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Response to name and its value for the early detection of developmental disorders: Insights from autism spectrum disorder, Rett syndrome, and fragile X syndrome. A perspectives paper

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Abstract

Background—Responding to one's own name (RtN) has been reported as atypical in children with developmental disorders, yet comparative studies on RtN across syndromes are rare.

Aims—We aim to (a) overview the literature on RtN in different developmental disorders during the first 24 months of life, and (b) report comparative data on RtN across syndromes.

Methods and procedures—In Part 1, a literature search, focusing on RtN in children during the first 24 months of life with developmental disorders, identified 23 relevant studies. In Part 2, RtN was assessed utilizing retrospective video analysis for infants later diagnosed with ASD, RTT, or FXS, and typically developing peers.

Outcomes and results—Given a variety of methodologies and instruments applied to assess RtN, 21/23 studies identified RtN as atypical in infants with a developmental disorder. We observed four different developmental trajectories of RtN in ASD, RTT, PSV, and FXS from 9 to 24 months of age. Between-group differences became more distinctive with age.

Conclusions and implications—RtN may be a potential parameter of interest in a comprehensive early detection model characterising age-specific neurofunctional biomarkers associated with specific disorders, and contribute to early identification.

Keywords

Autism spectrum disorder; response to name; reaction to name; early identification; developmental disorders; cross-syndrome comparison

Introduction

Scientists and clinicians have been tirelessly pursuing markers that enable the earlier detection of various developmental disorders. To date, a number of developmental disorders can be detected intrauterinely or during the neonatal period using effective screening tools. In some cases, physical features may raise an early suspicion of a certain disorder while in others, particular neuro-functional signs, such as the prominent and unique vocalisations in Cri du chat syndrome (chromosome 5p deletion syndrome), may lead to the early recognition of a certain condition. Early detection becomes more challenging when attempting to identify developmental disorders which manifest later in life, often beyond toddlerhood. In recent years, increased efforts have been devoted to study these late-detected disorders, such as autism spectrum disorder (ASD), Rett syndrome (RTT), fragile X syndrome (FXS), or Angelman syndrome (AS), to name but a few, through retrospective and prospective approaches (e.g., Bölte et al., 2016). The establishment of the prospective paradigm in studying high-risk sibling cohorts of ASD or attention deficit hyperactivity disorder (ADHD), for example, has enabled the developmental trajectories of these late recognised disorders to be more precisely studied. This has resulted in a better understanding of the early phenotypes of such disorders, and has contributed to the development of intervention programs aimed at improving the developmental outcomes of children, such as the Early Start Denver Model (Dawson, 2008; Dawson et al., 2010; Rogers et al., 2012; Sullivan, Stone, & Dawson, 2014). Some disorders, such as FXS, RTT, or AS, are however rarely studied using prospective approaches due to their hereditary nature (e.g., RTT is mainly caused by *de novo* mutations in the *MECP2* gene; (Neul et al., 2010) and/or their rarity: this impacts upon the possibilities of identifying parameters to enable early detection.

Early identification of a developmental disorder is a prerequisite for the implementation of targeted and timely intervention. The first two years of life (i.e., from birth to 24 months) are considered to be the most effective timeframe for intervention as the young brain is highly plastic, and can be re-wired to encourage a more preferable developmental trajectory (Chen, Cohen, & Hallett, 2002; Cioni, D'Acunto, & Guzzetta, 2011; Dawson, 2008; Dawson et al., 2012; Hadders-Algra, 2011, 2014). Unfortunately, a number of developmental disorders are not commonly diagnosed before preschool age. Some health care professionals have been advocating for global genetic screening at birth and in some disorders, whole genome sequencing might offer a promising option for earlier detection. With other disorders, however, such as ASD or ADHD, the genetic heterogeneity, the genotype-phenotype relation, and related epigenetic factors are not yet completely understood. Thus, searching

for neuro-functional markers, especially in the first two years of life where early signs emerge and consolidate, still remains indispensable for early identification that will subsequently enable early intervention (Marschik et al., 2017).

Notably, developmental disorders of different etiologies share a range of similar abnormalities. For example, autistic features are frequently also observed in individuals with FXS or RTT, although sometimes transient in nature (Niu et al., 2017). Multiple clinical conditions can also co-occur in the same individual, such as FXS with ASD, or ASD with ADHD (e.g., Abbeduto, McDuffie, & Thurman, 2014; Craig et al., 2015; Johnson, Gliga, Jones, & Charman, 2014). These overlapping characteristics and comorbidities complicate the identification of specific disorders. It is still to be examined whether a particular behavioural marker is (a) reliably associated with a specific disorder, (b) shared by different conditions, or (c) rather associated with a general developmental delay.

One frequently studied early behaviour is the response to one's own name. Response to name (RtN) requires an individual to detect and shift his or her attention to a signal that is socially meaningful and salient to the person named (e.g., by turning the head and looking at the person who called their name). Previous studies have applied modified head-turn preference procedures (Mandel, Jusczyk, & Pisoni, 1995) or near-infrared spectroscopy technology (Grossmann, Parise, & Friederici, 2010), and demonstrated that typically developing infants from 4.5 to 5 months of age onwards are sensitive to the sound pattern of their own name. Compared to another name, hearing their own names, especially when spoken by their mother, elicited greater activity in 6-month-old infant's medial prefrontal cortex, an area considered important in the process of self-referencing (Imafuku, Hakuno, Uchida-Ota, Yamamoto, & Minagawa, 2014). Furthermore, 5-month-old infants attended longer to objects presented on a screen after hearing their own name compared to another name (Parise, Friederici, & Striano, 2010). These findings suggest that by 6 months of age infants are not only sensitive to the sound pattern of their name, but also start to associate this signal to other social cues (e.g., the mother's voice), and use this socially meaningful signal to guide their attention to events and objects in the world. It is worthy to note that different areas of the brain are triggered in young infants when responding to their name in comparison to that seen in adults (Kampe, Frith, & Frith, 2003). This suggests that RtN is a developing behaviour in infants who are gradually learning to use a unique social cue (i.e., hearing their own name) to selectively orient their attention to meaningful aspects of their environment.

