## Heterogeneity in autism

*Identifying subgroups of autistic adults*

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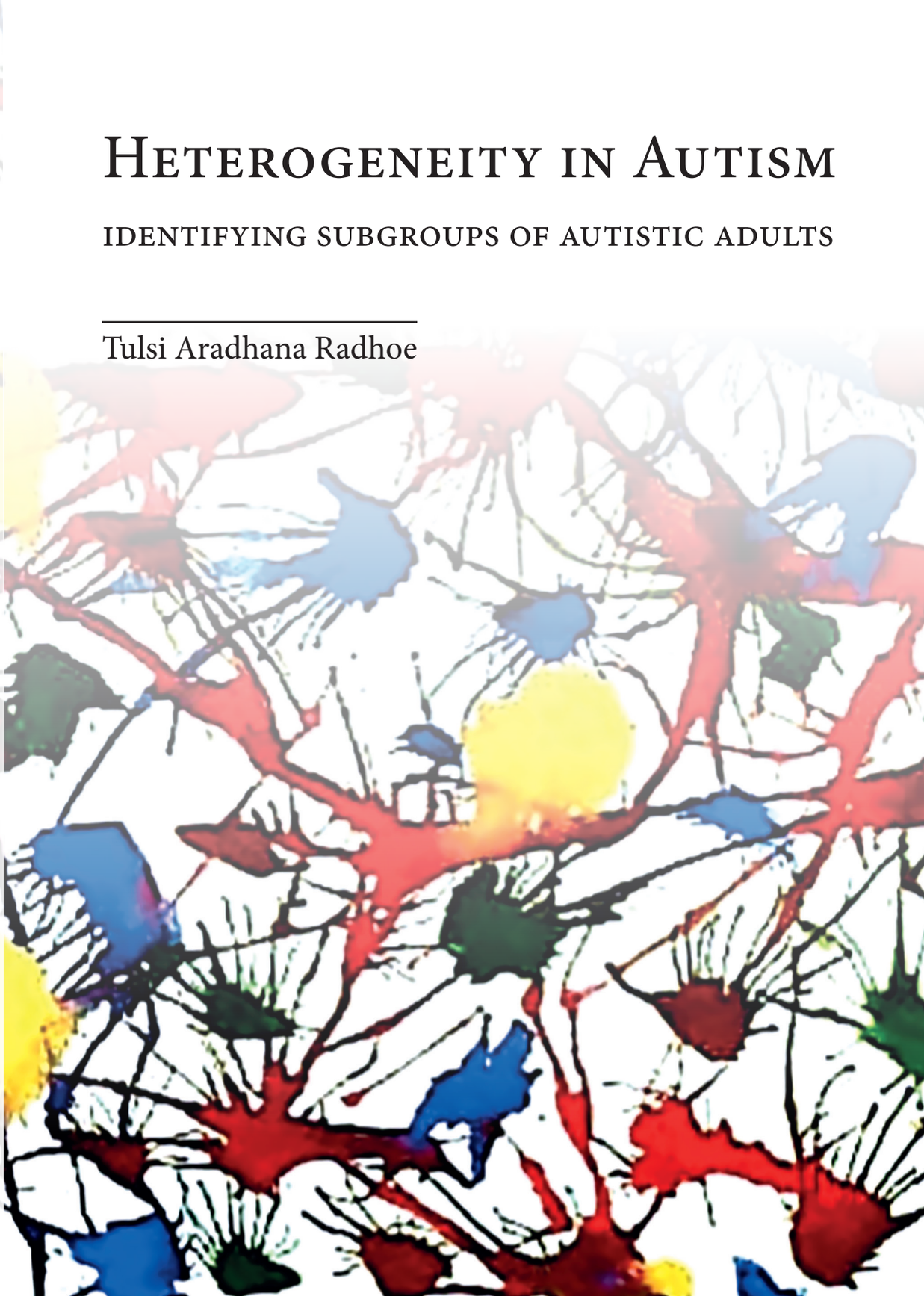
## identifying subgroups of autistic adults

Tulsi Aradhana Radhoe



# Heterogeneity in Autism:

## identifying subgroups of autistic adults

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# Heterogeneity in Autism:

## identifying subgroups of autistic adults

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door

Tulsi Aradhana Radhoe

geboren te Leiderdorp

# Contents



# Chapter 1

# Introduction

Life is characterized by individual differences. These differences are found across different categories of animals, plants, and bacteria, but also within specific categories. As an example, think of the category mammals, which includes many animals, such as dolphins, rabbits, and bats. If we are merely building a taxonomic tree, it may be sufficient to classify an animal as a mammal or perhaps a bird. However, if we aim to determine in which environment the animal thrives (e.g., on land, in air or water) or to know what to feed it (e.g., fish, meat, fruits) it is wise to consider the differences within this category. In science, the category "mammals" could be described as heterogeneous. Heterogeneity signifies "the quality or state of consisting of dissimilar or diverse elements" (Merriam-Webster, n.d.).

