UvA-DARE (Digital Academic Repository)

Autism as a multicausal system

Deserno, M.K.

Publication date
2019
Document Version
Other version
License
Other

[Link to publication](#)

6

SLEEP DETERMINES QUALITY OF LIFE IN AUTISTIC ADULTS: A LONGITUDINAL STUDY

6.1 ABSTRACT

Many individuals with autism report generally low Quality of Life (QoL). Identifying predictors for pathways underlying this outcome is an urgent priority. We aim to examine multivariate patterns that predict later subjective and objective QoL in autistic individuals. Autistic characteristics, comorbid complaints, aspects of daily functioning and demographics were assessed online in a two-year longitudinal study with 598 autistic adults aged 17-83. Regression trees were fitted to baseline data to identify factors that could predict QoL at follow-up. We found that sleep problems are an important predictor of later subjective QoL, while the subjective experience of a person's societal contribution is important when it comes to predicting the level of daily activities. Sleep problems are the most important predictor of QoL in autistic adults and may offer an important treatment target for improving QoL. Our results additionally suggest that social satisfaction can buffer this association.

6.2 INTRODUCTION

Low Quality of Life (QoL) is a primary problem in autistic adults (Van Heijst & Geurts, 2015, Ayres et al., 2017) and improving scientific insight into this phenomenon is urgent. Our current understanding of longitudinal trajectories of QoL in autistic adults, however, remains limited (Drmic et al., 2018). This is the case for at least two reasons.

The first concerns the lack of good data. Although the past decade has featured intensive investigation into the identification of characteristics involved in outcomes of autistic adults, reported findings are variable and sometimes even contradictory (e.g., Moss et al., 2017; Van Heijst & Geurts, 2015). Additionally, existing studies were mostly cross-sectional in nature (but see Moss et al., 2017 and Woodman et al., 2015) and focused on the relationship between specific characteristics and 'objective' QoL (e.g., independent living or the level of employment) instead of subjective QoL, i.e. the subjective evaluation of one's QoL. This focus risks neglecting the lived experience of autistic adults as an equally important source of information. Thus,

---

currently available data omit important aspects of QoL or lack longitudinal information necessary to identify predictors of QoL. The autism research community has therefore advocated the collection of large-scale longitudinal data on this population (see e.g., goals of the EU-AIMS Longitudinal European Autism Project) to illuminate the relationship between behavioral measures, demographics, and later QoL in autistic adults.

A second problematic issue is that impaired QoL, as observed in autistic adults (Moss et al., 2017), exhibits a highly complicated and heterogeneous causal background: a host of cognitive, social, environmental, biological, and health-related variables likely contribute to lower QoL, and do so in multiple time-dependent patterns of reciprocal interactions. Given this highly complex etiology, identifying predictors for pathways underlying QoL in the autism population requires the use of advanced multivariate statistical methodology that so far has not been employed.

The current study meets the above problems by applying a data-driven approach to uncovering subtypes in multivariate patterns associated with longitudinal changes in QoL. The analysis is executed on unique longitudinal data from the Netherlands Autism Register (NAR). The NAR is a register that contains repeated assessments of behavioral traits, life events, and health history of a comparatively large sample of autistic individuals. Using a data-driven methodology in this cohort, which covers the entire adult lifespan (17-83 years), we investigate whether we can identify characteristics that predict later QoL in autistic adults from patterns in autistic characteristics, comorbid complaints, aspects of daily functioning and demographics.

6.3   METHODS

6.3.1   *Sample Descriptives*

Participants were volunteers of the Netherlands Autism Register (NAR, www.nederlandsautismeregister.nl/english/) which is a large longitudinal database that collects information from over 2000 autistic individuals with an autism spectrum disorder (ASD) diagnosis of DSM-IV or DSM-5 on a broad range of health history, life events, and psychological traits (Begeer et al., 2013; Burke et al., 2015; see also Chapter 2). Participants are invited to complete a battery of questionnaires on an annual basis. In the present study, we included N=598 participants for the analysis with subjective QoL as an outcome variable and N= 544 for the analysis with objective QoL as an outcome variable. These sample sizes differ because the statistical analyses we chose do not allow for missing values in the outcome variable. All participants completed at least two waves of the NAR assessment

themselves (i.e., instead of a proxy) and reported an ASD diagnosis. Analyses in the present manuscript used data from two waves of data collection spanning two years (2015-2017) and focuses on multiple potential predictors. The sample included twice as many participants as comparable studies with similar analyses (e.g., Lever et al., 2015).