Due to the salient socio-communicative nature of RtN, it has been widely studied in individuals with socio-communicative deficits, especially among infants later diagnosed with ASD. RtN has also been included in several screening tools (e.g., Autism Diagnostic Observation Schedule, ADOS: Lord et al., 1989; 2012; Autism Observation Scale for Infants, AOSI: Bryson, Zwaigenbaum, McDermott, Rombough, & Brian, 2008). Recently, studies on RtN, together with other related social-reciprocal behaviors have been extended to individuals later diagnosed with RTT or FXS. In this article, we provide (a) an overview of studies that have investigated RtN in individuals with developmental disabilities; (b) new empirical data on RtN from children with ASD or FXS, adding a cross syndrome comparison of ASD, FXS, RTT, and the preserved speech variant of RTT (PSV); and (c) we

discuss perspectives of future research aiming at earlier diagnosis and the potential of RtN as one early marker for identifying developmental disorders.

Methods

Part 1: Overview of previous research

Search procedures—Two independent literature searches were conducted by two authors (LR, LM) and checked for completeness by a third author (KDB) within the electronic databases PubMed, ERIC, ProQuest, and Google Scholar in early October 2017 using the search terms: [react* to name/response to name/orient* to name] AND [neurodevelopmental/developmental disorders], [developmental disabilities], [autis*], [Angelman syndrome], [AD(H)D], [Asperger], [Canavan disease], [Coffin-Lowry syndrome], [developmental dyslexia], [fragile X syndrome], [monosomy 22q13], [Mowat-Wilson syndrome], [Noonan syndrome], [pervasive developmental disorders, not otherwise specified; PDD-NOS], [Pitt-Hopkins syndrome], [Prader-Willi syndrome], [Rett syndrome], [Smith-Magenis syndrome], [specific language impairment/communication disorder], [specific learning disorder], [Tourette syndrome], [Tuberous sclerosis]. The search resulted in 48 potential papers that were screened against the pre-determined inclusion criteria (see below). Nineteen papers were selected and then used for an ancestry search whereby authors of the included papers were searched in PubMed and Google Scholar search engines to locate any additional papers. Four further papers were then included leading to a final sample of 23 studies for analysis (Table 1).

Inclusion criteria—The pre-determined inclusion criteria were the following: (a) participants included in the study must have been at risk of, or have later received a diagnosis of a developmental disorder; (b) participants must have received an RtN assessment during the first 24 months of life; (c) analysis of RtN must have been one of the objectives of the study and data related to RtN must have been explicitly reported; and (d) studies must have been written in English and published in peer reviewed journals.

Part 2: Cross syndrome comparison

Within the framework of this article we compared data on RtN of individuals later diagnosed with ASD, FXS, RTT or PSV. The RTT data has been previously reported by our research group (Townend et al., 2015). Here we added retrospective video analyses of infants later diagnosed with ASD or FXS; for the age group 9 to 12 months we additionally report on data of a typically developing (TD) group. The identical RVA procedure was employed as reported in our previous study on RTT (Townend et al., 2015). Response rate is calculated by “response observed” divided by “response expected” (Table 2). An “opportunity” refers to one name prompt or more quickly succeeding prompts in the same situation. If within the same opportunity, a reaction was observed after the third name prompt or later, this was counted as “no response”.

Video recordings of the first 24 months of life of 33 individuals with a total running time of 1279 minutes were analysed. The footage was provided by parents who were not aware of their infants’ condition at the time of recording and included: 328 minutes of 13 individuals

with ASD (13 male), 664 minutes of 13 individuals with FXS (10 male), and 287 minutes recordings of 7 TD children (5 male). The previously published data on RTT comprised 10 female individuals with typical RTT and 5 with the preserved speech variant of RTT (PSV; Townend et al., 2015). All data were extracted from our real-world database GUARDIAN [Graz University Audiovisual Research Database for the Interdisciplinary Analysis of Neurodevelopment] that was built up over 15 years and comprises home video material with a total running time of more than a year (Pokorny et al., 2016). All children with FXS or RTT included in GUARDIAN had a clinical diagnosis and genetic confirmation of respective FMR1 or MECP2 mutation. Clinical diagnosis were in accordance with specific consensus criteria (e.g., Neul et al. 2010 for RTT) or widely accepted diagnostic instruments for ASD (e.g., ADOS), depending on the different diagnostic procedures of the referring centers. All available individuals with FXS, RTT, or ASD who had adequate video data of the first 24 months of life from the database have been included in the current study. The study was approved by the Institutional Review Board of the Medical University of Graz, Austria (24-226 ex 11/12) and the parents gave their informed written consent to participate in the study and to the potential publication of the results.

Results

Part 1: Overview of previous research

Participant Characteristics—Of the 23 studies included in this overview (highlighted with * in the Reference section), 20 focused on children with ASD, one focused on individuals with RTT (Townend et al., 2015), and one on individuals with FXS (Baranek et al., 2005). The remaining study reported on three infants who demonstrated a lack of social engagement, suggestive of autism spectrum disorder (Koegel, Singh, Koegel, Hollingsworth, & Bradshaw, 2014). Within the 20 ASD studies, 6 studies analysed infants at high-risk (HR_{ASD}) for ASD, i.e. siblings of children with ASD (Brian et al., 2008; Gammer et al., 2015; Miller et al., 2017; Nadig et al., 2007; Yirmiya et al., 2006; Zwaigenbaum et al., 2005); 8 studies compared children with ASD and intellectual disability (termed mental retardation, MR, in the studies of Muratori, Apicella, Muratori, & Maestro, 2011; Osterling, Dawson, & Munson, 2002; or developmental disabilities, DD, in Baranek, 1999; Clifford, Young, & Williamson, 2007; Trillingsgaard, Sørensen, N mec, & Jørgensen, 2005; Veness et al., 2012; Ventola et al., 2007; Wetherby et al., 2004); 3 studies included children with specific language impairment, developmental language delay, or language delay (SLI/DLD/LD: Gabrielsen et al., 2015; Veness et al., 2012; Ventola et al., 2007); 2 studies reported on early and late onset ASD groups (ASD-EO/ASD-LO: Osterling et al., 2002; Werner, Dawson, Osterling, & Dinno, 2000); and 1 study specifically reported on children with pervasive developmental disorder-not otherwise specified (PDD-NOS: Chawarska, Klin, Paul, & Volkmar, 2007).