## Heterogeneity in autism

In the field of psychology, we also make use of different categories, for instance when providing a diagnostic classification based on certain behavioral characteristics. In this case, heterogeneity indicates the issue that different mechanisms may drive a diagnosis for different subtypes of individuals (Feczko et al., 2019). One specific category within psychology that is known for its heterogeneity, is autism. People with an autism[1] diagnosis have certain similarities, and receive their diagnosis based on behavioral characteristics according to the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2013). Autistic people often experience difficulties with social communication or social interaction, such as struggling to keep a conversation going. Moreover, autism is characterized by — in DSM terminology — restricted, repetitive patterns of behavior or interests, for instance adhering to one's specific routines and experiencing distress if this routine changes. Many autistic people also experience hyper- or hyporeactivity to sensory input, such as being sensitive to noises or sounds. Aside from these similarities, there are many differences between autistic people ranging from biology to behavior (Masi et al., 2017). At the behavioral level, there are differences in the manifestation and extent of autism characteristics, but also in their experienced strengths and difficulties (Constantino & Charman, 2016; Mottron & Bzdok, 2020). For instance, while one autistic person may have difficulty with sharing their emotions with others, a different autistic person may not recognize this, but may be highly sensitive to sounds or temperature. This heterogeneity within the autism spectrum complicates the provision of tailored support and the formulation of prognoses.

[1] It is important to acknowledge that there is heterogeneity in the preferred terminology in the autism community (Bosman & Thijs, 2023; Buijsman et al., 2022; Kenny et al., 2016). Throughout this thesis, the term "autism" is used to refer to "autism spectrum disorders". Moreover, in line with the preference of many autistic people, identity-first language is used to describe autistic people.





Considering most of our knowledge on autism stems from childhood studies, the knowledge on autism in adulthood is limited (Tse et al., 2022; Wise, 2020). This is worrying given that (a) autism is a lifelong condition (Frith & Happé, 2020) and (b) we spend most of our lives in adulthood. Moreover, it has been shown that autistic adults have a poorer quality of life (QoL) compared to the general population (Ayres et al., 2018), and experience higher rates of all major psychiatric problems, such as depression, anxiety, and suicide attempts (Hand et al., 2020; Lever & Geurts, 2016b; Nylander et al., 2018). Even less is known about the aging process of autistic adults. The few studies that followed autistic adults throughout adulthood, indicate that there is significant heterogeneity in outcomes; varying from good to poor outcomes across domains (see for review Mason et al., 2021; Wise, 2020). Because of this heterogeneity, autistic adults often do not receive the targeted support they need and wish to receive (Hwang et al., 2017). Furthermore, many autistic adults feel uncertain about what to expect as they reach older age (Finch et al., 2022). Therefore, it is crucial to gain more insight into this heterogeneity to improve the support and the lives of autistic adults.

A potential approach to capture this heterogeneity is the identification of subgroups within the autism spectrum. There have been many studies that focused on the identification of subgroups in autism (Agelink van Rentergem et al., 2021). Many of these studies have focused on biological differences to inform us about the causes and markers of autism. While these studies may be informative for clinical practice on the long run, they do not necessarily result in clinical insights that are directly applicable to support or interventions. Moreover, only a few subgrouping studies have focused primarily on autistic adulthood (Elwin et al., 2017; Gonthier et al., 2016; Lewis et al., 2008; Lombardo et al., 2016; Ring et al., 2008), of which even fewer covered various clinically relevant measures (Bishop-Fitzpatrick et al., 2016; LaBianca et al., 2018). If the goal is to implement the knowledge in clinical practice —beyond merely gaining a better understanding of the heterogeneity — it is important to include clinically relevant measures (such as QoL).