6.3.2 *Measures*

We selected a set of potential predictors covering autism-specific characteristics, comorbid problems, aspects of daily functioning, and demographics. For the analysis, we selected only those twenty-five predictors with less than 40% missing values. As we aimed to cover as many behavioral facets of autism as possible we chose to include all standardized questionnaires in the NAR study. First, we included the five subscales of the Autism Quotient (Baron-Cohen et al., 2001), assessing communication, social skills, imagination, attention to detail, and attention switching. Second, we included the five subscales of the Sensory Perception Quotient (Tavassoli et al., 2014), i.e. vision, hearing, touch, smell, and taste. Third, we added the seven items of the Insomnia Severity Index (Bastien et al., 2001), i.e. severity of sleep-onset and sleep-maintenance difficulties, satisfaction with current sleep pattern, interference with daily functioning, noticeability of impairment attributed to the sleep problem, and the degree of distress caused by the sleep problem. Participants were asked to rate these items on a 5-point Likert scale: (1) not at all, (2) a little, (3) somewhat, (4) much (5) very much. All three questionnaires have been assessed within the 2015 wave of the NAR study, here referred to as T0. We furthermore selected a set of 8 single items to cover a wide range of domains related to QoL (Mason et al., 2018; see also Chapter 2), such as comorbid mental and physical diagnoses, subjectively perceived societal contribution, educational context, living situation, satisfaction with social contacts, and age. These domains were all separately assessed within the 2016 wave of the NAR study, here referred to as T1. Subjective QoL was measured with an item assessing how satisfied participants were with their own life (Begeer et al., 2017; Bartels & Boomsma, 2009). This item was answered on a 5-point Likert scale: (1) always or almost always happy, (2) more happy than unhappy, (3) equally happy and unhappy, (4) more unhappy than happy or (5) always or almost always unhappy. We selected an item assessing level of daily activities as an operationalization of objective QoL based on a 4-point scale: (1) unemployed, (2) supported daily activities, (3) unpaid daily activities, and (4) paid daily activities. Data on these items were available at multiple time points. To use the longitudinal information about autistic adults, we ran the analyses with assessments of these outcome variables at a later wave (i.e. 2017, here referred to as T2). In other words, we investigated whether characteristics at T0 and

T1 predict someone's response value to (i) satisfaction with one's life at T2 or (ii) level of daily activities at T2.

6.3.3 *Statistical Analyses*

To investigate whether we could predict inter-individual differences in QoL at a later measurement occasion, we used regression trees (Strobl et al., 2009). Classification and regression trees (CART) have been proposed as a data-analytic tool for (theory-guided) exploration of empirical data. Partitioning of the covariate space (of all predictor variables) is used to generate a final set of predictor variables and cut-off values within those predictors to derive non-overlapping groups of subjects with similar values of a selected response variable. Group membership can then be determined by running through the hierarchy of decision nodes, which are defined as those predictors that best explain heterogeneity in the cohort. This is based on a so-called greedy approach, which means that the best split is made at each step, rather than taking future steps into account. Each split in the regression tree is based on the idea of impurity reduction, selecting the exact cut-off value in the parent node that maximizes the isolation of subjects with different response patterns in the two daughter nodes.

We set stopping criteria in estimating a regression relationship between every two variables based on multiplicity adjusted (Bonferroni) p-values and required $p < 0.001$ for a split to be implemented. Regression Tree Analyses were performed using the R (version 3.4.0) package *party* (Hothorn et al., 2006). Please note that the regression tree algorithm used here employs p-values to select predictors, rather than either initially selecting many predictor variables and pruning the tree later, or tweaking a variable selection parameter using cross-validation. We did perform an additional check with the exact same predictors using a random forest algorithm to estimate the stability of the regression tree solution with the R-package *randomForest* (Liaw & Wiener, 2002). Random forests are sets of independently grown regression trees, where each tree is weighted in order to calculate each predictor's importance.

6.4 RESULTS

6.4.1 *Subjective Quality of Life*

Exploratory regression tree analyses yielded four subgroups, with distinct patterns of values on the predictor and outcome variables. The first subgroup is generally happy (subgroup 1, N=225, 38%). Two subgroups are generally neither happy nor unhappy (subgroups 2 and 3, N= 39 and 246, 6% and 41% respectively). The last subgroup is generally unhappy (subgroup 4, N=88, 15%). The first split shows

that having sleep problems that interfere with daily functioning is the most important predictor for different response values on subjective QoL over time. In other words, sleep problems separate a subgroups of participants who were generally unhappy to neither happy nor unhappy from those that were neither happy nor unhappy to generally happy[1]. The decision nodes are the degree to which your sleep problems interfere with your daily functioning, the number of comorbid (psychological) diagnoses and social satisfaction. The stability of these decision nodes was underlined by the results of the random forest algorithm: All three variables ranked among the four most important predictors (with the addition of the degree to which you worry about your sleep problems).

Specifically, the first split divided the sample into two daughter nodes based on whether they felt their sleep problems were either not at all/a little/somewhat interfering (≤ 2) or much/very much interfering (>2). For the severe interference group, a second split was based on whether they reported to be satisfied/neutral (≤ 2) or unsatisfied about their social contacts (>2). Among those who experienced mild or no interference through their sleep problems a second split was made based on whether they reported no or at least one comorbid psychopathological condition. In summary, we found four groups: (1) a subgroup of generally unhappy participants with sleep problems and low social satisfaction, (2) a subgroup of generally happy participants without sleep problems and comorbid disorders and two subgroups of generally neither happy nor unhappy participants who (3) either report sleep problems, but are socially satisfied, or (4) do not report sleep problems, but do report comorbid disorders. Table 6.1 depicts general descriptives for the whole sample.