Of the 23 studies included in this overview, 3 did not report on the participants' gender (Table 1; Trillingsgaard et al., 2005; Werner et al., 2000; Zwaigenbaum et al., 2005). Six studies did not include a control group (Chawarska et al., 2007; Gomez & Baird, 2005; Koegel et al., 2014; Townend et al., 2015; Trillingsgaard et al., 2005; Ventola et al., 2007), and one study was population-based (Stenberg et al., 2014). Sixteen studies included a

comparison group that either consisted of TD children or children with a low risk for receiving an ASD diagnosis (LR).

Study Design—The first assessment of RtN was conducted during the first year of life in 15 studies; the remaining 8 studies assessed RtN during the second year of life (Table 1). Thirteen studies conducted RtN assessments only once, six of them during the first year of life (Baranek, 1999; Baranek et al., 2005; Osterling & Dawson, 1994; Osterling et al., 2002; Werner et al., 2000; Yirmiya et al., 2006), the others during the second year of life (Brian et al., 2008; Clifford et al., 2007; Gabrielsen et al., 2015; Gomez & Baird, 2005; Stenberg et al., 2014; Ventola et al., 2007; Wetherby et al., 2004). The other 10 studies assessed RtN at multiple age points (Table 1).

RtN Assessment—Except for three studies mainly dealing with RtN (Miller et al., 2017; Nadig et al., 2007; Townend et al., 2015), all other articles in this overview assessed multiple early behaviours, with RtN being one of them. Various instruments and approaches to evaluate RtN were applied (Table 1). In five of the 11 prospective studies, the following standardized developmental assessments were administered: the ADOS (Brian et al., 2008), the Autism Diagnostic Observation Schedule-Generic (ADOS-G, Chawarska et al., 2007), the AOSI (Brian et al., 2008; Gammer et al., 2015; Zwaigenbaum et al., 2005), and the Systematic Observation of Red Flags (SORF, Wetherby et al., 2004; for Key please see Table 1). In four of the prospective studies, direct assessments were implemented where a researcher (Miller et al., 2017; Nadig et al., 2007; Wetherby et al., 2004) or the mother of the infant (Yirmiya et al., 2006) was instructed to elicit RtN. In addition to a direct observation in a semi-structured interactive play session, Trillingsgaard and colleagues (2005) also used a parental questionnaire to assess RtN retrospectively. Parental questionnaires were also used by four other research groups who calculated rate of RtN based on the relevant item within the Modified Checklist for Autism in Toddlers (M-CHAT, Stenberg et al., 2014; Ventola et al., 2007), the Temperament and Atypical Behavior Scale (TABS, Gomez & Baird, 2005), or the Communication and Symbolic Behavior Scale Developmental Profile Infant-Toddler Checklist (CSBS-ITC, Veness et al., 2012; for Key please see Table 1). Eight of the 23 studies adopted retrospective video analysis (RVA) to assess RtN (Baranek, 1999; Baranek et al., 2005; Clifford et al., 2007; Muratori et al., 2011; Osterling & Dawson, 1994; Osterling et al., 2002; Townend et al., 2015; Werner et al., 2000). The intervention study by Koegel and colleagues (2014) assessed RtN response rates during a baseline observation, intervention, and follow-up.

Interrater reliability—In the five studies that used parental questionnaires, interrater reliability could not be calculated (Gomez & Baird, 2005; Stenberg et al., 2014; Trillingsgaard et al., 2005; Veness et al., 2012; Ventola et al., 2007). A further five studies did not report on interrater reliability (Brian et al., 2008; Chawarska et al., 2007; Gammer et al., 2015; Miller et al., 2017; Zwaigenbaum et al., 2005). Of the remaining 13 studies, 6 reported intra-class coefficients (ICCs) ranging from 0.66 to 1.00 (Baranek, 1999; Baranek et al., 2005; Clifford et al., 2007; Nadig et al., 2007; Osterling et al., 2002; Werner et al., 2000), 5 reported Kappa values ranging from 0.67 to 1.00 (Gabrielsen et al., 2015; Muratori et al., 2011; Osterling & Dawson, 1994; Wetherby et al., 2004; Yirmiya et al., 2006), and a

further 2 reported the percentage of agreement ranging from 50 to 100% (Koegel et al., 2014; Townend et al., 2015).

Main findings on RtN—Of the included studies in this overview, RtN was identified as atypical (i.e., significantly different from that observed in the TD or LR groups, or the score on the related item of the standardised assessment was not within normal range) for children with developmental disorders in 21 studies, of which 19 focused on children with ASD. This result was observed irrespective of the method applied: it was observed in prospective studies using standardised assessments and/or direct observations, in studies using parental questionnaires, and in RVA (Table 1). The majority of the studies comparing RtN in individuals with ASD and their TD peers reported a lower rate of RtN in ASD (Clifford et al., 2007; Gabrielsen et al., 2015; Muratori et al., 2011; Osterling & Dawson, 1994; Osterling et al., 2002; Stenberg et al., 2014; Werner et al., 2000; Wetherby et al., 2004). Similar results were found when high-risk infants for ASD were compared with low-risk infants (Miller et al., 2017; Zwaigenbaum et al., 2005). In the intervention study by Koegel and colleagues (2014), low rates of RtN were reported during baseline in all three infants entering the study at ages 4 to 9 months. Following 10 to 17 weeks of a parent-led play based intervention, RtN rates improved and these results maintained 2 to 6 months post intervention (Koegel et al., 2014).

The results from Veness and colleagues (2012) were interesting in that RtN was assessed by an item on the caregiver checklist CSBS-ITC in four targeted groups (i.e., ASD, SLI, DD, and TD) at 8, 12, and 24 months of age. The caregivers were asked whether RtN is present at the time of assessment, offered with three options: “not yet”, “sometimes”, or “often”. Although a significant overall group difference of data analysis at 24 months was revealed, further post hoc test found no significant difference between any two groups. In their RVA study comparing individuals with ASD, intellectual disability, and TD, Muratori and colleagues (2011) found a significant difference in RtN between ASD and TD at the ages 7 to 12 months, but not at a younger or older age. In a prospective study, Nadig and colleagues (2007) reported no significant difference between HR_{ASD} and LR infants in RtN at 6 months, yet a significantly lower RtN rate of the HR_{ASD} infants at 12 months. Interestingly, in Yirmiya and colleagues (2006), RtN was reported as significantly better in the ASD group compared to the TD group at 4 months of age.