Once subgroups have been detected, a crucial step involves the validation of the subgroups; to determine whether the subgrouping solution is sensible. The suitable type of validation depends on the goal of the subgrouping study. However, in the literature thus far, subgroup validation is often hardly considered (see for review Agelink van Rentergem et al., 2021). Due to the absence of these validation procedures, it remains unclear whether the subgroups are genuinely sensible, which in turn restricts their (clinical) applicability. As an example of subgroup validation, Bishop-Fitzpatrick and colleagues (2016) aimed to capture the heterogeneity in QoL, and assessed the external validity of the subgroups on related measures, such as employment status. LaBianca and colleagues (2018) identified subgroups that differed in healthcare needs, and examined the

external validity using genetic risk factors. There have not been any subgrouping studies that considered the aging process by focusing on clinical predictions throughout autistic adulthood. Thus, there is a clear need for valid subgroups of autistic adults that can inform clinical practice on the adulthood developmental process, to improve the lives of people on the autism spectrum. The aim of this PhD thesis is to bridge this gap by advancing our knowledge on heterogeneity and aging with autism.

## Thesis overview

In **Chapter 2,** we first address subgroup identification in general aging and employ several validation procedures. We use community detection analysis to identify subgroups in 1478 adults aged 61 to 101 years with data from the Longitudinal Aging Study Amsterdam (Hoogendijk et al., 2016). The external and predictive validity of the subgroups is assessed for wellbeing and subjective cognitive decline. With a longitudinal data set of 1186 adults, the replicability and long-term stability of the subgroups is tested.

Chapters 3 to 6 were part of a larger study on aging and autism (see for protocol Chapter 8; Geurts et al., 2021). In **Chapter 3**, we focus on subgroup identification in autistic adults by analyzing a newly gathered data set of 375 autistic adults, 345 non-autistic adults and 123 adults with ADHD, aged 30-89 years. As input for the community detection analysis, we use 14 self-reported psychological, demographic and lifestyle variables that can potentially be modified with intervention. First, subgroups are identified in a combined data set of autistic adults and a non-autistic comparison group. Next, the heterogeneity in autism is examined by subgroup identification in a sample with only autistic adults. Finally, the specificity of the subgrouping result is assessed by repeating the analysis after adding a group of adults with ADHD. Two subgroup validation steps are adopted. The first step involves an direct replication: The total sample is split into two subsets, and subgroups are identified and compared across subsets. The second step concerns the external validity: The autism subgroups are compared on external outcomes, i.e., QoL, psychological, and cognitive difficulties.

In **Chapter 4,** we aim to test whether differences in mean cluster variable scores between the previously identified subgroups (in Chapter 3) also correspond to differences in correlational (network) structure. Based on the cluster variables and external variables (i.e., QoL, psychological, and cognitive difficulties) used in Chapter 3, we estimate and compare variable networks of (a) autistic and non-autistic adults, and (b) autism subgroups identified in Chapter 3. Gaussian Graphical Models are used for this purpose. Moreover, sex differences are explored in the networks of the autism subgroups by means of Mixed





Graphical Models.

**Chapter 5** involves a longitudinal follow-up of the cross-sectional study described in Chapter 3. The aim is to determine whether the previously identified subgroups are (a) stable as people age, and (b) predictive of future outcomes. To test the stability over time, subgroups are identified in two independent samples: Sample 1 (N=80 autistic adults) measured five years after baseline, and Sample 2 (N=241 autistic, 211 non-autistic) measured two years after baseline. For predictive validity, it is tested whether subgroups identified at baseline are predictive of outcomes measured after two to five years: QoL, psychological, and cognitive difficulties.

**Chapter 6** elucidates whether the identified autism subgroups (in Chapter 3) relate to differences in cognitive functioning. Some argue that autistic adults might be more vulnerable to cognitive aging (Klein et al., 2022; Vivanti et al., 2021), which causes many autistic adults to worry about their aging process. The aim of this chapter is to gain more insight into cognitive aging and the heterogeneity therein by considering the identified autism subgroups. Differences in the following areas are explored: (a) cognitive measures, (b) cognitive profiles (i.e., having an overall deviating or non-deviating cognitive profile), and (c) age-related cognitive effects (either cross-sectional or longitudinal).

In **Chapter 7**, the main findings are summarized and discussed. Moreover, the (clinical and theoretical) implications and future study prospects are discussed. All studies were preregistered at AsPredicted.org. The preregistrations are included in Chapter 8.



