Child 5		●			●									●						●						●					6		
	✓			✓	✓								✓	✓					✓	✓					✓	✓			✓		✓	6	4	1
Child 6		●			●			●			●			●						●						●					7		
	✓	✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓					✓	✓					✓						7	5	3
Child 7					●						●			●						●						●					5		
				✓		✓				✓		✓	✓		✓				✓						✓		✓				5	0	4
Total		2			3			1			2			3			0			3			0			3			1				
	2	1	0	3	2	2	1	0	1	2	1	2	3	2	1	0	0	0	3	2	0	0	0	0	4	1	1	1	0	1			

Abbreviations: NV = non-verbal behaviour; NL = non-linguistic vocalisation; L = (pre-)linguistic vocalisation; ● = function observed; ✓ = behaviour type observed.

3.5 Results of Study E

3.5.1 Study E: Communicative forms (related to RQ1a)

For Study E, the total amount of socio-communicative forms per participant with ASD ranged from three to nine in age band 9–12 months (median: 5, mean: 6), from four to eight in age band 13–18 months (median: 7, mean: 7), and from five to eleven in age band 19–24 months (median: 8, mean: 8). In age band 9–12 months, one of six participants (i.e., ASD 3) used (pre-)linguistic vocalisations for communicative purposes. In age band 13–18 months, three of four participants did so. In age band 19–24 months, (pre-)linguistic vocalisations for communicative purposes were observed in two of five participants. Word combinations were not observed in the dataset. Two participants used one gesture each in age band 9–12 months; one participant used two gestures in age band 13–18 months; three participants were observed to use at least one gesture in age band 19–24 months. Index finger pointing was observed in one participant, namely ASD 4, between 19 and 24 months of age. For details, please see Tables 12a, 12b, and 12c.

For Study E, the correlation between video duration and number of different forms was not significant for age band 9–12 months [r_s = .493, p = .321, n = 6] and age band 19–24 months [r_s = -.051, p = .935, n = 5]. Correlation was not calculated for age band 13–18 months due to limited cell size (n = 4).

3.5.2 Study E: Communicative functions (related to RQ2a)

The total number of different communicative functions observed per participant ranged from three to six in age band 9–12 months (median: 5, mean: 5), from three to five in age band 13–18 months (median: 5, mean: 5), and from two to five in age band 19–24 months (median: 5, mean: 4). In age band 9–12 months, all participants used at least one communicative form to ‘gain attention to self’ and to ‘answer’. ‘Request object’, ‘request action’, ‘request information’, and ‘choice making’ were not observed. In age band 13–18 months, all participants used at least one communicative form to ‘gain attention to self’ and to ‘answer’. ‘Request action’, ‘request information’, and ‘choice making’ were not observed. In age band 19–24 months, ‘answering’ was observed in all participants and none of the participants used communicative forms to ‘request information’ and ‘make choices’. ASD 2, the only participant from whom we had data available throughout the whole observation period, had five communicative functions in each age band. Tables 13a, 13b, and 13c list the observed communicative functions for the three distinct age bands.

For Study E, the correlation between video duration and number of different functions was not significant for age band 9–12 months [r_s = .500, p = .312, n = 6] and age band 19 – 24 months [r_s = .354, p = .559]. Correlation was not calculated for age band 13–18 months due to limited cell size (n = 4).

3.5.3 Study E: Verbal and non-verbal communication (related to RQ3a)

Tables 13a, 13b, and 13c list the behaviour types (i.e., NV, NL, L) that were used by each participant for the observed communicative functions. In age band 9–12 months, NV dominated over NL for three of the six observed communicative functions. NV and NL were equally often observed for 'attention to self' and 'imitation'. NL dominated over non-verbal behaviours for 'commenting'. L were used by one participant each for 'attention to self', 'answering', and 'imitation'. In age band 13–18 months, NV dominated over the other two behaviour types for 'social convention'. NV and L were equally often observed for 'request object' and 'imitate'. NL were observed to dominate over the other behaviour types for 'imitation'. All behaviour types were equally often observed to 'gain attention to self'. NV and NL were equally often observed for 'commenting' and 'answering'. In age band 19–24 months, NV dominated over the other behaviour types for 'social convention' and 'answering'. NV and NL were equally often observed for the other six present communicative functions. Two of five participants used L to 'gain attention to self'; L were not used for other communicative functions.

In a next step, the proportions of communicative functions for which the participants used non-verbal behaviours, non-linguistic vocalisations, and (pre-)linguistic vocalisations (i.e., NV_{prop}, NL_{prop}, L_{prop}) were calculated for each age band (Figure 2). Values for median, minimum, and maximum proportions are provided in Appendix 6.1 (Table 17). Statistical comparisons were not performed due to limited cell size in age band 13–18 months (n = 4).

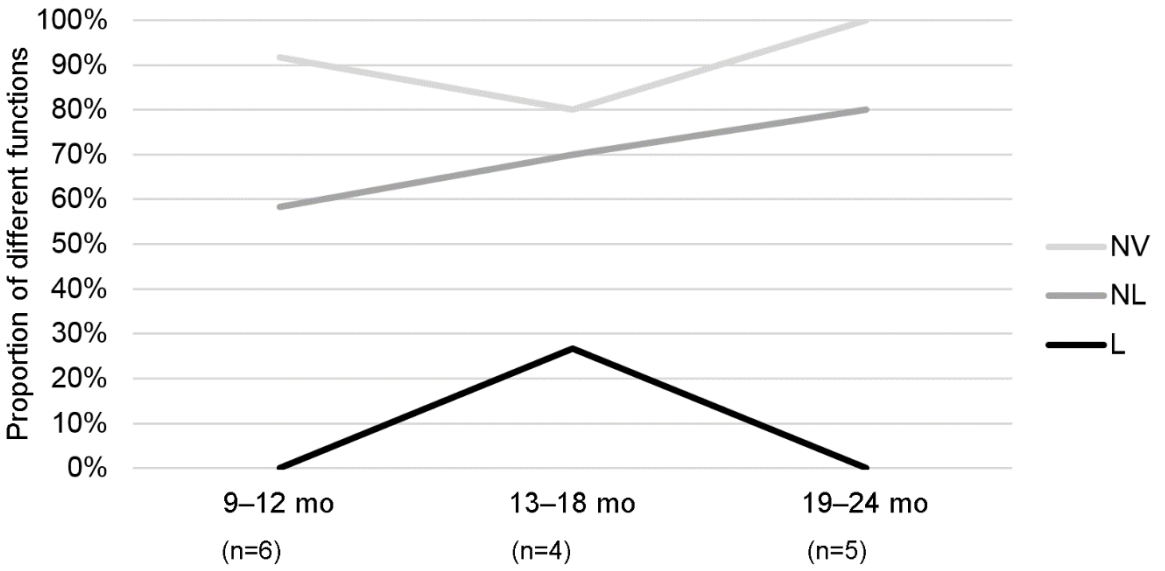

Figure 2: Median proportions of observed communicative functions for which the participants with autism spectrum disorder used the behaviour types ‘nonverbal behaviour’ (NV), ‘non-linguistic vocalisation’ (NL), and ‘(pre-)linguistic vocalisation’ (L) in the three age bands 9–12 months (mo), 13–18 mo, and 19–24 mo.

Table 12a: Communicative forms observed in six participants with autism spectrum disorder from 9–12 months of age.

Communicative forms	**9–12 months**					
	ASD 1	**ASD 2**	**ASD 3**	**ASD 4**	**ASD 5**	**ASD 6**
Body movements						
Moving closer					✓	
Touching/tweaking persons				✓	✓	
Retaining objects			✓			
(Imitation of) manual routine[1]		✓				✓
Clapping hands		✓	✓	✓		
Moving person away		✓				
Facial expressions/eye movements						
Eye contact	✓	✓	✓	✓	✓	✓
Smiling		✓	✓			✓
Gestures						
Passing an object				✓		
Shaking head indicating no			✓			
Non-linguistic vocalisations						
Unspecified vocalisations	✓	✓	✓	✓	✓	✓
Fussing		✓				
Crying	✓					
Pleasure vocalisation		✓	✓			✓
(Pre-)linguistic vocalisations						
Babbling			✓			
(Proto-)words			✓			
Total number of different forms	**3**	**8**	**9**	**5**	**4**	**5**

Abbreviations: ASD = autism spectrum disorder; ✓ = form observed in the dataset.
[1] Examples for manual routine: Participant gives a toy to his father after the father asked for the toy; participant pretends to eat an apple after the father pretended to do so.

Table 12b: Communicative forms observed in four participants with autism spectrum disorder from 13–18 months of age.

Communicative forms	**13–18 months**			
	ASD 1	**ASD 2**	**ASD 6**	**ASD 7**
Body movements				
Reaching			✓	✓
(Imitation of) manual routine[1]			✓	
Facial expressions/eye movements				
Eye contact	✓	✓	✓	✓
Smiling	✓	✓	✓	✓
Gestures				
Waving hello/bye-bye				✓
Please/I want				✓
Non-linguistic vocalisations				
Unspecified vocalisations	✓	✓	✓	✓
Pleasure vocalisation	✓	✓	✓	
Laughing			✓	
(Pre-)linguistic vocalisations				
Babbling	✓		✓	
(Proto-)words	✓			✓
Onomatopoetics				✓
Total number of different forms	**6**	**4**	**8**	**8**

Abbreviations: ASD = autism spectrum disorder; ✓ = form observed in the dataset.
[1] Examples for manual routine: Participant gives a toy to his father after the father asked for the toy; participant pretends to eat an apple after the father pretended to do so.

Table 12c: Communicative forms observed in five participants with autism spectrum disorder from 19–24 months of age.

Communicative forms	**19–24 months**				
	ASD 2	**ASD 4**	**ASD 8**	**ASD 9**	**ASD 10**
Body movements					
Reaching					✓
Moving closer				✓	
Moving/turning away			✓	✓	✓
Touching/tweaking persons				✓	✓
Rejecting objects/moving objects away					✓
(Imitation of) manual routine[1]		✓			✓
Clapping hands	✓				
Taking person somewhere by hand				✓	
Moving person away			✓		
Facial expressions/eye movements					
Eye contact	✓	✓	✓	✓	✓
Smiling	✓		✓	✓	
Gestures					
Waving hello/bye-bye		✓			
Index finger pointing		✓			
Passing an object				✓	
Shaking head indicating no					✓
Sending kisses		✓			
Non-linguistic vocalisations					
Unspecified vocalisations	✓		✓	✓	✓
Fussing	✓		✓	✓	✓
Pleasure vocalisation			✓	✓	
Laughing					
(Pre-)linguistic vocalisations					
Babbling				✓	
(Proto-)words			✓		
Total number of different forms	**5**	**5**	**8**	**11**	**9**

Abbreviations: ASD = autism spectrum disorder; ✓ = form observed in the dataset.
[1] Examples for manual routine: Participant gives a toy to his father after the father asked for the toy; participant pretends to eat an apple after the father pretended to do so.

Table 13a: Communicative functions (according to the Inventory of Potential Communicative Acts, IPCA; Sigafoos, et al., 2000a; Sigafoos, Arthur-Kelly and Butterfield, 2006) observed (●) or not observed ( ) for six participants between 9 and 12 months of age, later diagnosed with autism spectrum disorder. For each observed communicative function, the behaviour type (i.e., non-verbal behaviour, non-linguistic vocalisation, (pre-)linguistic vocalisation) is given.

Age band 9–12 months																																	
	Social convention			**Attention to self**			**Reject/ protest**			**Request object**			**Request action**			**Request information**			**Comment**			**Choice making**			**Answer**			**Imitate**			**Total**		
	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L
ASD 1		●			●															●						●					4		
	✓			✓	✓															✓					✓						3	2	0
ASD 2					●			●												●						●			●			5		
				✓	✓		✓													✓					✓	✓			✓			3	4	0
ASD 3		●			●			●												●						●			●			6		
	✓			✓	✓	✓	✓												✓	✓					✓		✓			✓	5	2	3
ASD 4		●			●																					●			●			4		
	✓			✓	✓																				✓			✓			4	1	0
ASD 5		●			●																					●						3		
	✓			✓	✓																				✓	✓					3	2	0
ASD 6		●			●															●						●			●			5		
	✓			✓	✓														✓	✓					✓	✓		✓	✓		5	4	0
Total		5			6			2			0			0			0			4			0			6			4				
	5	0	0	6	6	1	2	0	0	0	0	0	0	0	0	0	0	0	2	4	0	0	0	0	6	3	1	2	2	1			

Abbreviations: NV = non-verbal behaviour; NL = non-linguistic vocalisation; L = (pre-)linguistic vocalisation; ASD = autism spectrum disorder; ● = function observed; ✓ = behaviour type observed.

Table 13b: Communicative functions (according to the Inventory of Potential Communicative Acts, IPCA; Sigafoos, et al., 2000a; Sigafoos, Arthur-Kelly and Butterfield, 2006) observed (●) or not observed ( ) for four participants between 13 and 18 months of age, later diagnosed with autism spectrum disorder. For each observed communicative function, the behaviour type (i.e., non-verbal behaviour, non-linguistic vocalisation, (pre-)linguistic vocalisation) is given.

Age band 13–18 months																																	
	Social convention			**Attention to self**			**Reject/ protest**			**Request object**			**Request action**			**Request information**			**Comment**			**Choice making**			**Answer**			**Imitate**			**Total**		
	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L
ASD 1					●															●						●					3		
					✓	✓													✓	✓					✓	✓					2	3	1
ASD 2		●			●															●						●			●			5	
	✓			✓															✓	✓					✓	✓			✓		4	3	0
ASD 6		●			●															●						●			●			5	
	✓			✓	✓	✓													✓	✓					✓	✓		✓	✓		5	4	1
ASD 7		●			●						●															●			●			5	
	✓		✓	✓	✓	✓				✓		✓													✓	✓	✓		✓	✓	4	3	5
Total		3			4			0			1			0			0			3			0			4			3				
	3	0	1	3	3	3	0	0	0	1	0	1	0	0	0	0	0	0	3	3	0	0	0	0	4	4	1	1	3	1			

Abbreviations: NV = non-verbal behaviour; NL = non-linguistic vocalisation; L = (pre-)linguistic vocalisation; ASD = autism spectrum disorder; ● = function observed; ✓ = behaviour type observed.

Table 13c: Communicative functions (according to the Inventory of Potential Communicative Acts, IPCA; Sigafoos, et al., 2000a; Sigafoos, Arthur-Kelly and Butterfield, 2006) observed (●) or not observed ( ) for five participants between 19 and 24 months of age, later diagnosed with autism spectrum disorder. For each observed communicative function, the behaviour type (i.e., non-verbal behaviour, non-linguistic vocalisation, (pre-)linguistic vocalisation) is given.

Age band 19–24 months																																	
	Social convention			**Attention to self**			**Reject/ protest**			**Request object**			**Request action**			**Request information**			**Comment**			**Choice making**			**Answer**			**Imitate**			**Total**		
	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L
ASD 2		●			●															●						●			●			5	
	✓			✓	✓														✓	✓					✓	✓			✓			4	4	0
ASD 4																										●			●			2	
																									✓			✓			2	0	0
ASD 8		●			●			●												●						●						5	
	✓			✓	✓	✓	✓	✓											✓	✓					✓	✓						5	4	1
ASD 9					●			●						●						●						●						5	
				✓	✓	✓	✓	✓					✓	✓					✓	✓					✓							5	4	1
ASD 10		●			●			●			●															●						5	
	✓			✓	✓		✓	✓		✓	✓														✓							5	3	0
Total		3			4			3			1			1			0			3			0			5			2				
	3	0	0	4	4	2	3	3	0	1	1	0	1	1	0	0	0	0	3	3	0	0	0	0	5	2	0	1	1	0			

Abbreviations: NV = non-verbal behaviour; NL = non-linguistic vocalisation; L = (pre-)linguistic vocalisation; ASD = autism spectrum disorder; ● = function observed; ✓ = behaviour type observed.