6.4.2 *Objective Quality of Life*

Exploratory regression tree analyses yielded a tree with two decision nodes (see Figure 6.2), resulting in three terminal nodes representing three response values: a subgroup of participants who do work but in an unpaid employment setting, e.g. as an intern or volunteer (N=196), a subgroup of participants who work in a paid employment setting (N=336) and a smaller subgroup of participants who work in a, so called, workhome[2] setting (N=10). The first decision node (i.e., first split) shows that an individual's subjectively perceived societal contribution is the most important predictor for different response values on their level of daily activities one year later. The number of psychological comorbidities is the second decision node. The random forest

---

1 To improve the interpretation of the reported results we discussed the selection of predictors and all findings with help of a feedback panel consisting of autistic adults and professionals working with people in autism.

2 In the Netherlands, 'workhome' refers to a supported living environment that also incorporates a supported work environment.

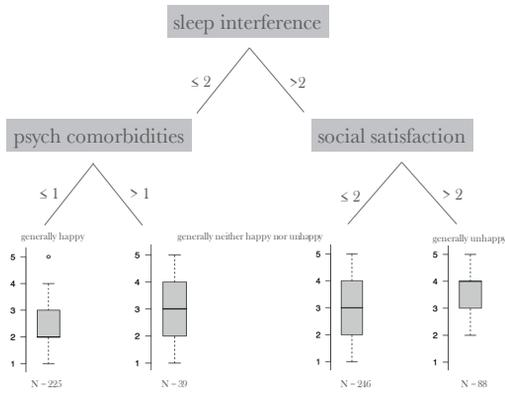Figure 6.1: Regression tree based on the NAR sample, grown with a requirement of p< 0.001 for a split to be implemented. The response node in this tree is the five-point scale of the satisfaction with one's life item at a later assessment wave of the NAR study. The p-values stem from binary association tests for variable and cut-off value selection. A low p-value equals high impurity reduction.

Table 6.1: Descriptives for all autistic adults in the NAR cohort participating at T0, T1 and
T2.

Variable	Descriptives	Subjective QoL (N=598)	Objective QoL (N=544)
Age in years	Mean / SD / range	42.8 / 15.5 / 17-83	44.2 / 14.5 / 17-82
Gender	Male / female	310 / 288	270 / 274
Employment	% Unemployed / % supported / % unpaid / % paid	20% / 11% / 27% / 41%	17% / 13% / 30% / 40%
AQ	Mean / SD / range	82.6 / 11.7 / 50-110	82.5 / 11.9 / 50 -110
SPQ	Mean / SD / range	44.4 / 15.4 / 3-93	44.3 / 15.5 / 3-93
ISI	Mean / SD / range	9.2 / 5.9 / 0-24	9.2 / 5.9 / 0-24

Note. QoL = Quality of Life; AQ = Autism Quotient; SPQ = Sensory Perception Quotient; ISI
= Insomnia Severity Index.

algorithm, too, ranked these variables as most important predictors
for an individual's level of daily activities.

Specifically, the first split separated the autistic adults in two sub-
groups: those that have the feeling they are unsuccessful in their con-
tribution to society (≤ 5) or those that feel successful in their societal
contribution (>5). Among those that evaluated themselves as success-
ful in their societal contribution, the regression tree analyses resulted
in a second split based on whether they reported three or less than
three comorbid psychological diagnoses or more than three comorbid
diagnoses.

6.5 DISCUSSION

This study shows that experiencing sleep problems is associated with
lower later subjective QoL, while the feeling that one cannot con-
tribute to society and reporting psychological comorbidities predict a
lower level of daily activities one year later.

The finding that sleep problems are highly predictive of subjective
QoL resonates with the fact that the role of sleep in autism has be-
come a subject of recent attention in the scientific literature. Between
44 and 86 percent of children with autism have difficulty falling or
staying asleep (Maxwell-Horn & Malow, 2017; Richdale & Schreck,
2009), which makes sleep problems one of the most urgent concerns
in daily life with autism. The current study underscores the impor-
tance of these problems as determinants of future QoL. Simultane-
ously, our results regarding 'objective' QoL highlight the importance
of establishing an individualized context where autistic adults feel
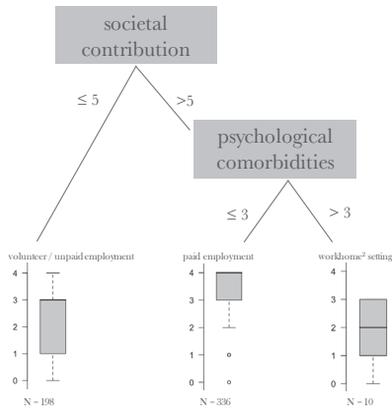
Figure 6.2: Regression tree based on the NAR sample, grown with a requirement of p< 0.001 for a split to be implemented. The response node in this tree is the five-point scale of level of daily activities at a later assessment wave of the NAR study. The p-values stem from binary association tests for variable and cut-off value selection. A low p-value equals high impurity reduction.

they can contribute to society. Earlier research has pointed in a similar direction: creating a professional context focusing on strengths and interests of autistic individuals boosts self-esteem and social engagement (Diener et al., 2015; Lee & Carter, 2012) which, in turn, might help individuals to reach their full potential in meaningful work.