Comparing RtN between infants later diagnosed with ASD and those with developmental delay or intellectual disability, the results were mixed and appeared to have depended on the methodology applied. Studies applying direct behavioural coding (Trillingsgaard et al., 2005; Wetherby et al., 2004), the M-CHAT (Ventola et al., 2007), or RVA (Clifford et al., 2007), for example, revealed atypical RtN in individuals with ASD, whereas the use of retrospective questionnaire did not (Trillingsgaard et al., 2005). Additionally, applying different statistical procedures, Muratori and colleagues (2011) demonstrated different findings related to RtN between individuals with ASD and intellectual disability. Differences in RtN were also related to the assessments used. For example, in the study by Brian et al. (2008), the ADOS indicated differences within the HR_{ASD} group between individuals who later received an ASD diagnosis and who did not. The AOSI, however, failed to identify

differences between the two groups. Nonetheless, both ADOS and AOSI differentiated HR_{ASD} infants with an ASD diagnosis from the low risk controls in RtN.

In the only study on RTT included in this overview, Townend and colleagues (2015) evaluated RtN in individuals with typical RTT and the preserved speech variant (PSV) of RTT. Ten individuals with typical RTT responded more often to their name calling than five individuals with PSV from 5 to 8 months of age. Reversely, from 9 to 24 months, individuals with PSV demonstrated higher RtN rates compared to individuals with typical RTT. Unfortunately, this study is limited as it did not include a control group. In the only study focusing on individuals with FXS, replicating a previous procedure (Baranek, 1999), Baranek and colleagues (2005) detected a significant difference among the groups (i.e., FXS, ASD, DD, and TD) in RtN assessed by the number of adult name prompts. Specific statistical comparison between any two groups was however, not reported.

Part 2: Cross-syndrome comparison: an exploratory study

Our new RtN data from the video analyses of young children later diagnosed with RTT, PSV, FXS, ASD, in comparison to the seven TD children, are presented in Table 2. We did not have sufficient video footage for the youngest age period (5 to 8 months) of children later diagnosed with FXS or ASD for a comparison, thus the cross-syndrome comparison focused on the age periods of 9 to 12, 13 to 18, and 19 to 24 months. From the TD group, sufficient data were available only for 9 to 12 months range. Due to small sample sizes, we decided to report only descriptive data in Table 2 and Figure 1.

Figure 1 shows changes in the RtN rate for each group across the three age periods. From 9 to 12 months of age, differences in RtN appeared to be substantial between TD infants and all other conditions in our sample (i.e., RTT, PSV, FXS, and ASD). At all age periods, individuals with RTT demonstrated the lowest rate of RtN amongst all of the groups. At 9 to 12 months, the RtN rate appeared to be similar among ASD, FXS, and PSV, yet differences became evident and more distinctive with age, with ASD showing lower rates of RtN than FXS and PSV, but higher than RTT. Three different developmental profiles appeared: (a) increasing RtN rate with age for children with FXS; (b) continuously declining RtN rate for children with RTT; and (c) a slightly increasing rate of RtN, followed by RtN rate deterioration for children with PSV or ASD, with the ASD group demonstrating a dramatic reduction from the first to the second half of the second year (Figure 1).

Discussion

In research and clinical practice, RtN is considered a critical behaviour related to infants' socio-communicative development. Understanding this easy-to-assess and early emerging function may contribute to our knowledge of impaired social development in late infancy and toddlerhood, and to the earlier recognition of certain developmental disorders. In the current article we (a) present an overview of the literature concerning RtN in infants with various developmental disabilities and (b) provide a cross-syndrome comparison of infants with ASD, FXS, RTT, PSV, and their TD peers.

In Part 1, we identified 23 studies, which utilised a variety of methodologies and instruments to analyse RtN during the first 24 months of life (Table 1). Due to the saliency of RtN in early socio-communicative development, it is not surprising that most articles involved in this overview focused on individuals with ASD. Only few studies analysed RtN in other developmental disabilities (e.g., Baranek et al., 2005; Gabrielsen et al., 2015; Townend et al., 2015). Because of the divergence of the approaches and assessments for evaluating RtN, findings from the previous studies are not always comparable and sometimes inconsistent (e.g., Brian et al., 2008; Trillingsgaard et al., 2005). In our current study (Part 2), we assessed RtN across four conditions (ASD, FXS, RTT, and PSV) during the first 24 months of life by applying the same RVA procedure, providing cross-syndrome data on a comparable basis. This explorative data, given limited sample sizes, revealed four clearly different trajectories in RtN for the four developmental disorders assessed (Figure 1). Twenty-one of the 23 studies overviewed in Part 1 reported RtN deficits from 9 months onwards. Our own study confirmed this finding that all infants later diagnosed with a developmental disorder presented a lower RtN rate in contrast to their typical developing peers by the end of the first year.

Atypical RtN was not uniquely associated with ASD. Numerous studies revealed that children with a later diagnosis of ASD do respond to their names, although usually at a diminished rate, and their TD peers as well as infants with other developmental disorders do fail on RtN tasks from time to time (e.g., Baranek et al., 2005; Gabrielsen et al., 2015; Miller et al., 2017; Nadig et al., 2007; Townend et al., 2015). The results of the present RVA study (Part 2) appear to be consistent with the existing literature (e.g., Baranek et al., 2005; Wolff et al., 2012) in that individuals with FXS presented less impaired RtN than individuals with ASD; and infants with RTT, possibly due to the severe phenotype and the period of regression, revealed an even lower rate of RtN than those with ASD from 9 to 24 months. Therefore, atypical RtN, especially if consistently observed during the first 24 months of life, may be a potential indicator of a general disintegrative development (e.g., Miller et al., 2017; Nadig et al., 2007). More importantly, the likelihood of failing RtN and the developmental profiles of this behaviour appear to be divergent across different developmental disorders (e.g., Baranek et al., 2005; Gabrielsen et al., 2015; Townend et al., 2015), suggesting that RtN may have the potential as one marker in the early identification of different conditions.