3.6 Results of Study F

3.6.1 Study F: Communicative forms (related to RQ1b)

For Study F, the total amount of socio-communicative forms per participant with TD ranged from five to 17 in age band 9–12 months (median: 11, mean: 11), from six to 22 in age band 13–18 months (median: 14, mean: 14), and from seven to 22 in age band 19–24 months (median: 15, mean: 15). In age band 9–12 months, five of eight participants used (pre-)linguistic vocalisations for communicative purposes. In age band 13–18 months, we observed (pre-)linguistic vocalisations in nine of the ten participants with TD; word combinations were noted for two of them. In age band 19–24 months, all participants used (pre-)linguistic vocalisations for communicative purposes; seven of eight participants used word combinations. Six of eight participants used one or more gestures in age band 9–12 months; nine of ten participants used two or more gestures in age band 13–18 months; all participants were observed to use gestures in age band 19–24 months. Index finger pointing was observed in all participants. For details, please see Tables 14a, 14b, and 14c.

For Study F, the correlation between video duration and number of different forms was significant for age band 9–12 months [r_s = .782, p = .022, n = 8], age band 13–18 months [r_s = .952, p = .000, n = 10], and age band 19 – 24 months [r_s = .762, p = .028, n = 8].

3.6.2 Study F: Communicative functions (related to RQ2b)

The total number of different communicative functions observed per participant ranged from four to eight in age band 9–12 months (median: 5, mean: 5), from five to nine in age band 13–18 months (median: 7, mean: 7), and from five to ten in age band 19–24 months (median: 8, mean: 7). In age band 9–12 months, all participants used at least one communicative form to ‘gain attention to self’, to ‘comment’, and to ‘answer’. ‘Request information’, and ‘choice making’ were not observed. In age band 13–18 months, all participants used at least one communicative form to ‘gain attention to self’, to ‘comment’, and to ‘answer’. ‘Choice making’ was not observed in this age band. In age band 19–24 months, ‘gaining attention to self’ and ‘answering’ were observed in all participants. Each communicative function was observed at least in one participant in this age band. For details, please see Tables 15a, 15b, and 15c.

For age band 9–12 months, the correlation between video duration and number of different functions was significant [r_s = .867, p = .005, n = 8]. The correlation between video

duration and number of different functions showed a trend in age band 13–18 months [r_s = .588, p = .074, n = 10]. For age band 19–24 months, the correlation between video duration and number of different functions was significant [r_s = .819, p = .013, n = 8].

3.6.3 Study F: Verbal and non-verbal communication (related to RQ3b)

Tables 15a, 15b, and 15c list the behaviour types (i.e., NV, NL, L) that were used by each participant for the observed communicative functions. In age band 9–12 months, NV dominated over NL for three of the eight observed communicative functions. NV and NL were equally often observed for 'attention to self' and 'request object'. NL dominated over non-verbal behaviours for 'reject/protest' and 'comment'. L dominated over the other behaviour types for 'imitation'. L were used by one to five participants for five different communicative functions. In age band 13–18 months, NV dominated over the other two behaviour types for 'social convention', 'request object', 'request action', 'request information', and 'answer'. NV and NL were equally often observed to 'gain attention to self'. NL were observed to dominate over the other behaviour types for 'reject/protest' and 'comment'. L dominated over the other behaviour types for 'imitation'. L were used for all observed communicative functions by one to eight participants each. In age band 19–24 months, NV dominated over the other behaviour types for 'social convention', 'request object', and 'request action'. NV and NL were equally often observed for 'reject/protest'. L dominated over the other two behaviour types to 'request information' and to 'imitate'. NV and L were equally often observed to 'gain attention to self' and to 'answer'. L were used by one to eight participants for all different communicative functions.

In a next step, the proportions of communicative functions for which the participants used non-verbal behaviours, non-linguistic vocalisations, and (pre-)linguistic vocalisations (i.e., NV_{prop}, NL_{prop}, L_{prop}) were calculated for each age band (Figure 3). Values for median, minimum, and maximum proportions are provided in Appendix 6.1 (Table 18). NV_{prop} did not change significantly with age, a Friedman test among three age bands ($n_{9–12}$ = 8, $n_{13–18}$ = 10, $n_{19–24}$ = 8) revealed $\chi^2(2)$ = 2.00, p = .368. However, NL_{prop} decreased significantly with age [$\chi^2(2)$ = 9.00, p = .011], with Kendall's coefficient of concordance being .75, indicating a large effect size. L_{prop}, on the other hand, increased significantly with age [$\chi^2(2)$ = 11.00, p = .004] with Kendall's coefficient of concordance being .92.

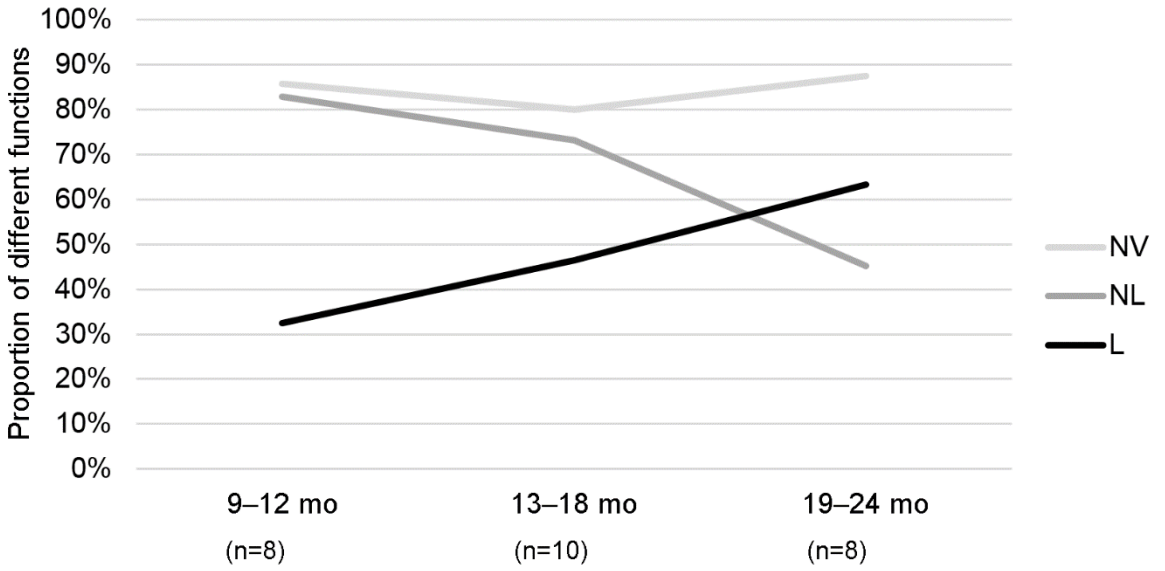

Figure 3: Median proportions of observed communicative functions for which the participants with typical development used the behaviour types ‘nonverbal behaviour’ (NV), ‘non-linguistic vocalisation’ (NL), and ‘(pre-)linguistic vocalisation’ (L) in the three age bands 9–12 months (mo), 13–18 mo, and 19–24 mo.

Table 14a: Communicative forms observed in eight participants with typical development from 9–12 months of age.

Communicative forms	**9–12 months**							
	TD 1	**TD 2**	**TD 3**	**TD 4**	**TD 5**	**TD 7**	**TD 9**	**TD 10**
Body movements								
Reaching	✓	✓	✓		✓	✓		
Moving closer				✓	✓			
Moving towards object					✓			
Moving/turning away					✓			
Touching/tweaking persons	✓			✓	✓			✓
Retaining objects		✓	✓					
Rejecting objects/moving objects away		✓	✓					
(Imitation of) manual routine[1]	✓	✓	✓		✓		✓	
Hand flapping			✓			✓		
Clapping hands					✓			
Touching objects						✓		
Opening mouth						✓		
Facial expressions/eye movements								
Eye contact	✓	✓	✓	✓	✓	✓	✓	✓
Smiling	✓	✓	✓	✓	✓	✓		✓
Gestures								
Waving hello/bye-bye		✓			✓			
Index finger pointing		✓				✓	✓	
Please/I want		✓						
Passing an object	✓		✓		✓			
Demonstrating an object			✓		✓			
Extending arms seeking comfort							✓	
Non-linguistic vocalisations								
Unspecified vocalisations	✓	✓	✓	✓	✓	✓	✓	✓
Fussing	✓	✓	✓		✓		✓	
Crying	✓	✓	✓	✓				✓
Pleasure vocalisation	✓	✓	✓		✓	✓	✓	
Laughing		✓	✓					
(Pre-)linguistic vocalisations								
Babbling	✓	✓	✓		✓			
(Proto-)words	✓	✓	✓	✓	✓			
Total number of different forms	**12**	**16**	**16**	**7**	**17**	**9**	**7**	**5**

Abbreviation: TD = typical development; ✓ = form observed in the dataset.
[1] Examples for manual routine: Participant gives a toy to his father after the father asked for the toy; participant pretends to eat an apple after the father pretended to do so.

Table 14b: Communicative forms observed in ten participants with typical development from 13–18 months of age.

Communicative forms	**13–18 months**									
	TD 1	**TD 2**	**TD 3**	**TD 4**	**TD 5**	**TD 6**	**TD 7**	**TD 8**	**TD 9**	**TD 10**
Body movements										
Reaching	✓	✓	✓	✓	✓	✓			✓	
Moving closer	✓	✓			✓	✓	✓		✓	
Moving/turning away		✓			✓	✓		✓		
Touching/tweaking persons	✓	✓		✓	✓	✓		✓	✓	
Rejecting objects/moving objects away								✓		
(Imitation of) manual routine[1]	✓	✓	✓	✓	✓	✓			✓	✓
Clapping hands				✓	✓					
Touching objects									✓	
Hugging persons	✓									
Taking persons somewhere by hand			✓	✓						
Facial expressions/eye movements										
Eye contact	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Smiling	✓	✓	✓		✓			✓	✓	✓
Gestures										
Waving hello/bye-bye		✓			✓					
Index finger pointing	✓	✓	✓	✓	✓	✓	✓		✓	✓
Please/I want		✓				✓			✓	
Passing an object	✓	✓		✓	✓	✓			✓	
Demonstrating an object		✓	✓	✓	✓		✓		✓	
Extending arms seeking comfort	✓	✓	✓		✓	✓				✓
Shaking the head indicating no										✓
Non-linguistic vocalisations										
Unspecified vocalisations	✓	✓	✓	✓	✓	✓		✓	✓	✓
Fussing		✓	✓	✓	✓	✓	✓	✓	✓	✓
Crying	✓	✓			✓	✓				✓
Pleasure vocalisations	✓	✓			✓	✓	✓	✓	✓	
Laughing		✓			✓			✓		
(Pre-)linguistic vocalisations										
Babbling	✓				✓	✓		✓	✓	
(Proto-)words	✓	✓	✓	✓	✓	✓			✓	✓
Onomatopoetics				✓	✓	✓				✓
Word combinations					✓					✓
Total number of different forms	**15**	**19**	**11**	**13**	**22**	**17**	**6**	**10**	**16**	**12**

Abbreviation: TD = typical development; ✓ = form observed in the dataset.

[1] Examples for manual routine: Participant gives a toy to his father after the father asked for the toy; participant pretends to eat an apple after the father pretended to do so.

Table 14c: Communicative forms observed in eight participants with typical development from 19–24 months of age.

Communicative forms	**19–24 months**							
	TD 1	**TD 2**	**TD 4**	**TD 5**	**TD 6**	**TD 7**	**TD 8**	**TD 9**
Body movements								
Reaching	✓	✓	✓			✓	✓	✓
Moving closer	✓	✓	✓	✓	✓		✓	✓
Moving towards object								✓
Touching/tweaking persons		✓		✓				✓
Retaining objects			✓					
Rejecting objects/moving objects away		✓						
(Imitation of) manual routine[1]	✓	✓		✓	✓	✓	✓	✓
Taking persons somewhere by hand		✓					✓	✓
Kissing persons on the cheek				✓				✓
Hiding behind person				✓				
Taking object away from other persons				✓				
Facial expressions/eye movements								
Eye contact	✓	✓	✓	✓	✓	✓	✓	✓
Smiling	✓	✓		✓	✓	✓		✓
Gestures								
Waving hello/bye-bye		✓						✓
Index finger pointing	✓	✓	✓	✓	✓	✓	✓	✓
Please/I want		✓						✓
Passing an object	✓			✓	✓		✓	✓
Demonstrating an object			✓	✓			✓	
Extending arms seeking comfort		✓						✓
Shaking the head indicating no		✓	✓	✓	✓			
Sending kisses							✓	✓
Nodding the head indicating yes			✓	✓				
Non-linguistic vocalisations								
Unspecified vocalisations	✓	✓	✓	✓			✓	✓
Fussing	✓	✓	✓				✓	✓
Crying	✓							✓
Pleasure vocalisation	✓	✓		✓			✓	✓
Laughing		✓		✓	✓		✓	
(Pre-)linguistic vocalisations								
Babbling/Babbling-like vocalisations						✓	✓	✓
(Proto-)words	✓	✓	✓	✓	✓		✓	✓
Onomatopoetics		✓		✓	✓		✓	✓
Word combinations	✓	✓	✓	✓	✓	✓	✓	
Total number of different forms	**13**	**20**	**12**	**19**	**11**	**7**	**17**	**22**

Abbreviation: TD = typical development; ✓ = form observed in the dataset.
[1] Examples for manual routine: Participant gives a toy to his father after the father asked for the toy; participant pretends to eat an apple after the father pretended to do so.

Table 15a: Communicative functions (according to the Inventory of Potential Communicative Acts, IPCA; Sigafoos, et al., 2000a; Sigafoos, Arthur-Kelly and Butterfield, 2006) observed (●) or not observed ( ) for eight typically developing participants between 9 and 12 months of age. For each observed communicative function, the behaviour type (i.e., non-verbal behaviour, non-linguistic vocalisation, (pre-)linguistic vocalisation) is given.

Age band 9–12 months																																	
	Social convention			**Attention to self**			**Reject/ protest**			**Request object**			**Request action**			**Request information**			**Comment**			**Choice making**			**Answer**			**Imitate**			**Total**		
	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L
TD 1		●			●			●												●						●					5		
	✓			✓	✓	✓	✓	✓											✓	✓	✓				✓	✓					5	4	2
TD 2		●			●			●			●									●						●			●			7		
	✓	✓		✓	✓	✓	✓	✓		✓	✓								✓	✓					✓	✓	✓			✓	6	6	3
TD 3		●			●			●			●									●						●			●			7		
	✓			✓	✓	✓	✓	✓		✓	✓								✓	✓					✓	✓	✓		✓	✓	6	6	3
TD 4					●			●												●						●						4		
				✓	✓	✓		✓												✓					✓	✓						2	4	1
TD 5		●			●			●			●			●						●						●			●			8		
	✓			✓	✓	✓	✓	✓	✓	✓	✓		✓						✓	✓					✓		✓			✓	7	4	4
TD 7					●						●									●						●						4		
				✓	✓					✓									✓						✓	✓						4	3	0
TD 9					●			●												●						●						4		
				✓	✓			✓												✓					✓							2	3	0
TD 10					●						●									●						●						4		
				✓	✓						✓									✓					✓	✓						2	4	0
Total		4			8			6			5			1			0			8			0			8			3					
	4	1	0	8	8	5	4	6	1	4	4	0	1	0	0	0	0	0	5	7	1	0	0	0	8	6	3	0	1	3			

Abbreviations: NV = non-verbal behaviour; NL = non-linguistic vocalisation; L = (pre-)linguistic vocalisation; TD = typical development; ● = function observed; ✓ = behaviour type observed.