A second important finding in our study contrasts with what one might expect: the severity of autistic symptoms was not selected in the predictive model for QoL. Thus, although it is often hypothesized in the literature that the severity of autistic symptoms predicts later outcome, autism-specific characteristic did not appear to be a strong predictor for future QoL in this autistic sample. Further studies are necessary to replicate this conclusion which, if correct, is of considerable importance.

Third, we found that 38% reported that they are generally happy and 15% of the participants actually reported that they are generally unhappy, which seems in contrast with the starting premise of this study that the majority of autistic adults reports a low QoL. However, previous studies have reported similar observations suggesting that measures focusing on subjective QoL instead of objective outcome measures do not show a substantial difference in self-reported QoL for autistic individuals compared to the general population (Moss et al., 2017; Hong et al. 2016).

The clinical utility of multivariate analyses in outcome ultimately rests on their value in helping guide intervention decisions. Since our data-driven approach yields groups of individuals that share their experience of subjective QoL or their objective QoL, it might offer one way forward for considering new targets with the aim to improve the QoL of autistic adults. In addition, although our findings are correlational, sleep problems may in fact be causally associated with autism symptoms, rendering possibilities for causal intervention. A recent study suggested a relationship between parent-reported reduced amounts of sleep and increased severity of the classic difficulties associated with autism (social/communication impairment and repetitive behaviors), maladaptive behaviors and other psychiatric comorbidities in children with autism (Veatch et al., 2017). The directionality of this relation is still to be determined and would require large, well-controlled studies that investigate subsets of autistic participants based on their sleep issues. The results of our study, however, suggest that intervening on the daily consequences of sleep problems and getting back on a regular sleeping schedule might improve quality of life for autistic individuals. In addition, our finding that psychological comorbidities matter for the quality of life in autistic adults is in line with current care guidelines highlighting that we should treat symptoms of comorbid conditions rather than autism characteristics.

6.5.1 *Limitations*

One limitation of our study is that we were constrained to a specific set of symptom data and environmental factors for determination of multivariate pathways. For example, the wide range of scores regarding QoL in some subgroups suggests that there might be other predictors which could result in another informative subgroup split. Moreover, recent studies have highlighted the importance of validating existing measures for outcome in the autism population (McConachie et al., 2018; Ayres et al., 2017; Cottenceau et al., 2012) so that we can make sure study results inform us on appropriate targets. Future research should replicate these findings in an independent sample, expanding the sample size and input features to establish a valid and clinically viable taxonomy for QoL in autism.

A second limitation might be that often individuals have a long-term level of happiness to which they always spontaneously return after life events of either valence (Diener & Diener, 1996). This has implications for the assessment of change in happiness-related measures in any population. In order to test detailed temporal dynamics one would need a large number of time-points with shorter time intervals. Future research on QoL in autistic adults could explore what impact the identified factors have on the short-term dynamics of QoL with e.g., experience sampling data. Nonetheless, our results provide first insights that can guide future research on predictors of subjective and objective QoL.

In conclusion, this study illustrates how regression tree analyses can be utilized to inform us on what factors should be targeted when aiming to increase QoL in autistic individuals. Our results specifically highlight the importance of sleep problems for subjective QoL, the presence of comorbid diagnoses, and the feeling that one can contribute to society for objective QoL. Using the identified paths, we can further investigate whether targeting malleable factors, such as sleep quality, can indeed improve the lifespan QoL of autistic adults.

LONGITUDINAL DYNAMICS IN ATYPICAL DEVELOPMENT: MUTUALISTIC COUPLING IN AUTISM?

7.1 ABSTRACT

Autism is a behaviorally-defined neurodevelopmental condition based on diagnostic criteria such as social and communication difficulties and restrictive and repetitive behavior. Currently, the field is moving away from the theoretical stance that these behaviors have a common cause, yet little is known about the dynamic processes that drive the co-development of these characteristics. Using a longitudinal design, the aim of the study presented here was to model the parallel growth of social and non-social autism-related behaviors in a cohort of infants at-risk for atypical development. Receptive language and fine motor skills were assessed on four measurement occasions in a group of 239 infants (122 girls and 117 boys, aged 6-36 months). Latent growth curve analyses were applied to investigate the cross-domain coupling of longitudinal changes in these domains. Our results suggested that improvement in language goes hand-in-hand with improvement in motor skills, and vice versa. We did not, however, find compelling evidence for mutualistic coupling between these skills. Group differences were observed in the variance of baseline levels of both language and motor skills, such that the at-risk rates of change suggest the possibility of further latent heterogeneity. Our results also suggest that those children who go on to receive a diagnosis of atypical development at age three are not specifically characterized by increased or decreased coupling between language and motor skills.

