



## 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](#)

**Citation for published version (APA):**

Deserno, M. K. (2019). *Autism as a multicausal system*. [Thesis, fully internal, Universiteit van Amsterdam].

**General rights**

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

**Disclaimer/Complaints regulations**

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

## 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

---

o Deserno, M.K., Fuhrmann, D., Borsboom, D., Begeer, S., Geurts, H.M., Bedford, R. & Kievit, R.A. *Longitudinal dynamics in atypical development: Mutualistic coupling in autism?* In preparation.

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](http://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 criteria (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

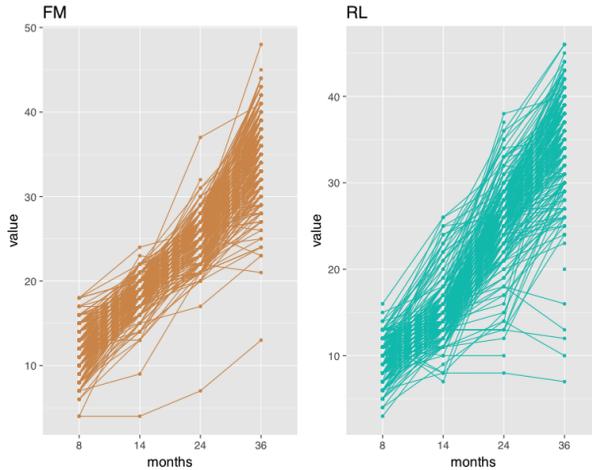


Figure 7.1: Trajectories for Receptive Language (RL) and Fine Motor (FM) development (Mullen Scale of Early Learning) over four assessments at (on average) 8, 14, 24, 36 months of age in 239 children at risk for atypical development.

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,

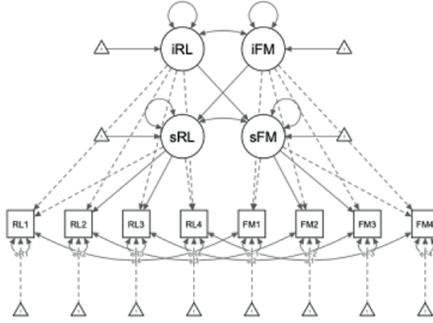


Figure 7.2: Parallel process model for receptive language (RL) and fine motor (FM) with freely estimated slope factor loadings at 14 and 24 months, error variances and structured residuals. Latent variables such as the intercepts (i) and slopes (s) are shown as circles, and observed variables are represented by rectangles (with numbers 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 typically ( $N=165$ ) by testing multigroup LGMs. In these model comparisons, 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 parameters 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 parallel 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 $\sim$ sFM | 0.963        | <0.0001 |
| iRL $\sim$ iFM | 0.763        | <0.01   |
| Regressions    | Standardized | p       |
| sRL $\sim$ iFM | 0.079        | 0.648   |
| sFM $\sim$ iRL | -0.127       | 0.445   |

| Parameters                  | df | X <sup>2</sup> | 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 Approximation; CFI = Confirmatory Fit Index.

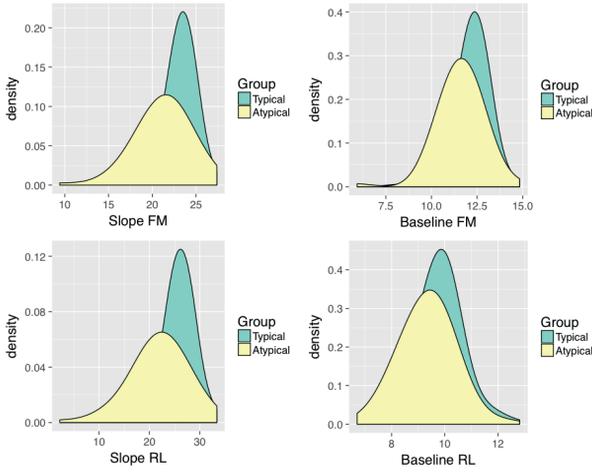


Figure 7.3: Group differences in model parameters for receptive language (RL) and fine motor (FM) for those children who develop typically versus those who develop atypically over time..

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/](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 & Garrett-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.