Table 15b: Communicative functions (according to the Inventory of Potential Communicative Acts, IPCA; Sigafoos, et al., 2000a; Sigafoos, Arthur-Kelly and Butterfield, 2006) observed (●) or not observed ( ) for ten typically developing participants between 13 and 18 months of age. For each observed communicative function, the behaviour type (i.e., non-verbal behaviour, non-linguistic vocalisation, (pre-)linguistic vocalisation) is given.

Age band 13–18 months																																	
	Social convention			**Attention to self**			**Reject/ protest**			**Request object**			**Request action**			**Request information**			**Comment**			**Choice making**			**Answer**			**Imitate**			**Total**		
	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L
TD 1		●			●						●			●			●			●					●			●				8	
	✓	✓		✓	✓	✓				✓		✓	✓	✓	✓	✓	✓		✓	✓					✓	✓	✓	✓			8	6	4
TD 2		●			●			●			●			●			●			●					●			●				9	
	✓			✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓		✓	✓	✓	✓				✓	✓	✓	✓		✓	9	5	8
TD 3					●						●			●						●						●			●			6	
				✓	✓	✓				✓	✓		✓							✓					✓					✓	4	3	2
TD 4					●			●			●			●						●						●			●			7	
				✓	✓	✓		✓		✓		✓	✓	✓	✓					✓	✓				✓		✓		✓	✓	4	5	6
TD 5		●			●			●			●			●						●						●			●			8	
	✓		✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓					✓	✓					✓	✓	✓	✓	✓	✓	8	6	6
TD 6					●			●			●			●						●						●			●			7	
				✓	✓	✓	✓	✓		✓	✓		✓							✓					✓	✓	✓			✓	5	5	3
TD 7		●			●			●												●						●						5	
	✓			✓	✓		✓	✓												✓					✓	✓					4	4	0
TD 8					●			●												●						●			●			5	
				✓	✓		✓	✓											✓	✓					✓	✓	✓			✓	4	4	2
TD 9		●			●			●			●									●						●						6	
	✓			✓	✓	✓		✓		✓	✓								✓	✓					✓	✓	✓				5	5	2
TD 10		●			●			●			●			●						●						●			●			8	
	✓			✓	✓	✓		✓		✓		✓		✓	✓					✓					✓	✓	✓			✓	4	5	5
Total		6			10			8			8			7			2			10			0			10			8				
	6	1	1	10	10	8	5	8	2	8	3	5	6	5	4	2	1	1	5	10	2	0	0	0	10	8	8	3	2	7			

Abbreviations: NV = non-verbal behaviour; NL = non-linguistic vocalisation; L = (pre-)linguistic vocalisation; TD = typical development; ● = function observed; ✓ = behaviour type observed.

Table 15c: Communicative functions (according to the Inventory of Potential Communicative Acts, IPCA; Sigafoos, et al., 2000a; Sigafoos, Arthur-Kelly and Butterfield, 2006) observed (●) or not observed ( ) for eight typically developing participants between 19 and 24 months of age. For each observed communicative function, the behaviour type (i.e., non-verbal behaviour, non-linguistic vocalisation, (pre-)linguistic vocalisation) is given.

Age band 19–24 months																																
	Social convention			**Attention to self**			**Reject/ protest**			**Request object**			**Request action**			**Request information**			**Comment**			**Choice making**			**Answer**			**Imitate**			**Total**		
	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L	NV	NL	L
TD 1		●			●			●			●									●						●			●			7	
	✓			✓	✓	✓	✓	✓	✓	✓									✓	✓					✓	✓	✓	✓		✓	7	4	4
TD 2		●			●			●			●			●			●			●						●			●			9	
	✓		✓	✓		✓	✓	✓		✓		✓	✓		✓	✓		✓	✓	✓	✓				✓		✓			✓	8	2	8
TD 4		●			●			●			●						●									●						6	
	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓						✓							✓	✓	✓				5	4	6
TD 5		●			●			●			●			●			●			●			●			●			●			10	
	✓		✓	✓	✓	✓			✓	✓		✓	✓		✓			✓	✓	✓		✓		✓	✓	✓	✓			✓	7	3	9
TD 6					●			●			●			●						●						●						6	
				✓		✓	✓			✓		✓	✓		✓					✓					✓	✓	✓				5	2	4
TD 7		●			●															●						●			●			5	
	✓			✓		✓													✓						✓		✓	✓		✓	5	0	3
TD 8		●			●			●			●			●						●						●			●			8	
	✓			✓	✓	✓		✓		✓	✓		✓	✓					✓	✓					✓	✓	✓	✓	✓	✓	7	7	3
TD 9		●			●			●			●			●						●						●			●			8	
	✓			✓	✓	✓	✓	✓		✓			✓	✓	✓					✓					✓	✓	✓	✓		✓	7	5	4
Total		7			8			7			7			5			3			7			1			8			6				
	7	1	3	8	4	8	5	5	3	7	2	4	5	2	4	1	0	3	5	6	1	1	0	1	8	6	8	4	1	6			

Abbreviations: NV = non-verbal behaviour; NL = non-linguistic vocalisation; L = (pre-)linguistic vocalisation; TD = typical development; ● = function observed; ✓ = behaviour type observed.

3.7 Cross-condition comparison

The results on the early socio-communicative development of the participants later diagnosed with RTT, PSV, FXS, or ASD, and of the participants with TD were described in Chapters 3.1–3.6. A detailed discussion on similarities and differences concerning the socio-communicative development in different LRDDs as well as the comparison with the TD group is provided in Chapters 4.1.3, 4.2.3, and 4.3.3.

Due to the heterogeneous nature of the video material in terms of number and types of settings and video durations, inferential statistics was not applied to compare numbers of communicative forms and functions between the groups. In the following, the groups were compared based on the proportions of communicative functions for which the participants used non-verbal behaviours, non-linguistic vocalisations, and (pre-)linguistic vocalisations (i.e., NV_{prop}, NL_{prop}, L_{prop}); inferential statistics to compare participant groups was conducted if the cell size was greater than five[29].

3.7.1 Cross-condition comparison: Verbal and non-verbal communication

A cross-condition comparison was performed on the proportions of communicative functions for which the participants used non-verbal behaviours, non-linguistic vocalisations, and (pre-)linguistic vocalisations (i.e., NV_{prop}, NL_{prop}, L_{prop}). Values for median, minimum, and maximum proportions are provided in Appendix 6.1 (Tables 16–19).

Figure 4 depicts the median proportions for age band 9–12 months. In age band 9–12 months, NV_{prop}, NL_{prop}, and L_{prop} were not significantly different among the four participant groups RTT (n = 6), FXS (n = 7), TD (n = 8), and ASD (n =6); i.e., NV_{prop}: Kruskal-Wallis $H(3)$ = 5.218, p = .157; NL_{prop}: Kruskal-Wallis $H(3)$ = 3.503, p = .320; L_{prop}: Kruskal-Wallis $H(3)$ = 6.846, p =.077. Still, differences in L_{prop} among groups approached significance [Kruskal-Wallis $H(3)$ = 6.846, p = .077] with TD showing higher L_{prop} (median = 32.50%) than the other groups (median for all the other three groups was 0%).

[29] Inferential statistical calculations were done in cooperation with Dr. Dajie Zhang, member of the Research Unit iDN.

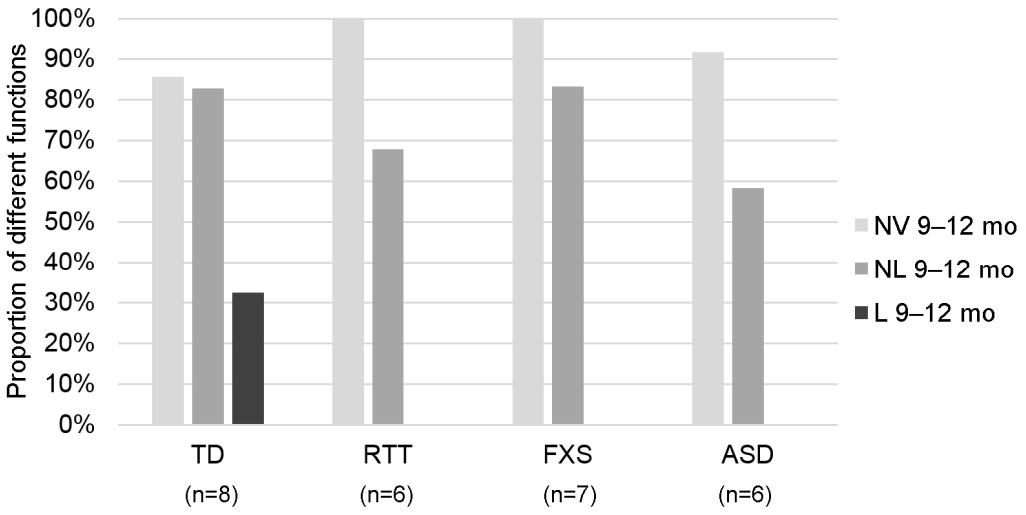

Figure 4: Median proportion of observed communicative functions for which the participants with typical development (TD), Rett syndrome (RTT), fragile X syndrome (FXS), or autism spectrum disorder (ASD) used the behaviour types 'nonverbal behaviour' (NV), 'non-linguistic vocalisation' (NL), and '(pre-)linguistic vocalisation' (L) in age band 9–12 months (mo).

In age band 13–18 months, NV_{prop} and NL_{prop} were not significantly different between the participants with TD (n = 10) and the participants with FXS (n = 7), i.e., NV_{prop}: Mann-Whitney U = 20.000, p = .161; NL_{prop}: Mann-Whitney U = 24.500, p = .315 (Figure 5). L_{prop} significantly differed between the participants with TD and the participants with FXS [Mann-Whitney U = 11.500, p = .019, η^2 = .31].

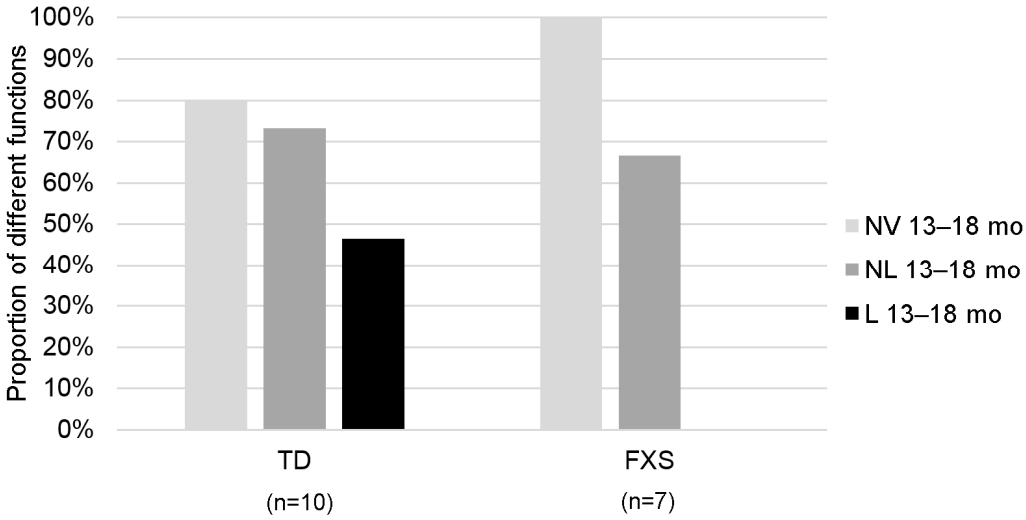

Figure 5: Median proportion of observed communicative functions for which the participants with typical development (TD) or fragile X syndrome (FXS) used the behaviour types 'nonverbal behaviour' (NV), 'non-linguistic vocalisation' (NL), and '(pre-)linguistic vocalisation' (L) in age band 13–18 months (mo).

In age band 19–24 months, NV_{prop} and NL_{prop} were not significantly different between the participants with TD (n = 8) and the participants with ASD (n = 5); i.e., NV_{prop}: Mann-Whitney U = 11.000, p = .222; NL_{prop}: Mann-Whitney U = 13.500, p = .354 (Figure 6). L_{prop} significantly differed between the participants with TD and the participants with ASD [Mann-Whitney U = .000, p = .002, η^2 = .66].

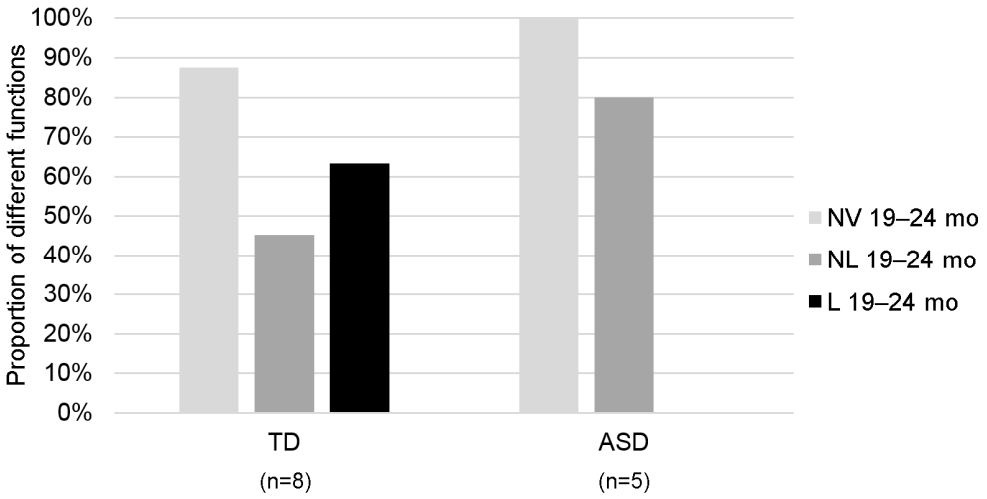

Figure 6: Median proportion of observed communicative functions for which the participants with typical development (TD) or autism spectrum disorder (ASD) used the behaviour types 'nonverbal behaviour' (NV), 'non-linguistic vocalisation' (NL), and '(pre-)linguistic vocalisation' (L) in age band 19–24 months (mo).

Figure 7 depicts L_{prop} of the TD, FXS, and ASD groups throughout the three age bands: L_{prop} steadily increased in the TD group; L_{prop} first increased and then decreased in the ASD group; L_{prop} increased from age band 13–18 months to age band 19–24 months in the FXS group.