7.2 INTRODUCTION

What captures our attention automatically and what we choose to attend to influences the way we experience and perceive the world around us. This, in turn, impacts the course of brain and behavioral development. For example, young children suffering from language impairments may also show atypical behavior in other domains, such as impoverished social skills due to reciprocal adverse effects of language limitations. Whereas traditional approaches often consider development as simple, linear systems, a complex systems

approach might be better suited for capturing developmental phenomena such as equilibration (Piaget, 1978; e.g., refining mental structures), self-organization (Köhler, 1940; Lorber et al., 2014; in the domain of learning) or emergence (Anderson, 2008; Van der Maas, 2006; in the domain of higher-order phenomena such as intelligence). The complex systems toolbox aims to capture the interaction between genetic, physiological, and social modes of functioning that might contribute to typical or atypical brain and behavioral development. In the current study, we investigate behavioral cross-domain coupling in infants at risk for atypical development. 'Coupling' is a term commonly used on longitudinal SEM models (e.g. McArdle & Hamagami) and captures the extent to which growth in one domain or variable is governed by the starting point in another.

In the last decade, a growing body of developmental literature is examining developmental changes from this perspective, attempting to capture the complex interrelations of developmental processes (Johnson, 2017; Kievit et al., 2017; Van der Maas, 2017). For example, atypically high performance in one domain, such as the savant abilities associated with some autistic phenotypes (e.g., heightened perception of detail or hyperlexia), may dampen the rate of development in motor domains (resulting in e.g., motor stereotypies; Ploeger, 2009). This is an example of negative coupling. A promising avenue to pursue from this perspective is the idea that observed heterogeneity in autism is a result of small differences amplifying to produce large differences in emergent phenotypes, similar to the heterogeneity we observe in typically developing individuals (Oliver et al., 2008). This interpretation is analogous to the mutualism model (Van der Maas et al., 2006), which proposes a network of multiple interacting and mutually reinforcing factors contributing to development of cognitive abilities. Notably, simulations demonstrate how small dynamic effects in these mutualistic causal pathways can amplify over time, and lead to developmental discontinuities.

One of the first empirical investigations of such mutualism has looked at the co-development of fluid reasoning and vocabulary (Kievit et al., 2017). The authors found strong support for the idea that variation in these cognitive domains arises through their mutual coupling. Individuals with higher initial scores in vocabulary show greater gains on matrix reasoning over time and vice versa (Kievit et al., 2017, with a recent replication demonstrating even stronger effects in younger children). A similar approach to the developmental interrelation between vocabulary knowledge and reading comprehension has shown one-way coupling, i.e., vocabulary knowledge acts as a driving force for an individuals gains in reading comprehension, but not vice versa (Quinn et al., 2015).

These examples suggest that the mutualism model might offer a fruitful empirical framework to investigate the longitudinal dynamics

of co-developing developmental domains. Its application to the study of *atypical* development, however, is scarce in the literature. One study suggested that the developmental *un*-coupling of cognition and reading might be the source of learning disability in the case of dyslexic readers (Ferrer et al., 2010). Typical readers showed bidirectional coupling, i.e. higher IQ predicted greater gains in reading comprehension, and vice versa. In dyslexic readers, mutualistic coupling was much smaller, suggesting that the general cognitive skills of readers with dyslexia did not increase as quickly with greater reading, nor did their reading ability benefit from general cognitive developments to the same extent as typical controls. This finding and simulation work (e.g. van der Maas et al., 2006) demonstrates that profound differences in phenotypes may arise purely from disruptions to the dynamic system, rather than deficits within a narrow domain. Given the magnitude of these effects, it may be plausible that other conditions characterized by atypical development, such as autism, may also be characterized by disrupted dynamic interactions between developmental domains. To the best of our knowledge however, such approaches have not yet been implemented in the realm of autism.

Autism is a behaviorally defined condition based on impaired social communication skills and stereotypies in motor and repetitive interests (APA, 2013). The coupled development of these domains has often been shown in typically developing children (Iverson, 2010; Leonard & Hill, 2014) and empirical evidence highlights the predictive association between impairments in infant motor functioning and autism-related impairments at a later stage (Bedford et al., 2016; Leonard et al., 2014; Brian et al., 2008). Although this attests to a growing interest in the longitudinal co-development of autism-related impairments, to the best of our knowledge no study has yet directly investigated this account of development in children with a higher risk for atypical development. In the current study, our aim was to investigate how the co-development of social and non-social characteristics can inform us on dynamic processes that drive atypical development. In the long run, such informed longitudinal models could enable us to detect developmental challenges in an early stage and intervene, when deemed appropriate, before they self-reinforce over time. First, we use latent growth models (Bauer, 2007) to model changes in language and motor skills and their interaction across four assessment waves in at-risk children between 8 and 36 months of age. We also applied multigroup growth curve model to investigate whether those infants that develop atypically differ in their rate of change and co-development of these skills from those that do not.