# Chapter 2

# Subgroups are associated with cognition and wellbeing

This chapter was published as:
Radhoe, T. A., Agelink van Rentergem, J. A., Kok, A. L., Huisman, M., & Geurts, H. M. (2021). Subgroups in late adulthood are associated with cognition and wellbeing later in life. Frontiers in Psychology, 12, 780575. doi: 10.3389/fpsyg.2021.780575

## Abstract

**Objectives**: In this study, we aim to discover whether there are valid subgroups in aging that are defined by modifiable factors and are determinant of clinically relevant outcomes regarding healthy aging.

**Method**: Data from interviews were collected in the Longitudinal Aging Study Amsterdam at two measurement occasions with a three-year interval. Input for the analyses were seven well-known vulnerability and protective factors of healthy aging. By means of community detection, we tested whether we could distinguish subgroups in a sample of 1478 participants (T1-sample, aged 61-101 years). We tested both the external validity (T1) and predictive validity (T2) for wellbeing and subjective cognitive decline. Moreover, replicability and long-term stability were determined in 1186 participants (T2-sample, aged 61-101 years).

**Results**: Three similar subgroups were identified at T1 and T2. Subgroup A was characterized by high levels of education with personal vulnerabilities, subgroup B by being physically active with low support and low levels of education, and subgroup C by high levels of support with low levels of education. Subgroup C showed the lowest wellbeing and memory profile, both at T1 and T2. On most measures of wellbeing and memory, subgroups A and B did not differ from each other. At T2, the same number of subgroups was identified and subgroup profiles at T1 and T2 were practically identical. Per T1 subgroup 47%-62% retained their membership at T2.

**Discussion**: We identified valid subgroups that replicate over time and differ on external variables at current and later measurement occasions. Individual change in subgroup membership over time shows that transitions to subgroups with better outcomes are possible.






## Introduction

Positive aging trajectories translate to higher wellbeing and better physical functioning, and lower health care costs for society (Bowling & Dieppe, 2005; A. A. L. Kok et al., 2017) but it is difficult to predict who will have such a positive trajectory, and who will require more support. Large differences exist in how people age (Hayden et al., 2011; Lowsky et al., 2013). The aging patterns observed in group studies are also diverse. Some groups show strong average decline in functioning as people age, others show less decline or even no decline at all (Grundy & Bowling, 1999; A. A. L. Kok et al., 2017; Wilson et al., 2002). As there are large individual differences it might be more informative to focus on aging patterns of subgroups instead of across the general population. If we overlook these interindividual differences, we may falsely conclude that there is no change due to aging, while in fact different outcomes (e.g., stability, decline or increase over time) apply to different subgroups. Thus, adopting a subgrouping approach provides us with information that otherwise would have been overlooked. In this study, we aim to identify subgroups of aging adults that are either more or less likely to experience subjective cognitive decline and decreased wellbeing; currently, and in the future. We use easy to measure and modifiable proxies of well-known vulnerability and protective factors for healthy mental aging as input variables.

A lack of subjective cognitive decline and a high wellbeing are both typical characteristics of healthy mental aging. People associate aging with a decrease in memory, and subjective cognitive decline is predictive of cognitive impairment and dementia in older adults (Geerlings et al., 1999; Jonker et al., 2000). However, aging does not necessarily lead to cognitive decline (Jonker et al., 2000; Lima-Silva & Yassuda, 2009; Silva et al., 2014). Similarly, while wellbeing tends to decrease with age, the speed and associated risk factors vary across studies and groups (Jivraj et al., 2014; Lukaschek et al., 2017). Whether wellbeing decreases over age also depends on which aspect of wellbeing is addressed; for example, life satisfaction is generally high in old age (e.g., Charles & Carstensen, 2010). Maintaining wellbeing is often a primary goal for healthcare of older adults as they age. In this study we use wellbeing as an umbrella term reflecting mental, social, physical and spiritual wellbeing, and personal circumstances, activities and functioning (Linton et al., 2016).