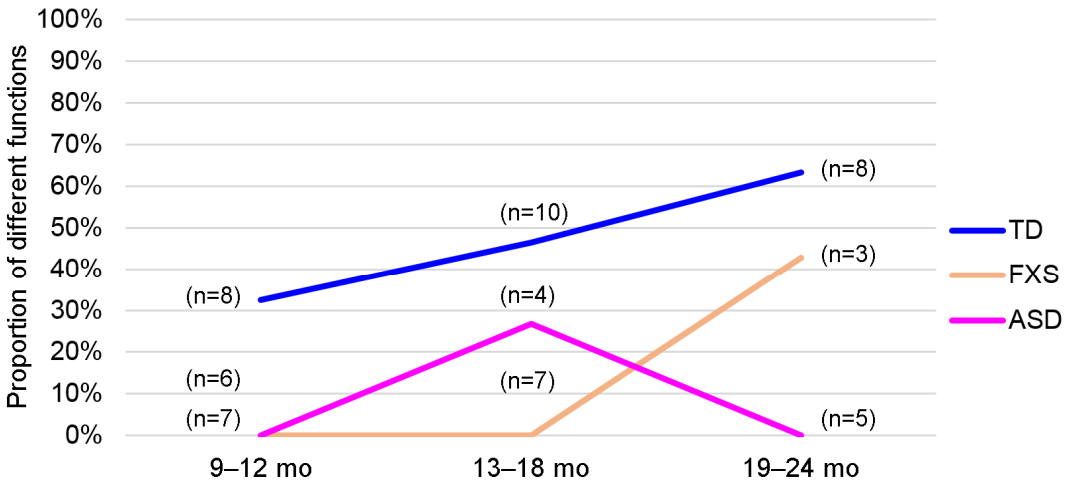

Figure 7: Median proportion of observed communicative functions for which the participants with typical development (TD), fragile X syndrome (FXS), or autism spectrum disorder (ASD) used the behaviour type '(pre-)linguistic vocalisation' (L) in the three age bands 9–12 months (mo), 13–18 mo, and 19–24 mo.

4 Discussion

The IPCA was repeatedly used to gather descriptive information on the potential communicative repertoires of children and adults with developmental disabilities (mostly RTT) by means of interviews of therapists with caregivers/teachers of the respective individuals (Sigafoos, et al., 2000a; 2000b; Sigafoos, Arthur-Kelly and Butterfield, 2006; Didden, et al., 2010; Braddock, et al., 2015). Marschik, et al. (2012a; including me as co-author and second coder) for the first time retrospectively applied the IPCA on children with a developmental disorder, namely PSV, before they were formally diagnosed. In the framework of this thesis, the IPCA was used for the first time to analyse the socio-communicative capacities of children with RTT, FXS, or ASD in their first 2 years of life by means of RVA (Bartl-Pokorny, et al., 2013b; Marschik, et al., 2014b; 2014c; Bartl-Pokorny, et al., 2016). Our results revealed peculiarities in the socio-communicative domains of our participants and indicated certain cross-condition differences.

In the following, the results for all research questions (RQs) related to three research topics (i) communicative forms, (ii) communicative functions), and (iii) verbal and non-verbal communication will be discussed.

4.1 Communicative forms (RQ1)

4.1.1 Communicative forms: Late recognised developmental disorders (RQ1a)

4.1.1.1 Communicative forms: Rett syndrome

Study A (Bartl-Pokorny, et al., 2013b) showed that individuals with RTT used various body movements (including the gesture waving hello/bye-bye that was noted for one participant), facial expressions/eye movements, and vocalisations for communicative purposes between 9 and 12 months of age. We found great inter-individual differences in the overall communicative repertoires of the participants with RTT (range of different communicative forms: 3–12). It is interesting to note that the one observed gesture was produced by the participant with the greatest number of different communicative forms (Child 3). It needs to be mentioned that Child 3 also had the most extensive video footage (i.e., 236 minutes) and therefore probably the most opportunities to produce communicative forms. We found that the longer the video material was the more different communicative forms were observed in the participants of Study A [r_s = .886, p = .019, n = 6]. On the one side, the unbalanced video material in terms of duration is one limitation of this thesis. On the other side, our major aim was the comprehensive description of the socio-communicative repertoires of individuals with a LRDD and we may have missed certain communicative forms when balancing the video material of the participants.

Interestingly, all vocalisations in the dataset were of non-linguistic character (e.g., crying, laughing); (pre-)linguistic vocalisations (e.g., babbling, proto-words) were not observed for communicative purposes. However, this does not necessarily mean that such behaviours were not observed in our corpus. To provide an example: The communicative form babbling was only noted if it was interpreted to fulfil communicative functions (e.g., to 'gain attention to self', to 'request an object'). The lack of (pre-)linguistic vocalisations is consistent with the findings of a previous study by Marschik, et al. (2013a)[30] showing that most females with RTT did not achieve certain early speech-language milestones. A reduced repertoire of communicative forms based on the IPCA protocol was also found in our previous study on individuals with PSV, even though conducted in the participants' second year of life (Marschik, et al., 2012a).

[30] It should be taken into account that the analysed video material of participants with RTT used for this thesis was partly overlapping with the video material used for previous publications on RTT by the Research Unit iDN.

Study C (Marschik, et al., 2014b) compared the socio-communicative development in the second year of life of one participant with RTT and one participant with PSV (and one participant with TD; see Chapter 4.1.2.1 for a comparison and discussion). Interestingly, the participant with RTT showed more overall communicative forms compared to the participant with PSV in the first two age bands, but had fewer communicative forms in age band 19–24 months. It is especially thrilling that the amount of different gestures decreased from three in age band 13–18 months to zero in 19–24 months in the participant with RTT, which may reflect the onset of regression in the second half of the second year of life. In contrast, the amount of different gestures increased from three to four in the participant with PSV whose regression was reported to start around her second birthday (Marschik, et al., 2014a[31]). Moreover, throughout the whole observation period the participant with RTT did not use her index finger to point, a communicative form that is considered essential for speech-language development (Capone and McGregor, 2004). She also did not use (pre)linguistic vocalisations in the video material of her first 2 years of life. In contrast, the participant with PSV used index finger pointing and (pre-)linguistic vocalisations for communicative purposes throughout the whole observation period.

Overall, the present findings reflect previous reports about profoundly reduced repertoires of communicative forms including gestural repertoires and early speech-language development in individuals with RTT or PSV (Tams-Little and Holdgrafer, 1996; Dahlgren Sandberg, et al., 2000; Didden, et al., 2010; Marschik, et al., 2009; Sigafoos, et al., 2011; Marschik, et al., 2012a; 2012b; 2012d; 2013). Our findings support the view that already the early (pre-regressional) development of individuals with RTT or PSV is atypical (e.g., Marschik, et al., 2013; 2014a).

4.1.1.2 Communicative forms: Fragile X syndrome

Study D (parts of the results were published in Marschik, et al., 2014c) showed that participants with FXS used various body movements, facial expressions/eye movements, and vocalisations for communicative purposes between 9 and 12 months of age. It was interesting to observe that one participant with FXS (Child 3) only used eye contact and smiling for communicative purposes in the 25 minutes of audio-video recordings we had available between 9 and 12 months of age. Only two of seven participants were observed to use babbling for communicative purposes; proto-words were not produced at all in age

[31] It may be interesting to note here that certain speech-language and socio-communicative abilities of the female with PSV were partly comparable with those of a preschool child when she was 11 years old (Marschik, et al., 2014a).

band 9–12 months. Similarly, Belardi, et al. (2017) found lower canonical babbling ratios in individuals with FXS compared to individuals with TD between 9 and 12 months of age. In age band 13–18 months, one of seven participants used (proto-)words and onomatopoetics and one used babbling for communicative purposes; in age band 19–24 months, all three participants used (proto-)words, but none used word combinations. The absence of babbling and the delayed onset of first words in the majority of the participants indicates an atypical speech-language trajectory. Speech-language delays including a delayed onset of first words have repeatedly been reported for individuals with FXS (Prouty, et al., 1988; Roberts, et al., 2001; 2002; Mirrett, et al., 2004; Brady, et al., 2006; Abbeduto, Brady and Kover, 2007; Finestack, Richmond and Abbeduto, 2009; Roberts, et al., 2009; Luyster, et al., 2011; Hinton, et al., 2013; Kover, et al., 2015). Also the gestural repertoires were found to be reduced in the participants of Study D with only one of seven participants using a single gesture (i.e., demonstrating an object) in age band 9–12 months, two of seven participants using either one or three gesture types in age band 13–18 months, and all three participants using either two or three gestures in age band 19–24 months. Reduced gestural repertoires in individuals with FXS during their first 2 years of life were also found in the study by Roberts, et al. (2002) and in the more recent studies by Hahn, et al. (2017) and Rague, et al. (2018), which were based on standardised assessments or parental questionnaires. In Study D, index finger pointing, an essential precursor to speech-language development, was not observed until the end of the first year of life and was seen only in three of seven participants in the second year of life. One participant (Child 7) was observed to use hand flapping with potential communicative intention in age band 9–12 months; two of seven participants used hand flapping in age band 13–18 months, and two of three participants in age band 19–24 months. Zhang, et al. (2018a) recently reported that hand flapping was the most common type of hand stereotypies observed in family videos of the first 2 years of life of individuals later diagnosed with FXS[32].

4.1.1.3 Communicative forms: Autism spectrum disorder

Study E (results were not published at the time of submission of this thesis) found a number of verbal and non-verbal behaviours that were used for communicative purposes by individuals with ASD throughout the first 2 years of life. Interestingly, eye contact was observed in each participant throughout the observation period. Reduced eye contact/avoidance of social gaze were however commonly reported findings of studies on infants and toddlers later diagnosed with ASD (e.g., Adrien, et al., 1993; Werner and

[32] Child 7 was also included in the study by Zhang, et al. (2018a).

Dawson, 2005; Zwaigenbaum, et al., 2005; Clifford, Young and Williamson, 2007; Clifford and Dissanayake, 2008; Shumway and Wetherby, 2009; Ozonoff, et al., 2010). Although our results did not support the findings of recuded eye contact/avoidance of social gaze in young individuals with ASD, it does not necessarily mean that the eye contact behaviour of our participants was normal. Our findings should be interpreted in the light of methodological issues that are inherent in the IPCA protocol: When filling in the IPCA protocol, it was not counted how often a behaviour occurs (based on opportunities), but a behaviour type was noted once when it first occurred in a participant and age band.

It was moreover interesting to observe that only half of the participants with ASD smiled in age band 9–12 months, whereas all participants with ASD were observed to smile in age band 13–18 months and three of five participants did so in age band 19–24 months. These findings mirror the inconsistent findings of previous studies on social smiling in young children with ASD (e.g., Adrien, et al., 1993; Zwaigenbaum, et al., 2005; Clifford, Young and Williamson, 2007; Bryson, et al., 2008; Clifford and Dissanayake, 2008).

As more participants with ASD used (pre-)linguistic vocalisations in age band 13–18 months than in age band 19–24 months, one might suppose the onset of a regression in the second half of the second year of life. Regression is a frequently described pattern for a considerable proportion of individuals with ASD that especially affects the speech-language and socio-communicative domains (e.g., Ozonoff, et al., 2008b; Barger, Campbell and McDonough, 2013; Brignell, et al., 2017; Ozonoff, et al., 2018). These findings, however, should be interpreted with caution as the cohort was very small and the participants of age band 19–24 months were not the same as those included in age band 13–18 months. Moreover, a potential regression in the second half of the second year of life is not reflected by the gestural repertoires of the present participants as the greatest amount of different gestures was found in age band 19–24 months. It may be interesting to note that only one participant used index finger pointing and he did so in age band 19–24 months. The reduced use of index finger pointing was consistent with the study by Braddock, et al. (2015); the authors applied the IPCA as a parental questionnaire and found that 42% of their investigated preschool children with ASD used index finger pointing for the functional categories of the IPCA. Due to the rare occurrence of (proto-)words and index finger pointing, it is not surprising that word combinations were not observed in our dataset. The absence or non-observation of word combinations in all participants by 24 months of age indicates a delay in their speech-language development and is consistent with findings of previous studies on young individuals with ASD (e.g., De Giacomo and Fombonne, 1998; Zwaigenbaum, et al., 2005; Landa and Garrett-Mayer, 2006; Barbaro and Dissanayake, 2012; Lazenby, et al., 2016).

4.1.2 Communicative forms: Late recognised developmental disorders vs. typical development (RQ1b)

4.1.2.1 Communicative forms: Rett syndrome vs. typical development

Due to heterogeneous video durations and settings in the videos, it is difficult to compare the absolute numbers of different communicative forms in individuals with RTT (Studies A–C; Bartl-Pokorny, et al., 2013b; Marschik, et al., 2014b; Bartl-Pokorny, et al., 2016) and individuals with TD (Study B, Study F). I decided to focus on the comparison of the different types of communicative forms in individuals with RTT or TD. The overall picture is the following: All participants with RTT and all participants with TD used body movements and/or facial expressions/eye movements for communicative purposes; however, the participants with RTT very rarely used gestures or (pre-)linguistic vocalisations, whereas these forms of communication were frequently observed for the participants with TD from 9–12 months onwards.

In detail, only one of six participants with RTT used one gesture in age band 9–12 months, whereas six of eight participants with TD used one or more gestures. Due to the frequently reported relationship between early gestures and later speech-language development (Capirci, et al., 1996; Acredolo and Goodwyn, 1998; Capone and McGregor, 2004; Iverson and Goldin-Meadow, 2005; Özçalışkan, Adamson and Dimitrova, 2016; Cadime, et al., 2017; Lüke, et al., 2017), our finding of a limited gestural repertoire is an early indicator of later speech-language difficulties in individuals with RTT.

Considering the largely absent gestural repertoires of our participants with RTT, it is not surprising that they were not observed to use (pre-)linguistic vocalisations in age band 9–12 months. In contrast, all female participants with TD used (proto-)words for communicative purposes (Study B; Bartl-Pokorny, et al., 2016). It should be noted that an absence of (proto-)words in age band 9–12 months is not a reliable indicator for a language delay as even in typically developing infants the first referential words are produced on average at 13 months of age (Bloom, Margulis and Tinker, 1993). For example, none of the male participants with TD from whom we had data available in age band 9–12 months was observed to produce (proto-)words at that age. It is however interesting that babbling – which is expected to occur in this age band in typically developing children (e.g., Paul, 2007) and was observed in four of the five females with TD (the only female with TD who did not use babbling produced (proto-)words) – was observed in none of the individuals with RTT. Here it should be noted that the male participants with TD also did not use babbling for communicative purposes in the videos of age band 9–12 months. As we included only

participants with a typical developmental outcome in Study F, the male participants with TD either used babbling in the video without communicative intention or did not use babbling in the video but still had acquired it at that age. For the participants with RTT, however, there is serious doubt that the babbling milestone was achieved at that age. Taken together, our findings reflect the often-reported inter-individual variability of young children with TD (e.g., Bates, et al., 1994; Fenson, et al., 1994; Bornstein, Hahn and Haynes, 2004; Eriksson, et al., 2012). In our study, the female participants with TD seemed to achieve certain speech-language milestones earlier than the males. This finding – although interpreted with caution due to limited number of participants and methodological issues of RVA – is consistent with the findings of Bornstein, Hahn and Haynes (2004) and Eriksson, et al. (2012).

Study C assessed the socio-communicative development of a participant with RTT, a participant with PSV, and a participant with TD and showed that the participant with TD had the most comprehensive communicative repertoire throughout the first 2 years of life. The participant with TD had more gestures and (pre-)linguistic vocalisations in all age bands compared to the participants with RTT or PSV.

Our findings are consistent with previous reports about reduced gestural repertoires as well as the lack of attaining early speech-language milestones in RTT and PSV (Tams-Little and Holdgrafer, 1996; Dahlgren Sandberg, et al., 2000; Marschik, et al., 2012a; 2012b; 2013).

4.1.2.2 Communicative forms: Fragile X syndrome vs. typical development

When comparing the different types of communicative forms between participants with FXS (Study D; parts of the results were published in Marschik, et al., 2014c) and participants with TD (Study F) throughout the first 2 years of life the overall picture presents as follows: All participants with FXS and all participants with TD used body movements and facial expressions/eye movements for communicative purposes; however, the participants with FXS rarely used gestures or (proto-)words in the first two age bands and no word combinations throughout the first 2 years of life whereas these forms of communication were frequently observed for the participants with TD from age band 9–12 months onwards.