7.3   METHODS

7.3.1   *Sample Descriptives*

Participants were infants taking part in the British Autism Study of Infant Siblings (BASIS, `www.basisnetwork.org`), an ongoing longitudinal research program with infants 'at-risk' for atypical development. These infants all had brothers or sisters with an autism diagnosis. For further details of recruitment and sample characteristics, please see Elsabbagh et al. (2013). Ethical approval for this specific study was obtained from the Ethics Review Board of the Faculty of Social and Behavioral Sciences, University of Amsterdam (2017-BC-8386). As part of the BASIS study, two hundred and fifty infants completed a battery of assessments at 8, 14, 24, and 36 months of age. We included all 239 participants (117 boys, 122 girls) who completed at least three assessments of the Mullen Scales of Early Learning (MSEL; Mullen, 1995) and the Autism Diagnostic Observation Schedule - Generic (ADOS-G; Lord et al., 2000) and whose diagnostic outcome had been assigned at 36 months. A group of expert clinical researchers reviewed all information gathered about an infant at the 24 and 36 months assessment (including MSEL, ADOS, and Vineland Adaptive Behavior Scales (VABS; Sparrow et al., 2005)). These experts then decided on the best estimate diagnosis according to DSM-5 critera (APA, 2013) and ICD-10 criteria (WHO, 1993). Based on these diagnostic classifications, the sample was split into two subgroups: 74 atypically developing infants and 165 typically developing infants. At 6 months the infants eventually classified as atypically developing scored 10.18 (SD=5.24) on the Autism Observation Scale for Infants (AOSI) on average, compared to a mean of 7.51 (SD=4.36) for those who develop typically (t(118.23)=-3.80, p<0.001). . At 36 months the atypical group had an average score of 9.2 (SD=5.18) on the ADOS while the typical group scored 3.86 (SD=3.31;t(97.33)=-8.09, p<0.001). Please see Bussu et al. (2018) for more details on classification and sample descriptives. Note that those infants classified as atypically developing did not necessarily all meet criteria for an autism diagnosis.

7.3.2   *Measures*

We focused on two subscales of the Mullen Scales of Early Learning (MSEL), a widely used and well-validated measure of cognitive functioning for children with developmental disabilities (Mullen, 1995). The MSEL is a standardized test for testing receptive and expressive language, visual reception, and gross and fine motor skills for the age range of 0 to 68 months. The assessment is conducted in the presence of the infant's parent. We selected two subscales representing a social and a non-social developmental domain, i.e. the receptive language

subscale and the fine motor subscale. The fine motor subscale spans 33 items assessing skills ranging from evidence of reflexes to drawing a triangle. The receptive language subscale has 33 items assessing skills ranging from comprehension, memory, and reflexes to noise. Four clinical researchers reviewed all information gathered at 24 and 36 months to determine diagnostic outcome (typical or atypically developing; see Gammer et al., 2015 for more details).

7.3.3 *Modeling framework*

The trajectories of the MSEL domains were then modelled using various latent growth curve models (LGM). Models were estimated using the R-package *lavaan* version 0.6-1 (Rosseel, 2012) in R version 3.4.0 ("You Stupid Darkness"). In our models, we freely estimate the slope factor loadings were freely estimated for timepoint 2 (14 months) and timepoint 3 (24 months) for both language and motor. This implementation, known as 'latent-basis' coefficients, is preferred here since a) we had no a priori hypotheses about the rate of change in these domains and b) we think it unlikely development will be purely linear. We use robust maximum likelihood estimator with a (Huan-Bentler) scaled test-statistic and robust (Huber-White) standard errors to account for deviations from multivariate normality. In this second step, we fit a multigroup growth curve model to test for group differences in individual parameters of the model. We used the full information maximum likelihood estimator (FIML) to account for missingness. To assess model fit we inspected the Comparative Fit Index (CFI), the Root Mean Square Error of Approximation (RMSEA) and the Standardized Root Mean Squared Residuals (SRMR). These indices are usually interpreted as follows (Hu & Bentler, 1999): CFI (acceptable 0.95-0.97, good > 0.97), RMSEA (acceptable < 0.08, good < 0.05), SRMR (acceptable 0.05 - 0.10, good < 0.05).

7.4 RESULTS

Figure 7.1 shows the domain-specific trajectories for the complete sample (N= 239) on the Fine Motor subscale of the MSEL (left) and the Receptive language subscale (right).
Receptive Language and Fine Motor latent growth curve model.
   Since we were interested in potential dynamic relations between the co-development of language and motor skills, we model their growth trajectories simultaneously. First, in order to analyze the mean growth trajectories of these domains, we fit a parallel process model (see Figure 7.2) to the full sample. This model regresses the slope of one domain on the intercept of the other domain ? Coupling would suggest that higher intercepts in one domain are associated with greater gains in another. This latent growth curve approach often
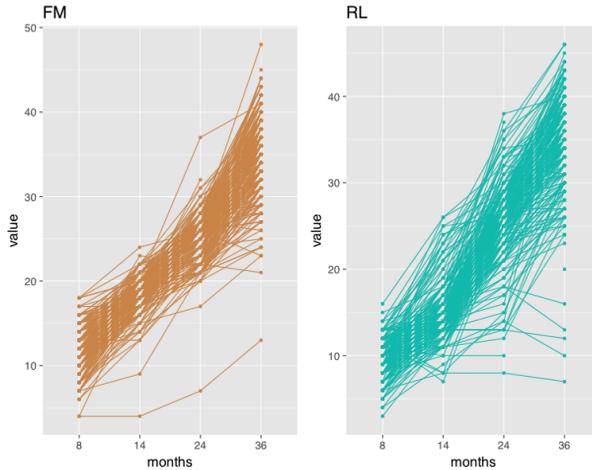
Figure 7.1: Trajectories for Receptive Language (RL) and Fine Motor (FM) development (Mullen Scale of Early Learning) over four assessments at (on average) 8, 14, 24, 36 months of age in 239 children at risk for atypical development.

yields more reliable convergence than similar models such as the dual change score model (McArdle, 2009; Kievit et al., 2018) and as such as more suitable for modeling an atypical sample with a moderate sample size (note that the BLCS, BDCS and PPM can be expanded and restricted to yield equivalent model specifications, but for the purpose of simplicity we will consider them as distinct in their canonical form). Notably, this parallel process model can capture similar coupling effects as the latent change score model This model showed acceptable fit: $X^2(16)=37.66$, p = 0.002; CFI = 0.966; RMSEA = 0.074; SRMR=0.068.