Atypical RtN is but one neurobehavioral marker among others in deviant early development, which, on its own, has limited potential to specifically detect a certain disorder. Together with additional age-specific atypicalities, it may well alert clinicians to initiate a diagnostic process. The consistent failure to respond to one's name appears to coincide with other social deficits such as lack of responding to and initiating joint attention, reciprocal positive affect, and engagement with toy play and positive adult led stimulation (Goin & Myers, 2004; Koegel et al., 2014; Miller et al., 2017; Oner, Oner, & Munir, 2014; Osterling & Dawson, 1994; Townend et al., 2015; Zwaigenbaum et al., 2005). In light of a bootstrapping perspective, consistent failures on a range of basic social skills appears to have significant negative implications for later communication and social development (Dawson, 2008; Miller et al., 2017; Oner, Oner, & Munir, 2014;). Given the fact that RtN is part of standardized assessments for ASD, e.g. in the ADOS, as one of many items on social

interaction, it may also have the potential to play a part in a heuristic model to detect developmental disorders commonly diagnosed beyond infancy (e.g. the Fingerprint-Model as proposed by Marschik et al., 2017). We assume that a particular combination of certain age-specific neurofunctional parameters (functions and dysfunctions defined by different levels of atypicality) constitute attribute-constellations, or fingerprints, that point to certain disorders. RtN must be seen in the complexity of the developing nervous system and its functions and not as a single parameter to detect developmental disorders.

Apart from involving RtN in more systematic and comprehensive assessments for early identification of developmental disabilities, one must consider its age-related significance. For example, Yirmiya and colleagues (2006) assessed RtN in 4-month-old infants and found an unexpected better RtN score in HR_{ASD} than in LR controls, although this score was not related to the developmental assessments at 14 months of age. Other studies (e.g., Miller et al., 2017; Muratori et al., 2011; Nadig et al., 2007) reported comparable RtN rates of children with a later ASD diagnosis and the TD controls at 6 months of age. Our current data also presented that differences in RtN between groups (i.e., ASD, FXS, PSV, and RTT) were less distinctive at 9 to 12 months, but became more evident with increasing age (Figure 1). These results confirm RtN to be an emerging behaviour during the first year of life. RtN assessed before the end of the first year might not serve as a reliable predictor for later development. In particular, the onset of ASD has been reported as gradual with a relatively broad window of symptom consolidation between 12 and 36 months of age (Jones, Gliga, Bedford, Charman, & Johnson, 2014; Mitchell, Cardy, & Zwaigenbaum, 2011; Ozonoff et al., 2010). Our findings coincide with the literature in that deficits in RtN became more obvious in individuals with ASD from 13 - 18 months to 19 - 24 months (Figure 1).

In our overview of research on RtN, we focused on data collections of the first 24 months of life; perhaps a more inclusive age period would capture the long term implications of atypicalities in RtN. In our empirical study, we applied RVA to assess RtN across conditions. Given the merits and restrictions of this methodology, which have been intensively discussed in the past, video examination has proven to be a valuable tool for observing infants with developmental disorders prior to their diagnosis (e.g., Goin & Myers, 2004; Marschik & Einspieler, 2011; Ozonoff et al., 2011; Palomo, Belinchón, & Ozonoff, 2006; Zwaigenbaum, Bryson, & Garon, 2013). Utilizing this method, we were able to address the issue of the scarcity of comparative studies in RtN in individuals with developmental disorders other than ASD. Due to the small sample size and the inherent limits of the methodology applied, our findings need to be interpreted with caution and replications with greater sample sizes are warranted. Still, we provide novel information for unravelling an essential early behaviour of social development through a cross-syndrome comparison.

Considering the promising results of Koegel and colleagues (2014) and existing early intervention programs (e.g., Dawson et al., 2010), it seems worthwhile to extend and investigate future intervention studies that target RtN in addition to other critical social interactive behaviours to determine the best possible approaches aiming at more preferable outcomes of developmental disabilities. Research on long term implications of RtN discrepancies for children with developmental disorders to determine the stability and reliability of this behavioural marker in the diagnostic process is warranted. In-depth

analyses during the first 24 months of life might reveal temporal and/or qualitative differences in the development of RtN and may shed light on the salience of this behaviour in developmental disorders that share similar phenotypical characteristics, e.g. autistic traits as seen in RTT and FXS. RtN, in connection with other developmental variables, may be a potential parameter of interest in our recently proposed 'Fingerprint-model' characterising neurofunctional biomarkers in association with specific disorders over time and contribute to their early identification (Marschik et al., 2017).

Conclusion

A significant finding that emerges from the literature is that consistently failing RtN appears to be a predictor of atypical development. RtN is easy to assess and may be one of the behavioural markers to be involved in the symptom-constellation based fingerprint approach. It may have the potential to contribute to the early differentiation of typical and atypical development in young children. Further assessment of RtN in TD children and individuals with various developmental disorders might shed more light on the importance of RtN as a differentiating behavioural marker of developmental and rare genetic disorders that manifest in more subtle ways.

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What this paper adds?

This paper adds an overview which evaluates the presence of response to name (RtN) during the first 24 months of life, and the association of RtN with various developmental disorders. It also adds a cross-syndrome comparison of early RtN in infants who were later diagnosed with ASD, RTT, PSV, or FXS. It was discussed to which extent deficits in RtN might be an early marker for specific disorders. The findings highlighted the potential value of including RtN assessment in our recently proposed ‘Fingerprint-Model’ characterising neurofunctional biomarkers in association with specific disorders, aimed at their early identification.

Figure 1.
Four developmental trajectories of individuals with ASD, FXS, RTT, or PSV in RtN rates over time.

Table 1

Summary of the 23 included studies.