The gestural repertoires of the participants with FXS were limited in all age bands in comparison to those of the participants with TD. The reduced gestural repertoires in the participants with FXS is in line with findings of former studies on children with FXS (Roberts, et al., 2002; Hahn, et al., 2017; Rague, et al., 2018) and might be an indicator of speech-

language difficulties (cf. Capone and McGregor, 2004). In fact, language development seemed to be delayed in the participants later diagnosed with FXS compared to the participants with TD which is also in line with the findings of former studies (Prouty, et al., 1988; Roberts, et al., 2001; 2002; Mirrett, et al., 2004; Brady, et al., 2006; Abbeduto, Brady and Kover, 2007; Finestack, Richmond and Abbeduto, 2009; Roberts, et al., 2009; Luyster, et al., 2011; Hinton, et al., 2013; Kover, et al., 2015); Child 2 was the only participant producing (proto-)words in age band 13–18 months and had the most comprehensive gestural repertoire with three different gestures including index finger pointing at that age. This is interesting as Child 2 was the only participant of Study D with comorbid ASD and anxiety disorder.

As already discussed in Chapter 4.1.1.2, one of seven participants with FXS used hand flapping for communicative purposes in age band 9–12 months, two of seven participants in age band 13–18 months, and two of three participants in age band 19–24 months. Two participants with TD were observed to use hand flapping for communicative purposes (i.e., to express excitement/pleasure) in age band 9–12 months, but not in the other two age bands. Interestingly, the motor pattern hand flapping was repeatedly described as hand stereotypy in individuals with FXS (e.g., Zhang, et al., 2018a). Therefore, our findings suggest that a discrimination between a behaviour as a (1) communicative form or (2) stereotypy needs to be done with caution. Studies on hand stereotypies should take into account the situational context in which a behaviour was observed and studies on communicative forms should be cautious not to over-interpret certain behaviours in terms of communicative intentions.

4.1.2.3 Communicative forms: Autism spectrum disorder vs. typical development

When comparing different types of communicative forms between participants with ASD (Study E) and participants with TD (Study F) throughout the first 2 years of life, the overall picture presents as follows: All participants with ASD and all participants with TD used body movements, facial expressions/eye movements, and non-linguistic vocalisations for communicative purposes; however, gestures and (pre-)linguistic vocalisations were only observed in a minority of the participants with ASD, whereas these forms of communication were frequently observed for the participants with TD from age band 9–12 months onwards.

Most of the participants with ASD did not use gestures or had very limited gestural repertoires of one or two gestures throughout the first 2 years of life. In contrast, all

participants with TD used gestures and most of them had repertoires of three or more gestures. Interestingly, only one participant with ASD used index finger pointing which was observed only in age band 19–24 months. In contrast, all participants with TD were observed to use index finger pointing for communicative purposes, three of them already in age band 9–12 months. These findings are in line with former studies that reported limited gestural repertoires in individuals with ASD compared to individuals with TD from 9–12 months of age onwards (Osterling, Dawson and Munson, 2002; Colgan, et al., 2006; Stone et al. 2007; Shumway and Wetherby, 2009; Veness, et al., 2012; Watson, et al., 2013; Chawarska, et al., 2014; Gordon and Watson, 2015; Özçalışkan, Adamson and Dimitrova, 2016).

Only one participant with ASD used babbling for communicative purposes in age band 9–12 months. Most of the participants with ASD had a delayed onset of babbling or did not use babbling with communicative intention throughout the observation period. Surprisingly, also half of the participants with TD were not observed to use babbling for communicative purposes in age band 9–12 months. Male participants with TD did not use babbling for communicative purposes in age band 9–12 months. Three of four male participants with TD used babbling in the second year of life; the other participant was observed to use (proto-)words and word combinations in age band 13–18 months. Also for some other participants with ASD or TD, (proto-)words were the first observed (pre-)linguistic vocalisations used for communicative purposes. We could not observe word combinations in participants with ASD. In contrast, the available audio-video material of all but one (i.e., TD 9, a male) participants with TD included word combinations in the first 2 years of life. Our findings are consistent with former studies reporting lower rates of canonical babbling and delayed expressive language development in individuals with ASD compared to individuals with TD (e.g., De Giacomo and Fombonne, 1998; Zwaigenbaum, et al., 2005; Landa and Garrett-Mayer, 2006; Barbaro and Dissanayake, 2012; Patten, et al., 2014; Lazenby, et al., 2016).

Interestingly, ASD 1 who had comorbid Tourette syndrome had the smallest repertoire of communicative forms in age band 9–12 months, whereas ASD 3 who had comorbid Tourette syndrome and ADHD had the most comprehensive repertoire of communicative forms in this age band. ASD 10 who had comorbid ADHD had similar amounts of communicative forms in age band 19–24 months compared to the children without comorbidities. It is difficult to interpret these findings as the number of participants with comorbidities was very limited and we did not have data available in all age ranges. It is however interesting to note that ASD 1 and ASD 3 had (proto-)words in the first or second age band.

As discussed in Chapter 4.1.1.3, it is not clear whether our data indicate a regression in speech-language capacities in the ASD group in the second half of the second year of life. A regression of certain capacities (mostly in the speech-language and socio-communicative domains) was recently suggested to occur in the majority of individuals with ASD (Ozonoff, et al., 2018). Anyway, the ASD group did not follow the same developmental pathway of clearly increasing speech-language capacities throughout the observation period from 9–12 months of age until 19–24 months of age as the TD group did.

4.1.3 Communicative forms: Cross-syndrome comparison (RQ1c)

Due to heterogeneous video material and the partly significant correlation of video duration with number of forms used by the participants (please see Results Section for details), I decided not to focus on total numbers when comparing the communicative forms of the participant groups. Instead, this Section provides a discussion of similarities and differences concerning types of communicative forms, especially gestures and (pre-)linguistic vocalisations, between the participants with RTT, FXS, or ASD. The findings were interpreted based on the insights we gained from participants with TD.

In age band 9–12 months, a comparison of the gestural repertoires revealed that only the participant with PSV used index finger pointing, whereas in the RTT, FXS, and ASD groups only one to maximally two participants used one gesture each and none of these was index finger pointing. Index finger pointing was observed in three of eight participants with TD. A comparison of the speech-language abilities revealed that the participant with PSV used (proto-)words, whereas none of the participants with RTT used (pre-)linguistic vocalisations, and only one of six participants with ASD, and two of seven participants with FXS used (pre-)linguistic vocalisations. At the same age, five of eight participants with TD used (pre-)linguistic vocalisations. On the first glimpse, these findings indicate similar and potentially reduced gestural and speech-language capacities for the age band 9–12 months in the developmental disorders RTT, FXS, and ASD. The individual with PSV seemed to be relatively better in terms of communicative forms at that age. However, one should be very careful when interpreting these findings. On the one hand, also the male participants with TD of Study F did not use (pre-)linguistic vocalisations in age band 9–12 months for communicative purposes which is actually similar to the male participants with ASD (although two of the three males with TD used index finger pointing). On the other hand, the differences between the participants with RTT and the participants with TD are even more pronounced when comparing female participants only, as all females with TD had (proto-)words at 9–12 months of age whereas none of the females with RTT did so. Further

research on larger cohorts is necessary to gain a more detailed picture of the similarities and differences in the socio-communicative repertoires of individuals with different LRDDs.

In age band 13–18 months, only a minority of participants with FXS or ASD used gestures, whereas almost all participants with TD did so. Interestingly, the participant with RTT and the participant with PSV used gestures as well. (Pre-)linguistic vocalisations were not observed in the participant with RTT and occurred only in two of seven participants with FXS. In contrast, three of four participants with ASD, the participant with PSV, and nine of ten participants with TD used (pre-)linguistic vocalisations; two participants with TD even used word combinations in age band 13–18 months. These findings show that the FXS and the ASD group had similar gestural repertoires that seemed to be reduced compared to those of the participants with TD. Concerning the speech-language development between 13 and 18 months, the ASD group seemed to be more comparable to the TD group than to the FXS group. One should not draw conclusions on the gestural and speech-language development of individuals with RTT and PSV based on only one participant each.

In age band 19–24 months, all participants with FXS, the participant with PSV, all participants with TD and at least three of five participants with ASD used gestures, whereas the participant with RTT did not. The observed gestural repertoires of the participants with TD were more comprehensive than the gestural repertoires of most of the participants with a LRDD. All participants with TD, the participant with PSV, and two of three participants with FXS used index finger pointing. Due to the well-documented importance of index finger pointing for speech-language development (Butterworth, 2003; Rohlfing, Grimminger and Lüke, 2017), it is not surprising that the participants of these groups seemed to have better speech-language capacities than the participants of the ASD group (only one of five participants had index finger pointing and only one produced words) and the participant with RTT (neither index finger pointing nor words).

It was interesting to observe that the TD group increased the socio-communicative capacities in terms of gestures and (pre-)linguistic forms to a greater extent than the FXS group that in turn increased the socio-communicative capacities to a greater extent than the ASD group. Actually, it remains inconclusive whether our ASD data indicate a regression of certain socio-communicative forms in the second half of the second year of life (please see Chapters 4.1.1.3 and 4.1.2.3 for a more detailed discussion).

One may argue that the differences between the conditions would have been more obvious if we had counted the amount of different (proto-)words (i.e., types) in the dataset or provided a type-token ratio (Kauschke, 2000; Kauschke, et al., 2015). If we had done so, the interpretation would probably still be difficult, as the number of different words is most

likely dependent on (1) the available video duration and (b) the amount and types of communicative settings[33]. As the major aim of this thesis was to comprehensively describe the socio-communicative repertoires of individuals with developmental disorders, we decided to include all available video material. The selection of certain scenes (based on for example number of situational events and persons evident, level of physical restriction, level of social interaction; e.g., Baranek, et al., 2005) might have been, on the one hand, easier to compare different LRDDs, but, on the other hand, might have drawn a more limited picture of the socio-communicative repertoires than our approach did.

Another limitation of this thesis that is related to the method of retrospective analysis of family videos is the heterogeneous reporting of medical data and differing diagnostic reports. This includes the use of different diagnostic assessments (e.g., ADOS, ABC, CARS for the participants with ASD, for details see Chapter 2.1.5.) and varying details on symptom severity and comorbidities.

[33] For example, the book reading of a father with his daughter where the father asks the daughter to name the objects in the book probably elicits more different words compared to a joint ball game.

4.2 Communicative functions (RQ2)

4.2.1 Communicative functions: Late recognised developmental disorders (RQ2a)

4.2.1.1 Communicative functions: Rett syndrome

In Study A (Bartl-Pokorny, et al., 2013b), we observed various communicative functions according to the IPCA in the participants with RTT in age band 9–12 months. ‘Gaining attention to self’ and ‘answering’ were observed for all participants. ‘Answering’ was rather an orientation towards a caregiver when he/she was talking with the participant than an answer to a question, which is actually an age-adequate observation (e.g., Chapman, 2000; Paul, 2007).

Five of six participants showed ‘commenting’ behaviours that were adequate to certain situations (e.g., pleasure vocalisations during a funny game). Four of six participants showed ‘rejecting’ behaviours. To better interpret these findings, further research should analyse those situations in more detail where no adequate reactions were observed (e.g., no reaction when hurt or when water splashed into the face), which was not part of the IPCA protocol, but was still observed in the data.

‘Social conventions’ (mainly response to name or greeting as a response to adult initiations) were only observed in three of six participants. This is interesting as deficits in response to name have frequently been reported in the literature on ASD (e.g., Osterling and Dawson, 1994; Osterling, Dawson and Munson, 2002; Wetherby, et al., 2004; Clifford, Young and Williamson, 2007; Gammer, et al., 2015; Miller, et al., 2017). Based on our observations in Bartl-Pokorny, et al. (2013b), we performed a study focusing on response to name in infants and toddlers later diagnosed with RTT (Townend, et al., 2015) and, recently, a cross-condition comparison on response to name in individuals with developmental disorders in the first 2 years of life (Zhang, et al., 2018b). In these studies, we counted the proportions of name calls that were responded by the individuals. All individuals of Study A were also included in the article by Townend, et al. (2015) and, consequently, in Zhang, et al. (2018b). As supposed from Study A, a low response rate in individuals with RTT was found at the end of the first year of life (Townend, et al., 2015; Zhang, et al., 2018b). Interestingly, Didden, et al. (2010) found that ‘social convention’ was among the most prevalent communicative functions according to the IPCA in older children and adults with RTT.

Moreover, none of the participants with RTT 'requested information' or 'made choices', which was also observed for individuals with PSV during the second year of life (Marschik, et al., 2012b). Interestingly, we noticed an absence of opportunities for 'choice making' in the video material. Therefore, it remains open whether this socio-communicative function had been acquired at that age by our participants. Didden, et al., (2010) applied the IPCA as a questionnaire and found that 'choice making' was among the most prevalent communicative functions in children and adults with RTT. The fact that 'requesting information' did not occur in the participants of Study A between 9 and 12 months of age was not surprising as even in TD children this function may not be acquired before 16 months of age (Chapman, 2000; Paul, 2007). It is however 'suspicious' that 'requesting information' was observed neither in the participant with RTT nor in the participant with PSV in the second year of life (Study C; Marschik, et al., 2014b).

'Imitation' was observed in half of the participants with RTT in age band 9–12 months, and in both the participant with RTT and the participant with PSV in the second year of life. In comparison, Marschik, et al. (2012a) reported that three of five individuals with PSV 'imitated' in the second year of life. For a comparison of the behaviour types that were 'imitated', please see Chapters 4.3.2.1 and 4.3.3.

Whereas only one of six participants 'requested an action' in age band 9–12 months, most of the females with PSV from our previous study did so during the second year of life (Marschik, et al., 2012a). The rare occurrence of 'requesting an action' in age band 9–12 months is surprising taking into account that the onset of 'requesting behaviours' was reported to typically occur around 9 months of age (Carpenter, Mastergeorge and Coggins, 1983; Kutsuki, et al., 2009). The participants with RTT or PSV in Study C were observed to 'request an action' in the second year of life. At least half of the participants with RTT 'requested objects' in age band 9–12 months. For a more detailed interpretation, please see Chapter 4.2.2.1 on the comparison of socio-communicative functions of the participants with RTT and the participants with TD.

4.2.1.2 Communicative functions: Fragile X syndrome

In Study D (parts of the results were published in Marschik, et al., 2014c), we observed various communicative functions according to the IPCA in the participants with FXS throughout the first 2 years of life.

In age band 9–12 months, 'gaining attention to self' and 'answering' were observed for all participants, whereas 'request action', 'request information', 'choice making', and

‘imitation’ were observed in none of the participants. An imitation deficit in children with FXS (although at a mean age of 34 months) was previously reported by Rogers, et al. (2003). It was interesting to observe that only one participant used the communicative function ‘rejecting/protesting’. Carpenter, Mastergeorge and Coggins (1983) reported for their typically developing participants that rejecting was the first communicative function to emerge around 8 months of age.

In age band 13–18 months, ‘requesting an action’ was still not observed. The achievement of this function seemed to be delayed in our participants when taking into account that requesting behaviours typically emerge around 9 months of age (Carpenter, Mastergeorge and Coggins, 1983; Kutsuki, et al., 2009). In this regard, it was interesting to note that only two of seven participants were observed to ‘request an object’. This is a much smaller proportion than in age band 9–12 months (five of seven). It remains open whether the rarer occurrence of ‘request an object’ in age band 13–18 months compared to age band 9–12 months was due to different settings in the video material. Moreover, ‘imitating’ and ‘rejecting/protesting’ were still observed only in three of seven participants with FXS. ‘Requesting information’ and ‘choice making’ remained absent in the video material of age band 13–18 months.