Subjective cognitive decline and wellbeing in older age could be affected by behavior, psychological, and/or social factors (e.g., physical activity, alcohol use, social support) as well as (neuro)biology (e.g., genetics, brain structure) (Chen et al., 2014; Eva et al., 2015). In this study, we focus on factors for which easy to administer and inexpensive measures are available. We particularly focus on those factors that could be influenced by psychological interventions and/or environmental changes. By focusing on variables

that are easy to measure and modifiable in nature rather than factors that are expensive to measure and fixed, we hope to discover subgroups that can inform and guide clinical practice and preventive health services.The relationship between risk and protective factors and aging outcomes is complex. Many different factors have been shown to influence aging outcomes, some of which may be intercorrelated and may be reflective of a more general common risk factor, while other factors may independently affect outcomes (Christensen et al., 2001). Furthermore, some factors may directly influence outcomes, while other factors affect outcomes in their interaction (e.g., Sauter et al., 2021; Windsor et al., 2020). The advantage of examining factors together is that we can reduce this complexity. By taking a multivariate approach, we reduce the complexity of interacting individual differences on a large number of variables to a limited number of interpretable profiles.

In the literature, different types of input variables have been used to construct subgroups, which has resulted in varying numbers of subgroups with varying characteristics. For example, neurocognitive test variables were used to identify three latent classes of cognitive performance in older individuals (Costa et al., 2013). Another study identified five subgroups of older adults using social engagement activity patterns (Croezen et al., 2009). Nine profiles of functional status were identified using measures of psychological functioning in older adults as part of the Berlin Aging Study (Smith & Baltes, 1997). When subgroups are defined by non-modifiable variables, their usefulness is inherently limited, as the subsequent subgroups are also more or less set in stone. Moreover, the validity of most obtained subgroups and their stability over time remains an open question. A lack of systematic validation of subtypes will lead to a proliferation of subtypes of questionable utility (Agelink van Rentergem et al., 2021).

In this study, we perform three subgroup validation techniques. First, we assess external validity by investigating whether subgroups differ in subjective cognitive decline and wellbeing. Second, we assess predictive validity by determining whether subgroups differ in subjective cognitive decline and wellbeing after three years. Third, we assess longitudinal stability of subgroups by repeating the community detection analysis on data collected after three years. Specifically, we assess whether the same number of subgroups is identified after three years, and whether subgroup profiles are the same. With these validation techniques, we assess whether subgroups generalize to other domains, have predictive value for other domains, and are stable over time.





## Materials and Methods

### Study sample

Data was requested from the Longitudinal Aging Study Amsterdam (LASA), an ongoing prospective study of older adults living in the Netherlands (Hoogendijk et al., 2016). LASA's objective is to investigate the determinants, trajectories, and consequences of physical, emotional, cognitive, and social functioning related to aging (Huisman et al., 2011). The study is based on a nationally representative sample of adults aged 55 to 85 years (born in 1908-1937), recruited from municipal registries in the Netherlands, who completed interviews at home. In 1992, the first 3107 adults participated (cooperation rate 62%). Since baseline, measurements were repeated about every three years. In 2002-2003, a refresher sample of 1002 participants aged 55 to 65 (born in 1938-1947) was added. Participants from the first and refresher sample were measured together from the regular follow-up measurement of 2005-2006 onwards. LASA data are available for research and can be requested by submitting an analysis proposal to the LASA Steering Group (see www.lasa-vu.nl for more info).

For our study, data from the seventh and eight wave of data collection were included. See Supplementary Materials (S9.1.1) for the names of the specific data files used in the current study. 1601 participants were included from the seventh wave (2008-2009, T1), of whom 1478 were analyzed after removing observations with too many missing values (see below). 1275 participants were included from the eighth wave (2011-2012, T2), of whom 1186 were analyzed. The T1-sample (675 men, 803 women) had a mean age of 73 years (SD=8.29, range=61-101). The T2-sample (537 men, 649 women) had a mean age of 75 years (SD=7.58, range=64-100).

### Measures

Selection of cluster variables was guided by their 1) relation to cognitive decline and/or wellbeing (Beydoun et al., 2014; S. T. Chen et al., 2014; Goh et al., 2012; MacDonald et al., 2011; Prenderville et al., 2015), 2) individual differences in the aging population, 3) quick and large-scale measurement through self-report, and 4) modifiability. The variables fit with these guiding principles to varying degrees. For example, the impact of negative life events may be indirectly modifiable as their effect can be modified through interventions; one's education is unlikely to change at older age but may be modifiable earlier in life; alcohol use is directly modifiable. Both education and excessive alcohol use have recently been named among the most important modifiable factors with respect to increased risk of dementia (G. Livingston et al., 2020). In total, we included seven cluster variables.

***Cluster variables***

A detailed description including psychometric properties can be found in the Supplementary Materials (S9.1.2).

