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Autism as a multicausal system

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SUMMARY AND GENERAL DISCUSSION

Looking at the literature concerned with psychometric models, the field of psychological science has been in transition for quite some time now. Inspired by theoretical developments away from reductionism alongside statistical and technical advances, a novel complexity-based paradigm has emerged and taken the field by storm. This thesis might be considered a first stepping stone towards the application of statistical translations of this complexity-based paradigm to the autism realm. More importantly, however, it might pave the way towards more formal models connecting different levels of factors and mechanisms that drive atypical development and its consequences.

8.1 THIS THESIS

This thesis project originates from the promise of tapping into understudied knowledge sources in the rapidly moving field of autism research. We were keen to explore the application of the network approach, both theoretically and methodologically, to the wealth of autism data collected in both clinical and research settings to find a new way of looking at the developmental outcome of the autistic population. More importantly, however, we put the network toolbox to novel use to combine and compare the knowledge and reports of autistic individuals with information provided by clinical experts. We studied the interrelationship within and between atypical development and well-being and found that there are unique relations that relate autism characteristics to each other and to aspects of well-being. More theoretically, we argued that considering atypical development as an adaptive response to a system of factors can advance our understanding of how these different atypical profiles arise and how they, in turn, impact quality of life (QoL) throughout the lifespan. Similarly, advances in modelling development enable us to ask a novel set of questions concerned with how atypical cognitive characteristics might interact over time. Statistical models always imply a set of assumptions about the origin and relationships among the variables under investigation. Certain kinds of information, such as the interaction between domains in atypical development, can be entirely obscured when choosing a different model. This thesis, therefore, illustrates what novel insights can be gained from studying atypical development as a phenomenon that arises from interactions among observable processes.

We outlined several data-driven analytic approaches to various levels of atypical development and outcome. Our results provoke more fine-grained hypotheses about the importance of specific tributaries within the multivariate system of autism. In the first two chapters of this thesis, for example, we have provided a detailed mapping of the multivariate system of factors contributing to how happy autistic adults are. The resulting structures highlight the importance of opportunities to build and maintain social contact, in whatever context and frequency. We found that insistence on sameness is the aspect of autistic behaviors that often complicates social contact and has a strong impact on the QoL of autistic individuals. We have explored this output regarding its congruence with expert ratings and its longitudinal workings. We found that the influence of social satisfaction on QoL remains over time, but our results suggested that whether or not individuals reported sleep problems plays a more important role when it comes to later QoL. I would like to use the concluding chapter of this thesis to discuss several implications and potential research avenues that follow from our work.

Essentially, we are still wondering about a very fundamental question: what is atypical development and what is the best way to conceptualize and study it? The level of heterogeneity and complexity in individuals' developmental trajectories is so prominent that researchers and clinicians doubt whether common labels can provide much predictive utility for trajectories of atypically developing individuals. In the case of autism, there is accumulating empirical support for viewing autistic characteristics as separable since they often occur in isolation in family members and the general population (Happé & Ronald, 2008; Ronald et al. 2006a; Piven et al. 1997; Pickles et al. 2000). An attempt to explain the isolated occurrence of autism-related behaviors is the fractionation theory of Happé and colleagues (Happé et al. 2006; Happé & Ronald, 2008; Brunsdon & Happé, 2014). This account proposes that autistic impairments are relatively unrelated and caused by different cognitive problems (Happé & Ronald, 2008). Following this theoretical account, Brunsdon and Happé (2014) predict that the (atypical) development of social (communication) and nonsocial features (repetitive behaviors and interests) should be seen as relatively independent (see their report for a detailed review of the empirical evidence in line and opposing this stance). In the networks reported in this thesis, we find unique connections between these characteristics, suggesting that they are not completely independent, but mutually reinforcing (see Chapter 3 and 5). Out of curiosity and in the process of writing this discussion, we translated these opposing theoretical stances into simple testable SEM-models, using assessments of communicative deficits, social impairments and repetitive behaviors in children at-risk for atypical development based on the Vineland Adaptive Behavior Scales (Sparrow et al., 1984). We speci-

fied the three domains as either correlated (model 1) or uncorrelated (model 2) indicators of ADOS-scores and compared these models for the data reported on in Chapter 7. Our results showed that a model with social and non-social features as correlated indicators showed significantly better fit than the one with uncorrelated indicators. This simple analysis highlights what the work incorporated in this thesis has attempted to show: atypical development and its consequences are best characterized as a multivariate complex system that reveals not only symptom-environment but also symptom-symptom interactions. We do not find fractionation in autistic features and its consequences, but correlated characteristics that potentially influence each other. These results pave the way for several future investigations.

8.2 THE ROAD AHEAD

The network focus of this thesis has proven to be a fruitful framework to shed light on the way in which these characteristics are correlated within the atypical well-being system as well as the system of autistic characteristics itself. Having established that these systems can best be characterised as multivariate and defined by the interrelations of individual factors within the system, I would argue that a focus on small interactions between different network features can inform us on what drives specific developmental trajectories. For now, we have looked at within-level (behavior being one level) interactions between behavioral aspects of atypical development in Chapter 7. It should be noted, however, that in our choice regarding the inclusion of factors we were limited by the available information within existing data. Although we have aimed to cover the most important components of autism and QoL, the resulting networks, undoubtedly, do not delineate a complete picture of all relevant factors. Improving the framework to become informative across all other levels of influence, such as genetic influences or neural antecedents, comes with a novel set of challenges: What could be considered the exhaustive multivariate system of tributaries to atypical development, i.e. where does it 'end'? And, what are the mechanisms connecting different levels that contribute to an atypical phenotype? Up until now, the network approach does not provide clear answers to these questions. Taken together, however, there are some promising future roads connecting these questions with the strengths of the presented paradigm for autism research.