The data of age band 19–24 months have to be interpreted with caution due to the limited number of participants (n = 3). Taking into account the limited speech-language capacities (i.e., no word combinations as discussed in Chapter 4.1.1.2) it is not surprising that none of the three individuals with FXS ‘requested information’ in age band 19–24 months. It remains open whether the participants acquired this socio-communicative function at a later age in development. The absence of ‘choice making’ in the participants with FXS is partly related to a lack of opportunities in the video material. The IPCA applied in RVA may not be a reliable tool to describe ‘choice making’ capacities in children. ‘Imitation’ still seems to be reduced as we observed only one participant with FXS to imitate certain behaviours in age band 19–24 months. Surprisingly, all participants with FXS ‘requested actions’, which might reflect a delayed onset of this socio-communicative function as it was not observed before. An analysis of the ‘answering’ function on a token-basis might reveal peculiarities in individuals with FXS that did not become evident with our applied methodology. The IPCA does moreover not allow evaluating response to name in the participants as the function ‘social convention’ was noted whenever it was noticed the first time in an age band.

Overall, our findings indicate peculiarities in the development of certain communicative functions in the FXS group.

4.2.1.3 Communicative functions: Autism spectrum disorder

In Study E (results were not published at the time of submission of this thesis), we observed various communicative functions according to the IPCA in the participants with ASD throughout the first 2 years of life.

In age band 9–12 months, 'gaining attention to self' and 'answering' were observed for all participants, whereas 'request object', 'request action', 'request information', and 'choice making' were not observed. We were surprised to note an absence of requesting behaviours in the dataset as such behaviours were previously reported to emerge at around 9 months of age (Carpenter, Mastergeorge and Coggins, 1983; Kutsuki, et al., 2009). We did not observe any opportunities for 'choice making' in the video material, which explains the absence of this function in our results (e.g., Palomo, Belinchón and Ozonoff, 2006; Marschik and Einspieler, 2011; Ozonoff, et al., 2011b). 'Imitation' was observed in four of six participants with ASD in age band 9–12 months and in three of four in age band 13–18 months, which does not necessarily support previous research suggesting deficits in imitation in children with ASD (e.g., Mars, Mauk and Dowrick, 1998; Zwaigenbaum, et al., 2005; Young, et al., 2011; Poon, et al., 2012). However, it should be taken into account that we noted whether a function was observed at least once (i.e., types) and not how often it was observed (i.e., tokens). In age band 13–18 months, only one child showed a requesting behaviour (i.e., 'requesting an object'). The rare occurrence of requests mirrors the findings by Winder, et al. (2013) who revealed deficits in the spontaneous initiation of communicative acts in individuals at high risk for ASD compared to individuals at low risk for ASD when they were 13 and 18 months old. 'Gaining attention to self' and 'answering' were observed in all our participants with ASD in age band 13–18 months, whereas 'reject/protest', 'request action', 'request information', and 'choice making' were not observed at all. A relatively high proportion of the participants with ASD was observed to use communicative forms for the function 'social convention', mostly manifesting itself through response to name (and partly through greeting), throughout the whole observation period. On the first glimpse, these findings seemed to be inconsistent with other reports on deficits in response to name in the first 2 years of life of individuals with ASD (e.g., Osterling and Dawson, 1994; Osterling, Dawson and Munson, 2002; Wetherby, et al., 2004; Clifford, Young and Williamson, 2007; Gammer, et al., 2015; Miller, et al., 2017; Zhang, et al., 2018b). These studies, however, reported reduced response rates and not an absence of response to name in individuals with ASD. In the IPCA protocol, a participant with a reduced response rate would have the same result for 'social convention' as a participant with a typical response rate. This is likely the reason for the unexpected high proportion of 'social convention' in our data. Zhang, et al. (2018b) analysed partly the same participants as in Study E for response to name and

found a relatively low response rate for individuals with ASD in the first two age bands as well as a decline of the response rate in age band 19–24 months.

Study E revealed that in age band 19–24 months all participants were observed to 'answer', whereas none of the participants was observed to 'request information' or 'make choices'. An absence of 'requesting information' at that age indicates a developmental delay of this socio-communicative function as 'requesting information' typically emerges around 16 months of age (Chapman, 2000; Paul, 2007). It, however, remains open whether this function appeared later in development. Braddock, et al. (2015) applied the IPCA as a parental questionnaire on preschool children with ASD and found that 'requesting information' was the least commonly reported function of the IPCA for their participants. Furthermore, in our study, only one participant 'requested an object' and one participant 'requested an action'. The rare occurrence of 'requesting an action' is consistent with the findings by Braddock, et al. (2015). Interestingly, a smaller proportion of participants than in the first two age bands was observed to use communicative forms for the functions 'social convention', 'gaining attention to self', 'commenting', and 'imitating'. A decline is contrary to what one would expect for typically developing children and would be consistent with the frequently reported regression of certain capacities in children with ASD (e.g., Ozonoff, et al., 2008b; Barger, Campbell and McDonough, 2013; Brignell, et al., 2017; Ozonoff, et al., 2018). This finding is however difficult to interpret due to the limited sample size and the fact that we did not have data available of the same participants for all age bands. Moreover, differences in numbers of opportunities inherent in the video material could lead to the described differences. The comparison with the TD group from Study F helps to interpret these findings (please see Chapter 4.2.2.3).

4.2.2 Communicative functions: Late recognised developmental disorders vs. typical development (RQ2b)

4.2.2.1 Communicative functions: Rett syndrome vs. typical development

The comparison of communicative functions in participants with RTT (Studies A–C; Bartl-Pokorny, et al., 2013b; Marschik, et al., 2014b; Bartl-Pokorny, et al., 2016) or TD (Study B, Study F) faces similar difficulties than the above-provided comparison of communicative forms. Due to the different video durations and settings in the videos (e.g., for age band 9–12 months, the correlation between video duration and number of functions was significant for both participant groups), I will likewise focus more on the different types of functions than

on absolute numbers. The overall picture of age band 9–12 months is the following: The participants with RTT and the participants with TD used communicative forms for similar communicative functions: ‘Gaining attention to self’ and ‘answering’ occurred in all participants, whereas ‘choice making’ and ‘requesting information’ were never observed. In age band 9–12 months, no opportunities for ‘choice making’ were observed in the video material of both groups. It remains open whether this socio-communicative function had been acquired at that age by our participants. Actually, the only opportunity for ‘choice making’ in the whole dataset of Studies A–F was observed for TD 5 in age band 19–24 months. These results suggest that RVA is probably not an adequate method to assess this socio-communicative function. ‘Requesting information’ was neither observed in the participant with RTT nor in the participant with PSV of Study C in the second year of life. In contrast, ‘requesting information’ occurred in two of ten participants with TD in age band 13–18 months and in three of eight in age band 19–24 months. The emergence of ‘requesting information’ in the second year of life is an age-adequate observation (Chapman, 2000). It remains open whether this function was classified as absent in the other participants because it was only absent in the available video material or had not been acquired at that age.

Furthermore, only one participant with RTT and one participant with TD ‘requested an action’ in age band 9–12 months. This finding is surprising as requesting behaviours were reported to typically emerge around 9 months of age (Carpenter, Mastergeorge and Coggins, 1983; Kutsuki, et al., 2009). ‘Requesting an object’, however, was observed in half of the participants with RTT and in the majority of the participants with TD between 9 and 12 months of age. Based on our data, one may suppose ‘requesting an object’ to be an earlier emerging requesting behaviour than ‘requesting an action’. Interestingly, in the study of Carpenter, Mastergeorge and Coggins (1983) the majority of their participants used ‘requesting an action’ earlier in life than ‘requesting an object’. In Study F, ‘requesting an action’ was observed in the majority of individuals with TD in the second year of life. ‘Requesting an action’ was also observed in the participant with RTT and in the participant with PSV of Study C in the second year of life. Marschik, et al. (2012a) reported this function to occur in three of five participants with PSV in the second year of life.

Similar results were obtained for ‘imitation’; actually, a slightly greater proportion of the participants with RTT than the participants with TD used communicative forms for ‘imitation’ in age band 9–12 months. When comparing the participants with RTT only with the female participants with TD, a slightly greater proportion of participants with TD than participants with RTT ‘imitated’. For a comparison of the behaviour types that were ‘imitated’, please see Chapters 4.3.2.1 and 4.3.3.

Interestingly, ‘social convention’ (mainly manifesting itself through response to name) was only observed in half of the participants with RTT and in half of the participants with TD. In contrast to this finding, our recent study by Zhang, et al. (2018b)[34] revealed clear differences between largely the same individuals of the RTT and the TD group: The individuals with RTT had a considerably lower response rate than the individuals with TD (25.64% vs. 65.85%). This indicates that the IPCA protocol needs some adaptations to map certain peculiarities that obviously only become evident when analysing tokens in addition to types.

4.2.2.2 Communicative functions: Fragile X syndrome vs. typical development

The comparison of communicative functions in participants with FXS (Study D; parts of the results were published in Marschik, et al., 2014c) or TD (Study F) revealed the following similarities: In age band 9–12 months, all participants of both groups used communicative forms for ‘attention to self’ and ‘answering’, and never used forms for ‘requesting information’ and ‘choice making’. The main difference between the groups in age band 9–12 months was that none of the participants of the FXS group ‘imitated’ and only one participant showed ‘rejecting/protesting’ behaviours, while ‘imitation’ was observed in three and ‘rejecting/protesting’ in six of the eight participants with TD. A slightly greater proportion of individuals with FXS was observed to use communicative forms for ‘social convention’ compared to the participants with TD. As for RTT, this finding is at first sight unexpected taking into account that Zhang, et al. (2018b) found a considerably lower response rate for individuals with FXS than for individuals with TD based on largely the same video material (35.29% vs. 65.85% between 9 and 12 months of age; Zhang, et al., 2018b). In contrast to the IPCA protocol that focused on types, Zhang, et al. (2018b) analysed number of responses based on number of opportunities.

In age band 13–18 months, three of seven participants with FXS were observed to use some ‘imitating’ behaviours, whereas eight of ten participants with TD did so. These findings are in line with those of Rogers, et al. (2003) who reported imitation deficits in children with FXS. None of the participants with FXS ‘requested an action’ whereas the majority of participants with TD did so. Also ‘requesting an object’ seemed to be rather limited in the participants with FXS compared to the participants with TD. Similar to age

[34] The original analysis of response to name in the individuals with RTT was published by Townend, et al. (2015).

band 9–12 months, a greater proportion of individuals with FXS compared to participants with TD was observed to use communicative forms for ‘social convention’. Further studies should analyse this function based on number of opportunities to find potential differences between participant groups.

Finally, in age band 19–24 months, ‘requesting an action’ was observed to a great extent in both groups. Compared to the participants with TD, the onset of ‘requesting an action’ seemed to be delayed in the participants with FXS. In contrast to the TD group, the FXS group never ‘requested information’ throughout the first 2 years of life. This is not surprising taking into account that none of the participants with FXS used word combinations at that age, but almost all participants with TD did so (please also see discussion of communicative forms in Chapters 4.1.1.2 and 4.1.2.2). However, especially the findings of age band 19–24 months have to be interpreted with caution as we only had available data of three participants with FXS for this age band.

4.2.2.3 Communicative functions: Autism spectrum disorder vs. typical development

The comparison of communicative functions in participants with ASD (Study E; results were not published at the time of submission of this thesis) or TD (Study F) revealed the following similarities: In age band 9–12 months, all participants of both groups used communicative forms to ‘gain attention to self’ and to ‘answer’. ‘Requesting information’ and ‘choice making’ were neither observed in the ASD group nor in the TD group (please see Chapter 4.2.1.3 for a discussion on ‘requesting information’ and ‘choice making’). Interestingly, ‘rejecting/protesting’ was observed only in one third of the participants with ASD, whereas it occurred in three fourths of the participants with TD. ‘Requesting an object’ did not occur in the participants with ASD, but it was observed in five of eight participants with TD. While only one participant with TD was observed to ‘request an action’, none of the participants with ASD did so. This was interesting to observe as requesting behaviours were previously reported to emerge around 9 months of age in typically developing infants (Carpenter, Mastergeorge and Coggins, 1983; Kutsuki, et al., 2009). Interestingly, a slightly greater proportion of participants with ASD compared to participants with TD showed some ‘imitation’ behaviours. The ASD and the TD group also had similar results for ‘imitation’ in age band 13–18 months. When comparing male participants only (as all participants with ASD were males), more participants with ASD than with TD used ‘imitation’. Therefore, our findings do not support previous studies based on different methodological approaches that suggested deficits in imitation in individuals with ASD (e.g., Mars, Mauk and Dowrick, 1998;

Zwaigenbaum, et al., 2005; Young, et al., 2011; Poon, et al., 2012). The types of behaviours that were 'imitated' are compared in Chapter 4.3.2.3. Further studies taking into account tokens in addition to types would be necessary to achieve a more precise picture of similarities or differences concerning the 'imitation' profiles of infants and toddlers with ASD or TD. Still, this remains difficult in RVA due to methodological issues such as heterogeneous settings including number of opportunities inherent in the data. A slightly higher proportion of the participants with ASD compared to the participants with TD was observed to use communicative forms for 'social convention' in the first two age bands. Interestingly, 'social convention' was not observed in the male participants with TD in age band 9–12 months. This is in contrast to the findings of Zhang, et al. (2018b) who found a lower response rate for the individuals with ASD compared to the individuals with TD (i.e., 39.53% vs. 65.85% between 9 and 12 months of age). It should be noted here that our study groups had partly different cultural backgrounds/ family languages, which might have an effect on the number of opportunities to elicit certain behaviours. Further studies should seek to recruit control groups from the same cultural background and language environment. In age band 13–18 months, only one of four participants with ASD showed a requesting behaviour (i.e., 'requesting an object'), whereas the majority of participants with TD 'requested objects and actions', and two of them even 'requested information'. Our findings mirror the findings by Winder, et al. (2013) who revealed deficits in the spontaneous initiation of communicative acts in toddlers at high risk for ASD compared to toddlers at low risk for ASD. Interestingly, 'rejecting/protesting' did not occur in the participants with ASD, whereas it was observed in most of the participants with TD. This may either depend on the settings that were analysed, or may be an indicator of reduced affective expressions that were previously reported for young individuals with ASD (e.g., Zwaigenbaum, et al., 2005; Clifford, Young and Williamson, 2007; Filliter, et al., 2015).

In age band 19–24 months, none of the participants with ASD, but three of eight participants with TD 'requested information'. This discrepancy is likely related to the absence of word combinations in the participants with ASD throughout the observation period. It should, however, be noted that none of the male participants with TD 'requested information'. Furthermore, 'requesting objects and actions' remained limited compared to the TD group. Interestingly, a smaller proportion of participants than in the first two age bands was observed to use communicative forms for the functions 'social convention', 'gaining attention to self', 'commenting', and 'imitating'. Here it should be mentioned that also a slightly smaller proportion of participants with TD used communicative forms for 'requesting action', 'commenting', and 'imitating' in age band 19–24 months compared to age band 13–18 months. Small variations are most likely related to differences in

opportunities for certain functions inherent in the video material. The direct comparison with our TD group therefore does not support an onset of regression of certain communicative functions in the ASD group in the second half of the second year of life.

4.2.3 Communicative functions: Cross-syndrome comparison (RQ2c)

Due to the heterogeneous video material and the partly significant correlation of video duration with number of functions observed for the participants (please see Results Section for details), I decided not to focus on total numbers when comparing the communicative functions of the participant groups. Instead, this Section provides a discussion of similarities and differences concerning the types of communicative functions between the participants with RTT, FXS, or ASD. The findings were interpreted based on the insights we had gained from the participants with TD.