*Negative life events.* Negative life events were evaluated with questions from the life event inventory (Tennant & Andrews, 1976). Participants reported whether they had experienced 12 different negative life events in the past three years (see S9.1.2). We calculated a sum score that ranged from 0 (no negative life events) to 12 (many negative life events) (see also (Comijs et al., 2011). Negative life events have strong associations with depressive symptoms and lower wellbeing (Kraaij et al., 2002). Resources such as social network, education and health status are inversely associated with the impact of negative life events later in life (Jopp & Schmitt, 2010).

*Education.* Responses on educational level were translated into years of education and ranged from 5 (elementary school not completed) to 18 (university education). Lower educational attainment is associated with subjective cognitive decline and is a strong predictor of dementia (Beydoun et al., 2014; S. T. Chen et al., 2014).

*Alcohol use.* Participants reported the number of days per week on which they drink alcohol and the number of alcoholic consumptions they drink each time. The possible number of alcoholic consumptions per week ranged from 0 (no alcoholic drinks) to 77 (or more) (see for a similar approach (Comijs et al., 2012; Pluijm et al., 2006). Alcohol use is related to cognitive decline (Heffernan, 2008; Mintzer, 2007) and can be targeted in interventions (Platt et al., 2016).

*Physical activity.* Physical activity was assessed during an interview using the LASA Physical Activity Questionnaire (Stel et al., 2004). Participants reported how often and for how long they performed various physical activities during the two weeks prior to the interview (see S9.1.2). We calculated the total time in minutes. A higher level of physical activity is associated with less cognitive decline and predicts wellbeing in older adults (Beydoun et al., 2014; Kadariya et al., 2019; McAuley et al., 2000) . Also, physical activity levels can be increased through interventions (Greaves et al., 2011; Müller-Riemenschneider et al., 2008).

*Emotional and instrumental support received.* We asked participants about people they are regularly in touch with and are important to them (van Tilburg, 1998). Participants reported the supportive emotional and instrumental exchanges with the nine most important network members, excluding the partner (see S9.1.2). Questions were answered with four response options, ranging from 'never' to 'often'. Sum scores for emotional





support received and instrumental support received were calculated varying between 0 (low level of support) and 36 (high level of support). Leading a socially active life and receiving sufficient social support are related to a higher wellbeing later in life (Gerstorf et al., 2016; Yaffe et al., 2009). Interventions for social support can be effective in increasing one's perceived level of social support (Hogan et al., 2002).

*Sense of mastery.* Mastery refers to the extent to which people view themselves as being in control of the forces that affect their lives in important ways (Pearlin et al., 1981). Mastery was assessed by the Pearlin Mastery Scale, consisting of seven items rated on a five-point scale ranging from 'strongly disagree' to 'strongly agree' (Pearlin & Schooler, 1978). We calculated a sum score varying between 7 and 35. Higher ratings indicate a stronger internal locus of control. A high level of mastery, or stronger internal locus of control, is related to a better memory performance and higher wellbeing (Amrhein et al., 1999; Robinson & Lachman, 2017; Verhaeghen et al., 2000). Mastery and self-efficacy can be increased through interventions (Mathisen & Bronnick, 2009).

***External validators***

*Subjective wellbeing.* Subjective wellbeing was measured with three different self-report questionnaires. First, we assessed satisfaction with life by two questions defined by(van Zonneveld, 1961). The first question asks about satisfaction with current life, the second about satisfaction with life as a whole. Both questions have five response categories ranging from 'very dissatisfied' to 'very satisfied'. We calculated a sum score ranging from 2 (low satisfaction with life) to 10 (high satisfaction).

Second, health-related quality of life was measured by the EuroQoL five dimensional questionnaire (EQ-5D). It consists of five questions and a visual analog scale. Responses on these items were converted into a weighted health state index according to the Time Trade OFF method (Dolan, 1997) ranging from 0 (low) to 1 (high).

Third, we measured functional health and wellbeing by the Short Form 12 (SF-12) health survey, a subset of the larger SF-36 (Ware et al., 1996). Sum scores were calculated for two summary scales of the SF-12, the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

*Subjective cognitive decline.* We asked whether participants experience memory complaints during a broader medical interview. This question is reliable in identifying people vulnerable to cognitive impairment or dementia (Geerlings et al., 1999). A score of 1 indicated memory complaints and a score of 0 indicated no complaints.