Author(s)	Participants	Design/Age of RtN assessment	Procedures/RtN Assessments	Results
Baranek (1999)	11 ASD (10M/1F) 10 DD (3M/7F) 11 TD (6M/5F)	RVA 9-12 months	Two 5 min segments coded (i.e., frequency of occurrence across 20 consecutive 15 sec intervals). RtN calculated by response frequency, and by number of prompts by adults over the two 5-min segments. IRR measured by ICC = 0.98.	Frequency of response was not significantly different for ASD, DD, and TD, but the number of adult name prompts needed to elicit a response was; specifically, ASD > DD > TD. Rate of name prompts was one of the significant variables on a classification analysis discriminating ASD from DD and TD.
Baranek et al. (2005)	11 FXS (10M/1F) plus the same participants as in Baranek (1999); 11 ASD (10M/1F) 10 DD (3M/7F) 11 TD (6M/5F)	RVA 9-12 months	RVA Replication of those in Baranek (1999). RtN calculated only by number of prompts by adults over the two 5-min segments. IRR measured by ICC = 1.0.	Procedures identical to those in Baranek (1999) Number of adult name prompts needed to elicit response was significantly different across groups. No statistical comparison between groups was reported.
Brian et al. (2008)	155 HR _{ASD} (83M/72F); 35 HR _{ASD-ASD} (21M/14F) 120 HR _{ASD-No ASD} (62M/58F) 73 LR (37M/36F)	Prospective at risk 18 months	Item 'Response to name' of the ADOS (higher scores denote increasing atypicality). Item 'Orients to name' of the AOSI (higher scores denote increasing atypicality). No IRR data reported.	RtN assessed by ADOS significantly different between HR _{ASD-ASD} and HR _{ASD-No ASD} (HR _{ASD-ASD} > HR _{ASD-No ASD}). Not significantly different assessed by AOSI. RtN assessed by ADOS and AOSI significantly different between HR _{ASD-ASD} and LR (HR _{ASD-ASD} > LR). RtN assessed by ADOS and AOSI not significantly different between HR _{ASD-No ASD} and LR.
Chawarska et al. (2007)	19 ASD (11M/8F) 9 PDD-NOS (9M) 3 DD (not included in analysis due to small sample size)	Prospective T1: 14-25 months T2: 29-40 months	Item 'Response to name' of the ADOS-G Module 1 (higher scores denote increasing atypicality). No IRR data reported.	ASD and PDD-NOS groups did not score within the normal range for RtN. RtN not significantly different between ASD and PDD-NOS (although ASD > PDD-NOS). RtN did not significantly change between T1 and T2 for ASD and PDD-NOS groups.
Clifford, Young, & Williamson (2007)	15 ASD (15M) 15 DD (9M/6F) 15 TD (9M/6F)	RVA 12-24 months	Two 5 min segments coded for frequency of 'response to name'. IRR measured by ICC = 0.90 (video segment 1), 0.83 (video segment 2).	RtN was significantly different between ASD and TD (ASD < TD). RtN was significantly different between ASD and DD (ASD < DD).

Author(s)	Participants	Design/Age of RtN assessment	Procedures/RtN Assessments	Results
Gabrielsen et al. (2015)	14 ASD (12M/2F) 14 LD (9M/5F) 14 TD (9M/5F)	Prospective 15-33 months	Two 10 min segments of videos (divided into 60 10 sec intervals) of clinical evaluations coded for response to name: Typical response = response within 3 sec of name being called Atypical response = no response within 3 sec of name being called. No IRR data reported explicitly for RtN; mean IRR for all behaviours as measured by kappa = 0.67.	Rates of Typical vs. Atypical responses were significantly different among the three groups, with ASD<LD and ASD<TD.
Gammer et al. (2015)	54 HR _{ASD} (21M/33F/); 17 HR _{ASD} -ASD (11M/6F) 36 HR _{ASD} -No ASD (10M/26F) 50 LR (21M/29F)	Prospective at risk T1: 6-10 months T2: 11-18 months	Item 'Orientation to name' of the AOSI (higher scores denote increasing atypicality). No IRR data reported.	RtN not significantly different between HR _{ASD} and LR at T1, but significantly different at T2 (HR _{ASD} >LR). RtN not significantly different between HR _{ASD} -ASD and LR at T1, but significantly different at T2 (HR _{ASD} -ASD>LR). RtN not significantly different between HR _{ASD} -No ASD and LR at T1, but significantly different at T2 (HR _{ASD} -No ASD>LR).
Gomez & Baird (2005)	65 ASD (58M/7F)	Retrospective questionnaire 12-23 months	Parents completed the TABS. RtN assessed by item 'Doesn't react to own name'. IRR not applicable.	RtN failure was reported by 68% of the parents.
Koegel et al. (2014)	3 infants with a lack of social engagement (2M/1F)	Multiple baseline across participants Infant 1: start: 4 months; weekly videos for 10 weeks; follow-up: at 6 months post intervention Infant 2: start: 7 months; weekly videos for 17 weeks; follow-up: at 2 months post intervention Infant 3: start: 9 months; weekly videos for 11 weeks; follow-up: at 2 months post intervention	RtN assessed by response rate. RtN assessed in weekly recorded videos (10 min; including play situations with parents) during baseline observations, intervention (i.e., modified PRT) and follow-up. IRR on RtN was 97% (range: 91%-100%) for infant 1, 92% (range: 70%-100%) for infant 2 and 86% (range: 50%-100%) for infant 3.	Low levels of RtN during baseline for all 3 infants. Improvement in RtN following intervention in all 3 infants. Results for RtN stable at follow-up for all 3 infants.
Miller et al. (2017)	96 HR _{ASD} (60M/36F); 20 HR _{ASD} -ASD (15M/5F) 76 HR _{ASD} -No ASD (45M/31F) 60 LR (36M/24F)	Prospective at risk T1-T6: 6, 9, 12, 15, 18, 24 months	'Orients to name' task adapted from the AOSI: Child sitting on parent's lap engaged with a toy. Examiner positioned behind child and calls name. Two 'presses' (with two prompts each) administered at T1-T6. 'Failing' score if no reaction to any press. No IRR data reported.	Likelihood of RtN failing score decreased over time for LR and HR _{ASD} -No ASD, but not for HR _{ASD} -ASD. Likelihood of RtN failing score significantly higher in HR _{ASD} -ASD than LR from T2 onwards. Likelihood of RtN failing score significantly higher in HR _{ASD} -ASD than HR _{ASD} -No ASD from T2 onwards. Likelihood of RtN failing score not significantly different between HR _{ASD} -No ASD and LR.