The major similarities of the groups throughout the first 2 years of life were that the functions ‘attention to self’ and ‘answering’ were observed for all participants with a LRDD or TD in almost all age bands. Therefore, these two categories seemed to be not suitable for a discrimination of infants and toddlers who develop typically from those with a later diagnosed developmental disorder. However, it is possible that an additional consideration of tokens would add to the discriminative value of these two functions. Such an implementation of a token analysis however would come along with certain methodological difficulties inherent in RVA such as heterogeneous numbers of opportunities for certain functions due to different video durations, types of settings, or cultural background of the families.

None of the participants with a LRDD ever ‘made choices’ in our dataset. Only one participant with TD was observed to ‘make a choice’ between two objects. Actually, this instance of ‘choice making’ was the only opportunity for this communicative function that I noticed in the video material analysed for my thesis. Therefore, RVA does not allow determining the age of acquisition of this socio-communicative function. It remains open whether this socio-communicative function had been acquired by the participants with LRDDs within the observation period. Therefore, ’choice making’ in combination with RVA seems to be not helpful when aiming to find differences in the socio-communicative domain of children with different LRDDs.

In age band 9–12 months, the ASD group had the highest proportion of individuals who used communicative forms to express ‘social convention’ (mainly manifesting itself through response to name). The RTT group, the FXS group and the TD group had similar

results for this category. On the first glimpse, this finding is surprising taking into account that Zhang, et al. (2018b) reported considerably lower response rates for individuals with ASD, RTT, or FXS compared to individuals with TD (for details please see Chapters 4.2.2.1–4.2.2.3). These findings suggest that, similar to 'gaining attention to self' and 'answering', a dichotomous decision between at least one occurrence and total absence of 'social convention' in a participant seems to be not sufficient to depict differences and similarities between individuals with different LRDDs. In the case of response to name, a number of studies on infants and toddlers (mainly with ASD) proved that this function described through response rate is a valuable marker for developmental deviances (for details, please see the overview part of the article by Zhang, et al., 2018b).

'Rejecting/protesting' was observed in the majority of participants with RTT or TD, but only in a minority of the participants with FXS or ASD in age band 9–12 months. In age band 13–18 months, the participants with ASD were not observed to 'reject/protest', whereas almost half of the participants with FXS and the majority of the participants with TD did so. In age band 19–24 months, three of five participants with ASD, one of three participants with FXS, and nine of ten participants with TD showed some 'rejecting/protesting' behaviour. To sum up, we found that through all age bands higher proportions of participants with TD were observed to 'reject/protest' compared to the individuals with a LRDD. Our findings furthermore indicate cross-syndrome differences at certain ages. However, larger cohorts are necessary to draw a precise picture of the development of 'rejecting/protesting' in individuals with ASD, RTT, or FXS.

'Requesting an object' was observed in half of the participants with RTT and in the majority of the participants with FXS or TD in age band 9–12 months; however, it was not observed in the ASD group. Interestingly, only a minority of participants with FXS were observed to 'request an object' in age band 13–18 months and only one participant with ASD did so. In contrast, this function occurred in eight of ten participants with TD at that age. In age band 19–24 months, two of three participants with FXS and one participant with ASD 'requested an object', whereas almost all participants with TD did so. When interpreting these findings, it should be taken into account that the sample size of the participants with FXS was very limited in the latter age band (n = 3). In sum, our findings suggest that 'requesting an object' in the first 2 years of life should be analysed further as its absence may function as an indicator for developmental deviances.

'Requesting an action' was observed only in one participant with RTT and in one participant with TD in age band 9–12 months, whereas it was observed in none of the participants with FXS or ASD. It was very interesting to observe that 'requesting an action'

occurred in the majority of participants with TD as well as in the participant with RTT and in the participant with PSV from Study C (Marschik, et al., 2014b) in age band 13–18 months, whereas it was not observed in any individual with FXS or ASD. Surprisingly, a few months later, the three investigated participants with FXS were observed to 'request an action'; also, the participant with PSV and at least one of five participants with ASD did so. The majority of individuals with TD 'requested an action' in age band 19–24 months. In sum, our findings indicate that 'requesting an action' might also function as an early indicator of developmental disorders and may help to differentiate between certain LRDDs.

As expected from the literature (Chapman, 2000; Paul, 2007), 'requesting information' did not occur in age band 9–12 months. Four of ten participants with TD 'requested information' in the second year of life. This function was however observed in none of the participants with a LRDD. This finding is not surprising taking into account that none of the investigated individuals with a LRDD used word combinations in the first 2 years of life. It is interesting that all four participants with TD who 'requested information' were females.

The majority of the participants from all conditions showed some 'commenting' behaviours throughout the whole observation period. Therefore, this socio-communicative function is most probably not a reliable indicator for a developmental disorder when just analysing whether a 'comment' occurred at least once in a participant. It might, however, be useful to focus more on the adequacy of used behaviours in certain situations. Further studies should focus on those situations in more detail where no adequate reactions were observed (e.g., no reaction when hurt).

A number of studies revealed a relationship between imitation and speech-language development (e.g., De Giacomo, et al., 2009; Souza, et al., 2015; Cochet and Byrne, 2016; De Giacomo, et al., 2018). As we found early language delays in the participants with LRDDs, one may expect reduced 'imitation' behaviours in these children. In age band 9–12 months, around half of the participants with RTT, ASD, or TD showed some 'imitation' behaviours. In contrast, none of the participants with FXS did so. In age band 13–18 months, almost all participants with ASD or TD 'imitated' and three of seven participants with FXS did so. In age band 19–24 months, 'imitation' in the FXS group still seemed to be limited as only one of three participants was observed to 'imitate'. Furthermore, the majority of participants with TD 'imitated' at the end of the second year of life. Surprisingly, only two of five participants with ASD were observed to do so. The findings for ASD indicate a decline of 'imitation' behaviours in the second half of the second year of life. This finding is however difficult to interpret due to the limited sample size and the fact that we did not have data

available of the same participants for all age bands. Nevertheless, our findings indicate different developmental pathways for ASD and FXS and suggest that 'imitation' might function as an early indicator of developmental disorders; the latter is in line with previous studies on children with ASD or FXS (e.g., Mars, Mauk and Dowrick, 1998; Rogers, et al., 2003; Zwaigenbaum, et al., 2005; Young, et al., 2011; Poon, et al., 2012).

4.3 Verbal and non-verbal communication (RQ3)

4.3.1 Verbal and non-verbal communication: Late recognised developmental disorders (RQ3a)

4.3.1.1 Verbal and non-verbal communication: Rett syndrome

In Study A (Bartl-Pokorny, et al., 2013b), we analysed the behaviour types (i.e., NV, NL, L) that were used by the participants with RTT for the observed communicative functions in age band 9–12 months. NV dominated over NL for seven of eight communicative functions (i.e., more participants used NV compared to NL to cover seven communicative functions). NL dominated over NV only for 'rejecting/protesting'. L was never observed. The preference of non-verbal over verbal communicative forms is in line with the findings of our study on individuals with PSV in the second year of life (Marschik, et al., 2012a). Similar findings were reported by Lavås, et al. (2006) for older females with RTT.

Study C (Marschik, et al., 2014b) analysed the behaviour types that were used by one participant with RTT and one participant with PSV from 9 to 24 months of age. While the participant with RTT was not observed to use L for communicative functions throughout the observation period, the participant with PSV occasionally used L for communicative purposes in the three age bands: L were used for one communicative function each in age band 9–12 months and 13–18 months and for five functions in age band 19–24 months. These findings indicate better speech-language abilities in the participant with PSV compared to the participant with RTT. Still, we observed a reduced pragmatic functionality of L in the participant with PSV, especially in the first two age bands. The present findings support the view that already the early (pre-regressional) development of individuals with RTT or PSV is atypical (e.g., Marschik, et al., 2013; 2014a).

4.3.1.2 Verbal and non-verbal communication: Fragile X syndrome

In Study D (parts of the results were published in Marschik, et al., 2014c), we analysed the behaviour types (i.e., NV, NL, L) that were used by the participants with FXS for the observed communicative functions.

We found a general preference of NV over NL and L to cover communicative functions throughout the whole observation period. For some of the communicative functions, two or three behaviour types were equally often used (e.g., NV and NL in age band 9–12 months for 'reject/protest' and 'request an object'; NV, NL, and L in age band

13–18 months for ‘imitate’). NL dominated over NV only for ‘commenting’ in age band 9–12 months. L dominated over the other behaviour types for none of the communicative functions. A predominance of NV for communicative purposes is, however, not surprising taking into account that for example the NV *eye contact* is an essential part of communicative acts, i.e., one may expect verbal behaviours to be frequently combined with *eye contact* and other NV. What is more telling is that L was used very sparsely compared to the other behaviour types, especially in the first two age bands (i.e., zero to two participants per age band used L for a specific communicative function). Statistical analysis revealed no significant changes between NV_{prop}, NL_{prop}, and L_{prop} from age band 9–12 months to age band 13–18 months [NV_{prop}: $Z = -1.604$, $p = .109$; NL_{prop}: $Z = -1.069$, $p = .285$; L_{prop}: $Z = -.447$, $p = .655$]. No increase of L_{prop} is contrary to what one may expect from typically developing children; our findings show that (pre-)linguistic vocalisations did not play an important role for communication until at least 18 months of age and indicate a reduced pragmatic functionality of L in the FXS group. Due to limited sample size in age band 19–24 months, inferential statistical methods could not be applied. From a descriptive point of view, L_{prop} increased compared to the first two age bands.

Our findings are in line with those of Belardi, et al. (2017) who showed a reduced volubility in infants with FXS, and are consistent with a range of former studies who found a delayed speech-language development in individuals with FXS (Prouty, et al., 1988; Roberts, et al., 2001; 2002; Mirrett, et al., 2004; Brady, et al., 2006; Abbeduto, Brady and Kover, 2007; Finestack, Richmond and Abbeduto, 2009; Roberts, et al., 2009; Luyster, et al., 2011; Hinton, et al., 2013; Kover, et al., 2015). To the best of our knowledge, our study is the first to investigate pragmatic functionality of L the first 2 years of life of children later diagnosed with FXS.

4.3.1.3 Verbal and non-verbal communication: Autism spectrum disorder

In Study E (results were not published at the time of submission of this thesis), we analysed the behaviour types (i.e., NV, NL, L) that were used by the participants with ASD for the observed communicative functions.

NV dominated over the other behaviour types for half of the communicative functions in age band 9–12 months, for one of six observed communicative functions in age band 13–18 months, and for two of eight observed communicative functions in age band 19–24 months. NL dominated over the other behaviour types for ‘commenting’ in age band 9–12

months and for ‘imitating’ in age band 13–18 months. L dominated over the other behaviour types for none of the communicative functions. For a great proportion of communicative functions, two or three behaviour types were equally often used (e.g., NV and NL in age band 9–12 months for ‘imitate’; NV, NL, and L in age band 13–18 months for ‘attention to self’). L was used rather sparsely compared to the other behaviour types, especially in age bands 9–12 months and 19–24 months. Braddock, et al. (2015) also reported that their investigated preschool children with ASD used relatively fewer words and gestures in comparison to body movements for communicative purposes. Interestingly, L was used for five of six communicative functions in age band 13–18 months, whereas it was used for only one of eight observed communicative functions in age band 19–24 months. As one would expect L to increase throughout the second year of life in typically developing children, a decline in the use of L in the participants with ASD may indicate the onset of regression in the second half of the second year of life. Regression is a frequently described pattern for a considerable proportion of individuals with ASD that especially affects the speech-language and socio-communicative domains (e.g., Ozonoff, et al., 2008b; Barger, Campbell and McDonough, 2013; Brignell, et al., 2017; Ozonoff, et al., 2018). This finding should, however, be interpreted with caution due to the limited sample size and the fact that we did not have data available of the same participants for all age bands. Due to limited sample size, inferential statistical methods could not be applied to compare the results of the three age bands.

4.3.2 Verbal and non-verbal communication: Late recognised developmental disorders vs. typical development (RQ3b)

4.3.2.1 Verbal and non-verbal communication: Rett syndrome vs. typical development

Here we compared verbal and non-verbal communication strategies in participants with RTT (Studies A, B, and C; Bartl-Pokorny, et al., 2013b; Marschik, et al., 2014b; Bartl-Pokorny, et al., 2016) and participants with TD (Studies B, C and F; Marschik, et al., 2014b; Bartl-Pokorny, et al., 2016). In age band 9–12 months, verbal behaviours were more important for communicative purposes for the TD than for the RTT group: NL either dominated over NV or were equally often observed as NV for half of the communicative functions in the TD group, but only for one of eight functions in the RTT group. Moreover, the participants with TD used L for more than half of the communicative functions and L dominated over the other behaviour types for ‘imitation’, whereas L did not occur at all in

the participants with RTT. The overall picture was the same when comparing the (female) participants with RTT with the female participants with TD only (Bartl-Pokorny, et al., 2016). Our descriptive findings indicate a reduced pragmatic functionality of NL and L in the RTT group at the end of the first year of life and therefore add to the body of knowledge on an atypical early (pre-regressional) development of individuals with RTT (e.g., Marschik, et al., 2013; 2014a). The results of the inferential statistical analyses are discussed in the framework of the cross-syndrome comparison in Chapter 4.3.3.

The findings of Study C (Marschik, et al., 2014b) suggested a reduced pragmatic functionality of L in the participant with PSV compared to the participant with TD throughout the first 2 years of life: The participant with TD used L for a greater proportion of communicative functions than the participant with PSV for all age bands. The participant with RTT did not use L throughout the observation period.

4.3.2.2 Verbal and non-verbal communication: Fragile X syndrome vs. typical development

Here we compared verbal and non-verbal communication strategies in participants with FXS (Study D; parts of the results were published in Marschik, et al., 2014c) and participants with TD (Study F). Throughout the first 2 years of life, verbal behaviours were more important for communicative purposes for the TD than for the FXS group: Whereas NL dominated over NV only for 'commenting' in age band 9–12 months and L did not dominate for any of the communicative functions in the FXS group, NL or L dominated over NV for three of eight to ten observed communicative functions in each age band in the TD group. Moreover, L was used for the majority of communicative functions in age band 9–12 months and for all communicative functions in the second year of life in the TD group, whereas L was used for a smaller proportion of the observed communicative functions and generally by fewer participants per communicative function. Interestingly, each participant with TD was observed to use L for 'imitation' in at least one age band, whereas only two of nine participants with FXS used L for 'imitation' and only in the second year of life. For age band 13–18 months, inferential statistical calculations were feasible due to sufficient cell sizes. L_{prop} was significantly greater in the TD group (n = 10) than in the FXS group (n = 7), i.e., Mann-Whitney U = 11.500, p = .019, η^2 = .31, whereas NV_{prop} and NL_{prop} did not differ between the participant groups, i.e., NV_{prop}: Mann-Whitney U = 20.000, p = .161; NL_{prop}: Mann-Whitney U = 24.500, p = .315. When interpreting these findings it should be taken into account that nine of ten participants with TD, but only two of seven participants with FXS ever used L in age band 13–18 months. The inferential statistical findings for age band

9–12 months are discussed in the framework of the cross-syndrome comparison in Chapter 4.3.3. In sum, our findings indicate a reduced pragmatic functionality of L in the FXS group. Our findings add to the body of knowledge on an atypical early speech-language development of individuals with FXS (Prouty, et al., 1988; Roberts, et al., 2001; 2002; Mirrett, et al., 2004; Brady, et al., 2006; Abbeduto, Brady and Kover, 2007; Finestack, Richmond and Abbeduto, 2009; Roberts, et al., 2009; Luyster, et al., 2011; Hinton, et al., 2013; Kover, et al., 2015).