There was significant variation in the intercepts of language and motor skills, indicating individual differences in baseline levels of these developmental domains at timepoint 1 (6 months on average). There was significant growth in both language and motor skills as well as significant variation in the growth trajectories of these domains, as indicated by the slope statistics (Table 7.1). The positive (significant) correlation between the two slope parameters (Table 7.1) suggests that more growth in one domain was associated with more growth in the other, suggesting co-development of the distinct domains. However, contrary to our hypothesis, we did not find significant cross-domain coupling between intercepts and slopes of language and motor skills. This indicates that, in the current sample,
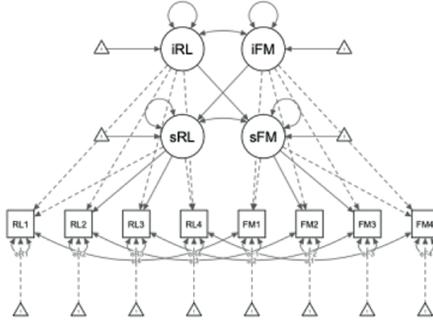
Figure 7.2: Parallel process model for receptive language (RL) and fine mo-
tor (FM) with freely estimated slope factor loadings at 14 and
24 months, error variances and structured residuals. Latent vari-
ables such as the intercepts (i) and slopes (s) are shown as circles,
and observed variables are represented by rectangles (with num-
bers 1-4 referring to the respective measurement occasion).

there is no significant driving effect of one of these domains on the
development of the other over time.

Multigroup growth curve model.

In a second step, we tested for differences and similarities between
children that develop atypically (N=73) and those that develop typi-
cally (N=165) by testing multigroup LGMs. In these model compar-
isons, we tested for group differences in specific parameters while
constraining all other parameters in the model to be equal across
the two groups. We start out with a model in which all parame-
ters are equality constrained. If this is an adequate approximation,
model comparison will prefer such a simpler model. If the model
does not seem to have adequate fit, we can subsequently free specific
parameters to examine whether estimating them independently for
both groups leads to an improvement in fit greater than expected by
chance in which case we can assume that the two groups differ on
the relevant parameter of interest. Our first multigroup model with
equality constraints on the intercept, slope and structured residual
parameters across groups did not fit the data well, see Table 7.2 for
the different models we subsequently tested based on the CFI.

Table 7.1: Group level parameters (intercept [i] and slope [s]) for the paral-
lel process model with Receptive Language (RL) and Fine Motor
(FM).

Parameters	Estimate	p
iRL	9.688	<0.0001
sRL	24.737	<0.0001
iFM	11.995	<0.0001
sFM	22.689	<0.0001
Covariances	Standardized	p
sRL~~sFM	0.963	<0.0001
iRL~~iFM	0.763	<0.01
Regressions	Standardized	p
sRL~~iFM	0.079	0.648
sFM~~iRL	-0.127	0.445

Parameters	df	X^2	p	AIC	BIC	RMSEA	CFI
All constrained	60	219.555	<0.001	9213.379	9310.602	0.149	0.693
Free intercepts and slopes	56	164.097	<0.001	9164.140	9275.253	0.127	0.792
+ free RL intercept var	55	153.853	<0.001	9159.511	9274.096	0.123	0.810
+ free FM intercept var	54	163.249	<0.001	9147.726	9265.783	0.130	0.790
+ free RL slope var	53	144.592	<0.001	9145.078	9266.608	0.121	0.824
+ free FM slope var	52	145.697	<0.001	9146.729	9271.731	0.123	0.820
+ free error vars	46	125.380	<0.001	9139.145	9284.980	0.120	0.847
+ free structured residuals	44	114.423	0.000	9138.422	9291.202	0.116	0.865

Note. df = degrees of freedom; AIC= Akaike Information Criterion; BIC=
Bayesian Information Criterion; RMSEA = Root Mean Square Error of Ap-
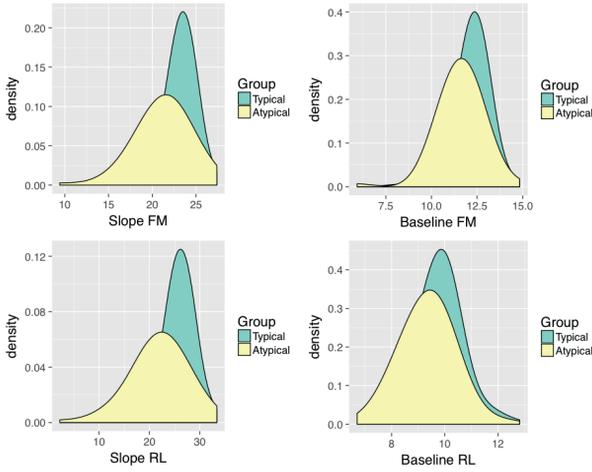proximation; CFI = Confirmatory Fit Index.