Author(s)	Participants	Design/Age of RtN assessment	Procedures/RtN Assessments	Results
Muratori et al. (2011)	15 ASD (10M/5F) 12 ID (7M/5F) 15 TD children (9M/6F)	RVA T1: 0-6 months T2: 7-12 months T3: 13-18 months	Video footage (at least 10 min per participant and age group) was coded. RtN assessed by ICBS, coding on the occurrence of response per minute, and name prompts by adults per minute, separately. No IRR data reported explicitly for RtN; mean IRR for all event behaviours of the ICBS as measured by kappa = 0.75.	Response rate was significantly different between ASD and TD at T2 (ASD<TD). No statistical comparison related to adult name prompts was provided. No more significant difference was found related to RtN at other ages. Response rate per minute was able to correctly identify the majority of ASD (93%) and ID (77%) at T3 on a discriminant analysis.
Nadig et al. (2007)	Data available for T1: 55 HR _{ASD} (34M/21F) 43 LR (23M/20F) Data available for T2: 101 HR _{ASD} (56M/45F) 43 LR (26M/17F) Data available for T1 and T2: 36 HR _{ASD} (gender not reported) 28 LR (gender not reported)	Prospective at risk T1: 6 months T2: 12 months	RtN procedure: Child sitting on parents lap/baby seat engaged with a toy. Examiner positioned behind child and calls name. Response score from 1-4 (1: response to first prompt, 2: no response after 3 prompts). 'Pass' test: Score 1-2 'Fail' test: Score 3-4 IRR measured by ICC = 1.0 (6 months), 0.88 (12 months).	RtN assessed by response score was not significantly different between HR _{ASD} and LR at T1 (trend: HR _{ASD} >LR). RtN assessed by response score was significantly different between HR _{ASD} and LR at T2 (HR _{ASD} >LR). LR were more likely to pass the name call test compared to HR _{ASD} at T1 and T2.
Osterling & Dawson (1994)	11 ASD (10M/1F) 11 TD (10M/1F)	RVA 12 months	Home video recordings of first birthday party (mean length: 10 min; range: 3-29 min). RtN assessed by 'Failure to orient to name per minute' (higher rate = fewer responses to name). No IRR data reported explicitly for RtN; mean IRR for coded behaviours as measured by kappa = 0.80.	RtN was significantly different between ASD and TD (ASD>TD).
Osterling, Dawson, & Munson (2002)	20 ASD (18M/2F): Further classified as ASD-ID or ASD-No ID: 14 ASD-ID (12M/2F) 6 ASD-No ID (6M/0F) Further classified as ASD-EO or ASD-LO: 13 ASD-EO (12M/1F) 7 ASD-LO (6M/1F) 14 ID (10M/4F) 20 TD (18M/2F)	RVA 12 months	Home video recordings of first birthday party. RtN assessed by response rate. IRR measured by ICC = 0.72.	RtN was significantly different between ASD and TD (ASD<TD). RtN was significantly different between ASD-ID and ID (ASD-ID<ID). RtN was significantly different between ASD-LO and ASD-EO (ASD-LO>ASD-EO). RtN was not significantly different between ID and TD.
Stenberg et al. (2014)	173 ASD (150M/23F) 51,853 non-ASD (26,447M/25,406F)	Population-based prospective 18 months	Item 'Response to name' of the parent-report questionnaire M-CHAT (yes/no decision - assessment of likelihood to fail RtN). IRR not applicable.	RtN was significantly different between ASD and non-ASD (likelihood to fail was greater in ASD than in non-ASD).
Townend et al. (2015)	10 typical RTT (10F) 5 PSV (5F)	RVA T1: 5-8 months T2: 9-12 months	Total of 2042 min of home video recordings. RtN assessed by response rate.	Reported descriptive data only due to limited sample size: Response rate at T1: typical RTT>PSV

Author(s)	Participants	Design/Age of RtN assessment	Procedures/RtN Assessments	Results
Trillingsgaard et al. (2005)	30 children with suspected ASD (25M/5F); 17 ASD (gender not reported) 13 DD (gender not reported)	T3: 13-18 months T4: 19-24 months	Mode of behavioural response (i.e., eyes and/or head, eyes and/or head and verbal, eyes and/or head and gesture). For 7% of coded behaviours, three coders discussed discrepancies until an agreement was achieved.	Response rate at T2, T3, T4: PSV>typical RTT Dominant response mode was eyes and/or head for typical RTT and PSV. Infrequent use of eyes and/or head and verbal from T1-T4 in typical RTT; no use of eyes and/or head and gestures. PSV used eyes and/or head and verbal as well as eyes and/or head and gestures only at T4.
Trillingsgaard et al. (2005)	30 children with suspected ASD (25M/5F); 17 ASD (gender not reported) 13 DD (gender not reported)	Retrospective questionnaire 0-24 months One direct observation session 23-47 months	Item 'Response to name' of a retrospective parental questionnaire (about development from 0-24 months), scored as normal (0), maybe deviant (1), or deviant (2). Response behaviour in a semi-structured interactive play session (23-47 months), scored as absent (0), uncertain (1), or present (2). No IRR data available due to live scoring without video recording.	RtN scores on retrospective questionnaire not significantly different between ASD and DD. RtN scores by direct observations significantly different between ASD and DD (DD>ASD).
Venness et al. (2012)	18 ASD (16M/2F) 20 SLI (15M/5F) 16 DD (12/4F) 60 TD (21M/39F)	Prospective T1: 8 months T2: 12 months T3: 24 months	Item 'Responding to name' of the parental questionnaire CSBS-ITC. Raw scores of the item were used for group comparison. RtN presence was scored as: not yet (0), sometimes (1), or often (2). IRR not applicable.	RtN scores revealed a significant group differences with H test at T3. Further post hoc test however found no significant difference between any of the groups. RtN score of each group was not provided. No significant result was found related to RtN at other ages.
Ventola et al. (2007)	150 ASD (123M/27F) 15 DD (12M/3F) 30 DLD (23M/7F)	Prospective 16-30 months	Item 'Response to name' of the parent-report questionnaire M-CHAT (yes/no decision – assessment of likelihood to fail RtN). IRR not applicable.	RtN was significantly different between ASD and DD (likelihood to fail was greater in ASD than in DD). RtN was significantly different between ASD and DLD (likelihood to fail was greater in ASD than in DLD). RtN not significantly different between DD and DLD.
Werner et al. (2000)	15 ASD (gender not reported); 12 ASD-EO (gender not reported) 3 ASD-LO (gender not reported) 15 TD (gender not reported)	RVA 8-10 months	Home video recordings (mean length: 15.8 min; range: 2-38 min). RtN assessed by response rate. No IRR data reported explicitly for RtN; IRR for coded behaviours as measured by ICC ranged from 0.66 to 0.90.	RtN was significantly different between ASD-EO and TD (ASD-EO<TD). RtN was similar between ASD-LO and TD.
Wetherby et al. (2004)	18 ASD (16M/2F) 18 DD (15M/3F) 18 TD (16M/2F)	Prospective 13-27 months	Videotapes of behaviour Samples (structured interactional setting to elicit social and communicative behaviours) were coded. Item 'Lack of response to name when called' of the SORF (higher score = fewer responses to name). No IRR data reported explicitly for RtN; IRR for SORF items as measured by kappa ranged from 0.82 to 1.00 (mean kappa = 0.94).	RtN was significantly different between ASD and DD (ASD>DD). RtN was significantly different between ASD and TD (ASD>TD). Score was higher for DD than for TD (not reported whether difference was significant).