8.2.1 *Levels of organization*

Both network theory and its accompanying analytical tools are indispensable for future advances in the study of complex psychological systems. No theory of a single risk factor for atypical development

can turn a blind eye to the system level effects of its interrelations. As shown in Chapter 3 and in Letina et al. (under review), there are multiple network metrics, well-established in other disciplines, that would be as informative in networks for psychological systems. For instance, motif analysis (introduced in Letina et al., under review) is aimed at investigating dominant 'patterns' in subnetworks within a bigger network and might be a good candidate to distinguish levels from each other. One could hypothesize, for example, that different levels reveal different patterns of organization (Eronen, 2015) in specific developmental stages. These developmental stages could potentially be characterized by an increase in level-specific (or local) network reactivity to influences from other levels which could be signalled by looking at such patterns. It might be insightful to investigate the effect of within-level patterns of behavior or brain parameters at different developmental stages on the within-level pattern of another level. The behavior of a system right before a tipping point (Van de Leemput et al., 2014), for instance, has recently gained attention in the context of psychopathological systems that approach a point of change, e.g. from 'healthy' to 'depressed'. While on a substantively different timescale, this idea is much in line with studies of developmental phase-specific interactions between intra-individual disturbances and development (e.g., Johnson, 2012; Ploeger et al., 2010; Clancy et al., 2000). The network framework enables us to study clinically relevant concepts, such as resilience in the face of challenges to typical functioning, on a more detailed micro-level of the system. After all, recent work has suggested that autism may be a "disorder of sensitive periods" (Johnson et al., 2015; Kroon et al., 2013; LeBlanc & Fagiolini, 2011).

8.2.2 *Cross-level causal cascades*

Mapping these patterns to different network configurations could then help us establish some intuition on what to look for when interested in pinpointing multivariate interrelations that reveal a huge impact on a developmental stage, within and across levels. We could then investigate the co-development of behavioral features and specific brain parameters of interest. A theoretical paper by Johnson et al. 2015 outlines a set of hypotheses that is concerned with the relation between brain adaptation and the development of neurotypical or atypical cognitive abilities. The authors speculate that developmental conditions, such as autism or attention deficit hyperactivity disorder are a "family of adaptation syndromes" that depend on genes whose expression patterns peak at different developmental stages. The relation between these expression patterns and behavioral traits within such developmental stages is a major issue in autism research. Within the network framework, we could investigate mutualistic processes

within and between different levels to such an extent that this information could be used as input to establish formal hierarchical model connecting these levels that are now predominantly studied in isolation. Once we create such a mapping, we would have a more detailed overview of the tributaries that are relevant for complex emergent phenomena (e.g., autism) in the developmental system. One promising modelling framework to test such a hierarchical causal cascade is the watershed model introduced by Cannon & Keller (2006) and Kievit et al. (2016) for psychological phenomena. This model conceptualizes developmental (potentially hierarchical) cascades of events leading to complex behavior as many upstream developmental contributions leading to a complex downstream consequence (Kievit et al., 2016). In addition, colleagues have advanced the network science toolbox to study so-called multi-source data, i.e. networks including nodes spanning different levels (e.g., genetic information or brain parameters; Tio et al., under review). Taken together, these methodological advances enable developmental researchers to translate their cross-level hypotheses into testable statistical models. It should be noted, however, that the quality of information extracted from models is always constrained by the quality of data used as input. Great promise may, therefore, lie in large-scale simulations from neural systems to brain regions to behavioral dynamics. These simulations allow us to explore complex phenomena in (atypical) development, such as self-organization (Johnson et al., 2015) or emergence (Anderson, 2008). Take the example of social relatedness. Typical social relatedness is a beneficial emergent phenomenon requiring an interacting network of attributes (social motivation, expressive skills, etc.). Within the current framework one could investigate whether atypical social relatedness is a submergenic process resulting from the loss of mutualistic interaction between those attributes, resulting from a deficient mutualistic relation between attributes or from an underlying factor from another level of the system that leads to the emergence of deficient network.

8.2.3 *Simulating patterns*

In the autism literature, there are multiple group-level phenomena that are repeatedly reported in different autistic samples. For instance, the autism population is often reported to reveal a lower group mean on cognitive skills (Brunsdon & Happé, 2014), slower development (Baron-Cohen, 1989) or self-selection effects such as niche construction (Bruineberg et al., 2018; Johnson et al., 2015; Jones & Klin, 2013). The network and SEM models discussed in this thesis provide us with a window of opportunities to test and simulate the relevance of small parameters for the emergence of group-level phenomena.

Eventually, one of the ultimate goals of psychological science would be to predict the consequence of a combination of person-specific factors to such an extent that one could predict the optimal time and variable to intervene on the system to prevent the difficult consequences some atypical developmental trajectories can have. For example, social unease related to autism could be a modelled as a result of sensory input and the interest system according to a set of learning rules that might explicate the emergence of atypical strategies for the distribution of attention (i.e. few highly aroused interests, language use or social interactions). In order to establish such a highly sensitive predictive framework, I would argue that we do not need to study all factors in isolation and sum them up, but take a starting point in investigating cross-level interrelations on a group level. Investigating the dynamics of multivariate systems over time can provide us with an additional dimension to look for risk factors or warning signals. These warning signals could very well lie in the behavior of the multivariate system and its network parameters before one can even observe early symptoms of atypical development.