Figure 7.3: Group differences in model parameters for receptive language (RL) and fine motor (FM) for those children who develop typically versus those who develop atypically over time..

This suggests that the groups differ in both person-specific and time-specific components of change: they differed in their mean intercept at both FM and RL, their growth trajectories of FM and RL (see Figure 7.3) and their time-specific residuals of the observed repeated measures. The groups did not differ in the covariance of intercepts between both domains, or in the cross-domain covariance between FM and RL, i.e. the intercept of FM and the slope parameter of RL, and vice versa. We did not find evidence for differences in cross-domain coupling that drive group differences. We did, however, find group differences in the intercept and slope variance in both domains: the atypically developing group display a much wider range of starting values *and* growth rates for both RL and FM (see Figure 7.3). This finding, combined with very strong correlations between the slopes, suggests that dynamic processes amplify small differences between individuals at 6 months result into (very) large individual differences in autism symptomatology at 36 months.

7.5 DISCUSSION

We examined parallel longitudinal changes in language and motor skills in children at-risk for atypical development. The results indicated that development of both language and motor skills could be captured by a non-linear latent growth curve model, in which there was positive growth, but with considerable individual differences in

both starting point as well as the rate of development over time in both domains. Changes in language co-varied strongly with changes in motor skills. Contrary to our hypothesis, we did not find compelling evidence for mutualistic coupling between these skills: Children's current motor skills did not seem to affect the rate of change in language skills or vice versa. Infants who later receive a diagnosis of atypical development at age three were not specifically characterized by increased or decreased coupling between language and motor skills compared to their peers. We observed group differences, however, in the variance of both baseline levels and trajectories of language and motor skills - The group of infants developing atypically showed a much wider range of trajectories and starting values than the group of typically developing children.

These differences could be driven by differences in coupling strength: basic simulations with different coupling strength values have shown that higher values result in a larger variance of scores over time (`http://brandmaier.de/shiny/sample-apps/SimLCS_app/`). Our results suggest that the interplay between fine motor skills and language skills (as assessed by the MSEL) does not differ between infants that end up with or without developmental atypicalities. It might very well be that these specific behavioral features and their interplay at the assessed developmental stages do not provide good prognostic values for atypical development. Chawarska et al. (2014), for example, found that the combination of six behavioural features (i.e. repetitive behaviours, eye contact, intonation, gestures, giving objects and spontaneous pretend play) show high predictive accuracy (83%) for the identification of autism, but poor eye contact or limited gestures alone did not show good predictive value. Estes et al. (2015) have, furthermore, shown a pattern of atypicalities in the sensorimotor domain at 6 months which then shifts to the social-communication domain after 12 months of age, suggesting another temporal ordering of the interplay of these domains. Future work should investigate dynamic coupling in different sets of developmental domains affected in autism, and possibly of higher temporal resolution, to evaluate these dynamics in different domains and on different timescales.

7.5.1 *Limitations*

Several potential explanations for the absence of mutualistic coupling between language and motor skills in this cohort might be related to the constraints of the data. One of these constraints is related to the small number of children developing atypically, resulting in group comparisons with N=165 typically developing children versus only N=73 atypically developing children. It is also important to note that our results are inevitably dependent on the measures of language and motor skills that we used. The extent to which our measure is

sensitive to change defines the likelihood to find evidence for coupling between the two domains. Another constraint is related to the within-timepoint variance of infant age: the age range within assessments was 2 months on average. Given that cognitive development in these early years is quite rapid and highly individual, these age differences could obscure group-level effects in the current study. Landa et al (2012), for example, found four distinct developmental trajectories across multiple developmental domains, which could very well mean that it is essential to distinguish between these subgroups to investigate differences in mutualistic coupling. Similarly, it is conceivable that mutualistic coupling between these domains occurs earlier or later in development, resulting in other mechanisms, such as self-feedback, once (or before) a certain equilibrium of skills is reached. It has often been suggested, for example, that healthy development up until 6 months of age does not protect against atypical development, especially for infants with autism (Landa & Garett-Mayer, 2006; Ozonoff et al., 2010; Young et al., 2009). Future studies should further investigate these timeframes and their domain-specificity in autism. Exploring cross-domain coupling parameters across the life span is a fruitful framework to advance our understanding of (a)typical development. Potentially, differences between typically and atypically developing infants in the interplay of a set of developmental domains over time could be investigated by looking at group-specific network structures with network analytic tools (Borsboom & Cramer, 2013). As we advance our understanding of developmental patterns in autism, we can eventually work towards empirically grounded diagnostic algorithms (Landa et al., 2012). In addition, these advances might pave the way towards more formal (hierarchical) models connecting different levels of factors and mechanisms that drive atypical development and its consequences.