4.3.2.3 Verbal and non-verbal communication: Autism spectrum disorder vs. typical development

Here we compared verbal and non-verbal communication strategies in participants with ASD (Study E, results were not published yet) and participants with TD (Study F).

In the ASD group, NL dominated over the other behaviour types for one of six observed functions in age band 9–12 months and 13–18 months respectively and for no observed function in age band 19–24 months (i.e., 1/6, 1/6, 0/8), and L did not dominate over the other behaviour types. In the TD group, similar results were found for NL (i.e., 2/8, 2/9, 1/10), but L dominated over the other behaviour types for one of eight functions in age band 9–12 months, for one of nine functions in age band 13–18 months, and for two of ten functions in age band 19–24 months. Moreover, the ASD group used L for half of the communicative functions in age band 9–12 months, for almost all functions in age band 13–18 months, but only for one of eight observed functions in age band 19–24 months. In contrast, the TD group used L for the majority of communicative functions in age band 9–12 months and for all communicative functions in the second year of life. When interpreting these findings one should be very cautious as we observed gender differences in our participants with TD, even though the cell sizes were too small for inference statistical calculations. Therefore, when comparing the participants with ASD (all were males) only with the male participants with TD, the participants with ASD actually used L for a greater proportion of communicative functions than the participants with TD in the first two age bands.

Furthermore, it was interesting to observe that each participant with TD used L for ‘imitation’ in at least one age band, whereas only two of ten participants with ASD did so. For age band 19–24 months, inferential statistical calculations were feasible due to sufficient cell sizes. L_{prop} was significantly greater in the TD group (n = 8) than in the ASD group (n = 5), i.e., Mann-Whitney U = .000, p = .002, η^2 = .66, whereas NV_{prop} and NL_{prop}

did not differ between the participant groups, i.e., NV_{prop}: Mann-Whitney U = 11.000, p = .222; NL_{prop}: Mann-Whitney U = 13.500, p = .354. The inferential statistical findings for age band 9–12 months are discussed in the framework of the cross-syndrome comparison in Chapter 4.3.3.

In sum, the importance of L for communication seemed to decrease in the second half of the second year of life in the ASD group. In contrast, L became continuously more important for communicative purposes in the TD group when focusing on both females and males, and increased from 9–12 months to 13–18 months and stayed relatively stable from 13–18 months to 19–24 months when focusing on the male participants only. These findings could reflect the onset of regression in the ASD group; however, our findings should be interpreted with caution because we did not have data available of the same participants for all age bands.

4.3.3 Verbal and non-verbal communication: Cross-syndrome comparison (RQ3c)

In this chapter, the verbal and non-verbal communication strategies were compared between the participants with RTT, FXS, or ASD. The findings were interpreted based on the insights we had gained from the participants with TD.

Overall, L were more important for communicative purposes for the participants with TD than for the participants with a LRDD with reduced pragmatic functionality of L in the participants with a LRDD. We had sufficiently large cell sizes to compare RTT, FXS, ASD, and TD based on inferential statistical calculations for age band 9–12 months. We found that the participants with TD tended to show higher L_{prop} (median = 32.50%) than the other groups (median for all the other three groups was 0%; Kruskal-Wallis $H(3)$ = 6.846, p = .077); no differences were found for NV_{prop} and NL_{prop}. We did not have sufficiently large cell sizes to compare LRDDs in the other two age bands based on inferential statistical calculations.

The atypical/delayed speech-language development that we observed for all LRDD groups is not surprising taken into account that only a very limited number of participants with a LRDD used L for ‘imitation’, whereas each participant with TD did so. We had previously reported an absence of L for ‘imitation’ in the second year of life for participants with PSV (Marschik, et al., 2012a).

The developmental pathways of (pre-)linguistic communication strategies were as follows: L_{prop} increased in the participants with FXS throughout the observation period although L_{prop} values indicated relatively lower speech-language capacities compared to the TD group. L_{prop} of the participants with ASD initially increased and then decreased indicating a potential regression of communicative abilities. A similar reduced use of L for communicative purposes was previously reported by Marschik, et al. (2012a) for individuals with PSV in their second year of life. The only participant with RTT from whom we had video material available throughout the whole observation period did not use L for communicative purposes at all (Study C; Marschik, et al., 2014b). This is consistent to the consensus of PSV as a relatively mild variant of RTT (e.g. Zappella, 1992; Renieri, et al., 2009; Marschik, et al., 2013). L_{prop} of the participants with TD continuously increased throughout the observation period and was higher for all age bands compared to the LRDD groups. Our results are however preliminary due to our limited group sizes and the heterogeneity of the video material. Further studies on larger cohorts with comparable video settings are needed to gain a clear picture of potential differences in verbal and non-verbal communication strategies between infants and toddlers with LRDDs and those with TD.

4.4 Concluding remarks

When this thesis was started, the understanding of the pre-diagnostic socio-communicative development of children with LRDDs was very limited, especially for RTT and FXS (e.g., Roberts, et al., 2002, Marschik, et al., 2009; see Chapters 1.3.1–1.3.3 for details). Comprehensive descriptions of the pre-diagnostic communicative repertoires of individuals with LRDDs were missing, but urgently needed to gain a more detailed picture of the pre-diagnostic socio-communicative development. This in turn is necessary with regard to the future earlier identification of LRDDs and the opportunity for earlier intervention.

In order to extend the knowledge on the pre-diagnostic socio-communicative development, we analysed family videos of the first 2 years of life of children later diagnosed with RTT, FXS, or ASD. The so-called retrospective video analysis (RVA) is a frequently used approach to investigate the pre-diagnostic development of children with LRDDs. It is especially valuable for LRDDs with low familial recurrence risk such as RTT where prospective at risk studies are hardly feasible. Despite its proven value in the detailed description of behavioural features, developmental trajectories, and the improvement or regression of functions, RVA has certain limitations that are addressed in Chapters 4.1–4.3 (e.g., Palomo, Belinchón and Ozonoff, 2006; Marschik and Einspieler, 2011; Ozonoff, et al., 2011b). For the retrospective analysis of socio-communicative capacities based on family videos, we applied the IPCA, a protocol that was originally designed to develop individual intervention strategies for children with developmental disorders that are associated with communicative deficits (Sigafoos, Arthur-Kelly and Butterfield, 2006).

Our approach proved to be a valuable method to provide comprehensive descriptions of the socio-communicative domain by longitudinally analysing socio-communicative forms and functions in individuals with LRDDs. This thesis revealed socio-communicative peculiarities in children later diagnosed with RTT, FXS, or ASD from the end of their first year of life onwards. Our results confirm previous reports on the delay of the emergence or potential non-achievement of certain speech-language milestones and on reduced gestural repertoires of children with RTT, FXS, or ASD (e.g., Roberts, et al., 2002; Zwaigenbaum, et al., 2005; Hinton et al., 2013; Marschik et al. 2013a; Watson, et al., 2013; Patten, et al., 2014; see Chapter 4.1 for details). Our findings extend the knowledge on the pre-diagnostic socio-communicative development by showing for example a reduced initiation of communicative acts in children with LRDDs compared to children with TD (‘requesting objects/actions/information’; see Chapter 4.2 for details). To the best of my knowledge, this thesis was the first to investigate the functional use of the observed vocalisations in the first 2 years of life of children with RTT, FXS, or ASD, and revealed that

(pre-)linguistic vocalisations were hardly used for communicative purposes (e.g., for 'imitation'; see Chapter 4.3). Furthermore, this thesis for the first time compared the socio-communicative domains of RTT, FXS, ASD, and TD, and suggested condition-specific developmental pathways (see Chapters 4.1.3, 4.2.3, and 4.3.3 for details): The results for the TD group mirrored the well-known typical continuous progression of speech-language capacities and their increased use for communicative functions referring to objects/events in the environment or to previous speech acts (e.g., Bates, Camaioni and Volterra, 1975; Bates, et al., 1994; Fenson, et al., 1994; Menyuk, Liebergott and Schultz, 1995; Chapman, 2000; Kauschke, 2000; Paul, 2007; Eriksson, et al., 2012; Rudolph and Leonard, 2016). In contrast, the socio-communicative capacities slowly increased in the FXS group throughout the observation period indicating a delay of socio-communicative forms and functions; the ASD group showed an increase-decrease pattern of certain socio-communicative capacities, especially in the functional use of (pre-)linguistic vocalisations, indicating a regression of communicative capacities. Ozonoff, et al. (2018) recently suggested that regression in ASD might be under-reported using certain methods (especially retrospective parental reports, categorical questions to parents/examiners) and may actually be rather the rule than the exception. Based on our findings, we believe our method is a promising approach to detect regression of communicative capacities and to describe its pattern in detail.

The results of this thesis may have implications for (1) further research on the early socio-communicative domain of children with LRDDs, (2) earlier diagnosis and intervention of LRDDs, and (3) intervention planning.

First, further studies may use an adapted version of the IPCA adding a token-based analysis and reducing the repertoire of investigated functions. This is because we found that certain peculiarities obviously only become evident when analysing tokens in addition to types (e.g., 'social convention'; Zhang et al. 2018; see Chapter 4.2.2 for details) and certain functions seem to be not properly assessable through family videos due to lack of opportunities or emergence at a later age (i.e., 'choice making', 'requesting information'; see Chapter 4.2.3 for details). Applied on larger cohorts, the adapted methodology would certainly lead to new insights on, for example, the frequency of (in)appropriate reactions to certain situations, the proportion of communicative acts that are initiated vs. responded by the children, or the combination of certain communicative forms to reach communicative goals. In this way, it would be very likely to enable a more precise description of developmental trajectories and to reveal further disorder-specific peculiarities in the socio-communicative domain. Moreover, our approach may be applied to other LRDDs to

increase the knowledge on their early socio-communicative development and to detect similarities and differences of various LRDDs.

Second, the findings of this thesis suggest potential communication-related behavioural markers (e.g., reduced (pre-)linguistic vocalisations and gestural repertoires, reduced initiation of communicative acts, reduced functional use of (pre-)linguistic vocalisations) associated with the investigated disorders. A future goal could be to sensitise paediatricians but also caregivers to these markers in order to earlier initiate diagnostic procedures. This may avoid diagnostic odysseys for families and improve developmental outcomes by enabling an earlier intervention focusing on behavioural deficits as they emerge.

Third, the better understanding of relative strengths and weaknesses in the socio-communicative domain of children with RTT, FXS, or ASD may improve the intervention planning for children with one of these disorders. The feasibility of this aim appears promising as the same measurement, the IPCA, was initially designed for intervention planning.

Although we detected certain developmental peculiarities that were more obvious in either RTT (e.g., absence of (pre-)linguistic vocalisations), FXS (e.g., reduced ‘imitation’), or ASD (e.g., reduced ‘requesting an object’), an earlier diagnosis of specific disorders based on a single developmental domain is very unlikely. Most probably, a comprehensive interdisciplinary approach combining a socio-communicative assessment based on IPCA-related parameters with signal-based parameters from the speech-language domain such as acoustic vocalisation parameters and parameters from other developmental domains, e.g., the motor and cognitive domains (cf. Marschik, et al., 2017), is a promising approach to succeed.

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6 Appendix

6.1 Additional statistical values

Table 16: Median, minimum, and maximum proportions of observed communicative functions for which the participants with fragile X syndrome used non-verbal behaviours, non-linguistic vocalisations, and (pre-)linguistic vocalisations in the three age bands 9–12 months, 13–18 months, and 19–24 months.

FXS group	9–12 months			13–18 months			19–24 months		
	NV_{prop}	NL_{prop}	L_{prop}	NV_{prop}	NL_{prop}	L_{prop}	NV_{prop}	NL_{prop}	L_{prop}
N	7	7	7	7	7	7	3	3	3
Median	1.0000	.8333	.0000	1.0000	.6667	.0000	1.0000	.6667	.4286
Minimum	.75	.00	.00	.67	.00	.00	1.00	.00	.17
Maximum	1.00	1.00	.33	1.00	.83	.71	1.00	.71	.80

Abbreviations: FXS = fragile X syndrome; NV_{prop} = proportion of communicative functions for which the participants used non-verbal behaviours; NL_{prop} = proportion of communicative functions for which the participants used non-linguistic vocalisations; L_{prop} = proportion of communicative functions for which the participants used (pre-)linguistic vocalisations.

Table 17: Median, minimum, and maximum proportions of observed communicative functions for which the participants with autism spectrum disorder used non-verbal behaviours, non-linguistic vocalisations, and (pre-)linguistic vocalisations in the three age bands 9–12 months, 13–18 months, and 19–24 months.

ASD group	9–12 months			13–18 months			19–24 months		
	NV_{prop}	NL_{prop}	L_{prop}	NV_{prop}	NL_{prop}	L_{prop}	NV_{prop}	NL_{prop}	L_{prop}
N	6	6	6	4	4	4	5	5	5
Median	.9167	.5833	.0000	.8000	.7000	.2667	1.0000	.8000	.0000
Minimum	.60	.25	.00	.67	.60	.00	.80	.00	.00
Maximum	1.00	.80	.50	1.00	1.00	1.00	1.00	.80	.20

Abbreviations: ASD = autism spectrum disorder; NV_{prop} = proportion of communicative functions for which the participants used non-verbal behaviours; NL_{prop} = proportion of communicative functions for which the participants used non-linguistic vocalisations; L_{prop} = proportion of communicative functions for which the participants used (pre-)linguistic vocalisations.

Table 18: Median, minimum, and maximum proportions of observed communicative functions for which the participants with typical development used non-verbal behaviours, non-linguistic vocalisations, and (pre-)linguistic vocalisations in the three age bands 9–12 months, 13–18 months, and 19–24 months.

TD group	9–12 months			13–18 months			19–24 months		
	NV_{prop}	NL_{prop}	L_{prop}	NV_{prop}	NL_{prop}	L_{prop}	NV_{prop}	NL_{prop}	L_{prop}
N	8	8	8	10	10	10	8	8	8
Median	.8571	.8286	.3250	.8000	.7321	.4643	.8750	.4524	.6333
Minimum	.50	.50	.00	.50	.50	.00	.70	.00	.38
Maximum	1.00	1.00	.50	1.00	.83	.89	1.00	.88	1.00

Abbreviations: TD = typical development; NV_{prop} = proportion of communicative functions for which the participants used non-verbal behaviours; NL_{prop} = proportion of communicative functions for which the participants used non-linguistic vocalisations; L_{prop} = proportion of communicative functions for which the participants used (pre-)linguistic vocalisations.

Table 19: Median, minimum, and maximum proportions of observed communicative functions for which the participants with Rett syndrome used non-verbal behaviours, non-linguistic vocalisations, and (pre-)linguistic vocalisations in age band 9–12 months.

RTT group	9–12 months		
	NV_{prop}	NL_{prop}	L_{prop}
N	6	6	6
Median	1.0000	.6786	.0000
Minimum	.75	.00	.00
Maximum	1.00	1.00	.00

Abbreviations: RTT = Rett syndrome; NV_{prop} = proportion of communicative functions for which the participants used non-verbal behaviours; NL_{prop} = proportion of communicative functions for which the participants used non-linguistic vocalisations; L_{prop} = proportion of communicative functions for which the participants used (pre-)linguistic vocalisations.

6.2 Own publications

During my doctoral study, I have published the following SCI/SSCI listed articles as first author or co-author (in alphabetical order):

Bartl-Pokorny, K.D., Landerl, K., Einspieler, C., Enzinger, C., Gebauer, D., Fink, A., Zhang, D., Kozel, N., Kargl, R., Seither Preisler, A., Vollmann, R., Marschik, P.B., 2011. Dyslexia and its neural signature. *Klinische Neurophysiologie*, 42(3), 166-71.

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