Author(s)	Participants	Design/Age of RtN assessment	Procedures/RtN Assessments	Results
Yirmiya et al. (2006)	21 HR _{ASD} -ASD (13M/8F) 21 LR (13M/8F)	Prospective at risk 4 months	RtN procedure: Infant sitting in baby seat engaged with a toy. Mother calls name from each side of the seat (3 name calls, then change of side; first 9 name-calling attempts were included in analysis). 3 types of behaviours were coded for each group: (1) did not search mother at all (2) searched mother, but did not find her (3) searched mother and found her at least once IRR measured by kappa = 0.86.	At 4 months, significantly more HR _{ASD} -ASD than LR searched mother and found her at least once; significantly more LR than HR _{ASD} -ASD did not search mother at all; HR _{ASD} -ASD and LR was not significantly different on "searched mother, but did not find her".
Zwaigenbaum et al. (2005)	65 HR _{ASD} (gender not reported) 23 LR (gender not reported) Data available at T1: 44 HR _{ASD} (gender not reported) 15 LR (gender not reported) Data available at T2: 65 HR _{ASD} (gender not reported) 23 LR (gender not reported)	Prospective at risk T1: 6-7 months T2: 12-14 months	Item 'Orientation to name' of the AOSI. No IRR data reported.	Failure in RtN in individual HR _{ASD} infants at T1. RtN was significantly different between HR _{ASD} and LR at T2.

Numbers taken from the original paper by Gammer et al. (2015). There are inconsistencies between the reported number of female participants from the HR_{ASD} group and the numbers reported for the HR_{ASD}-ASD and HR_{ASD}-No ASD group.

Abbreviations: ADOS = Autism Diagnostic Observation Schedule; ADOS-G = Autism Diagnostic Observation Schedule-Generic; AOSI = Autism Observation Scale for Infants; ASD = Autism Spectrum Disorder; ASD-EO = early onset ASD; ASD-LO = late onset ASD; ASD-NO ID = individuals with ASD with normal intellectual ability; ASD-ID = individuals with ASD with accompanying intellectual disability; CSBS-ITC = Communication and Symbolic Behavior Scale Developmental Profile Infant-Toddler Checklist; DD = Developmental Disabilities; DLD = Developmental Language Disorder; F = female; HR_{ASD} = individuals at high risk for ASD (i.e., younger siblings of children with ASD); HR_{ASD}-ASD = individuals at high risk for ASD and later diagnosed with ASD; HR_{ASD}-No ASD = individuals at high risk for ASD without a later ASD diagnosis; ICBS = Infant and Caregiver Behavior Scale; ICC = intra-class coefficient; ID = intellectual disability; IRR = interrater reliability; LD = Language Delay; LR = individuals at low familial risk for neurodevelopmental disorders; M = male; M-CHAT = Modified Checklist for Autism in Toddlers; min = minutes; PDD-NOS = Pervasive Developmental Disorder-Not Otherwise Specified; 'Press': Calling the infants name at normal volume up to a total of two times; 'Prompt': One instance of calling the infants name; PRT = Pivotal Response Treatment; PSV = Preserved Speech Variant; RtN = reaction to name; RTT = Rett Syndrome; RVA = Retrospective Video Analysis; sec = seconds; SLI = Speech Language Impairment; SORF = Systematic Observation of Red Flags; T = Time of RtN assessment; TABS = Temperament and Atypical Behavior Scale.

Table 2

RTn in children later diagnosed with RTT*, PSV*, FXS, ASD, and in TD infants.

Age (months)	Number of cases				Number of opportunities				Response not possible				Response expected			
	RTT	PSV	FXS	ASD	TD	RTT	PSV	FXS	ASD	TD	RTT	PSV	FXS	ASD	TD	TD
5-8	8	2	n/a	n/a	n/a	57	40	n/a	n/a	n/a	15	3	n/a	n/a	n/a	n/a
9-12	9	3	9	13	7	51	53	45	57	52	12	10	11	14	34	41
13-18	5	5	9	11	n/a	67	33	56	61	n/a	10	2	10	14	57	n/a
19-24	6	4	7	8	n/a	37	52	67	62	n/a	5	4	15	7	32	n/a

Age (months)	Response observed				No response				Response rate (%)				Total recording time (min)			
	RTT	PSV	FXS	ASD	TD	RTT	PSV	FXS	ASD	TD	RTT	PSV	FXS	ASD	TD	TD
5-8	16	10	n/a	n/a	n/a	26	27	n/a	n/a	n/a	38.10	27.03	n/a	n/a	356	n/a
9-12	10	15	12	17	27	29	28	22	26	14	25.64	34.88	35.29	39.53	512	287
13-18	10	15	25	20	n/a	47	16	21	27	n/a	17.54	48.39	54.35	42.55	590	81
19-24	4	20	30	11	n/a	28	28	22	44	n/a	12.50	41.67	57.69	20.00	268	n/a

* reported in Townend et al., 2015

Key:

Number of cases = number of participants for whom video recordings were available during the defined age period.
 Number of opportunities = total number of opportunities that the collective participants' names were called in the video recordings for the defined age period. An opportunity is defined as one name prompt or more quickly succeeding prompts in the same situation.
 Response not possible = total number of times that the collective participants' responses to their names being called could not be included, for example, when they were already looking at the person who called their name or the infant was out of the view.
 Response expected = total number of opportunities minus response not possible.
 No response = total number of times that the collective participants responded.
 Response rate = total number of times that a response was expected but no behavioral response was observed.
 Response rate = response observed divided by response expected during the defined age period.
 n/a = no video available or insufficient footage available.