***Additional descriptive variables***

The following additional variables were not used as cluster variables or external validators but were used to further describe the subgroups: Age, country of origin, marital status and sex (all measured at the first wave of LASA), medication use, household composition, fluid intelligence, depression diagnosis, anxiety diagnosis, and ADHD symptoms (all measured at the same occasion as the cluster and external validation variables). These last measures were included to characterize internalizing and externalizing problems. See S9.1.3 for a more detailed description of the measurement instruments and descriptive analyses.

## Statistical analyses

The analysis plan was preregistered at AsPredicted.org (Chapter 8, AsPredicted number: 27409).

***Missing data***

If participants had less than two missing values on the seven cluster variables, we included them in the analysis. We considered 10% an acceptable amount of missing data for imputation (Bennett, 2001). For mastery, we recoded a maximum of one missing value to the median of the participant's responses on the other mastery items. For negative life events, we recoded a maximum of one missing value to 0 (i.e., the event did not occur in the past three years).

If participants had missing values on two or more of the seven cluster variables, they were excluded from analysis. At T1, 123 participants out of 1601 were excluded due to missing data, which led to 1478 analyzed participants. At T2, 89 participants out of 1275 were excluded, which led to 1186 analyzed participants.

***Community detection analysis***

To establish subgroups, we used a state-of-the art method, called community detection. Community detection is a non-parametric clustering method that stems from the mathematical discipline of graph theory (Dorogovtsev & Mendes, 2003; Newman, 2010). With this method, we take into account the multivariate structure of different risk and protective factors of subjective cognitive decline and wellbeing. People with similar profiles on the input variables have a higher likelihood of being assigned to the same subgroup than people with dissimilar scores. Research so far suggests that the added value of this novel method compared to Latent Profile Analysis —which is commonly used to investigate heterogeneity— could be the identification of subgroups that are more stable over time with improved clinical predictive value (Blanken et al., 2020).





Our goal was to identify the community structure in a network of people. Cluster variables were first standardized to *z*-scores, to prevent differences in measurement scales from affecting results. We then created a pairwise Pearson correlation matrix containing relationships between scoring patterns of all pairs of individuals (see for similar approach Karalunas et al., 2014). Pairs of individuals whose scoring patterns on cluster variables are similar show a high correlation in this matrix.

A network was created containing nodes, which represent people in this case, connected by edges, which are correlations between people in this study. A community is a subgraph in the larger network, where the number of internal edges (within the community) is larger than the number of external edges (between communities) (Fortunato & Hric, 2016). In other words, nodes in a community have a higher likelihood of connecting to each other than to nodes from other communities (Barabási & Pósfai, 2016).

Multiple algorithms can be applied to identify communities. We had three criteria for the algorithm. First, it should deal with weighted edges, i.e., correlations. Second, it should deal with positive and negative correlations. If we would only include positive correlations, we may include people who are dissimilar in the same community, which interferes with our goal of creating homogeneous subgroups. Third, it should not result in overlapping communities. If people belong to multiple communities, we cannot transfer them from one community to another (more favorable) community. The Spinglass algorithm meets these criteria and was selected (Reichardt & Bornholdt, 2006). This algorithm rewards internal edges between nodes of the same subgroup. Second, it penalizes missing edges between nodes in the same subgroup. Third, it penalizes existing edges between different subgroups. Fourth, it rewards non-existing edges between different subgroups. We assigned equal importance to existing edges and non-existing edges, and to positive and negative weights, between individuals, by setting the γ-parameter to 1. We also calculated the modularity index *Q*, which measures the quality of the assignment of nodes into communities (Newman & Girvan, 2004). The maximum value is *Q*=1, indicating a strong community structure. In practice, most values range from 0.3 to 0.7.

***Descriptive analyses of subgroups***

We performed six ANOVAs and six Pearson's $\chi^2$ tests on additional variables to describe the identified subgroups. These analyses are described in more detail in S9.1.3.

***Subgroup validation***

To assess external validity of subgroups, we compared subgroups on wellbeing and subjective cognitive decline measured at T1. To assess predictive validity, we compared subgroups on these same variables, this time measured at T2. We considered the

subgrouping solution meaningful if subgroups differed significantly on these external variables, using ANOVA and logistic regression, with subgroup membership at T1 as the independent variable.

To assess the longitudinal stability of the subgroups identified at T1, we repeated the community detection analysis on data collected at T2. We created a contingency table of subgroup assignment at T1 versus assignment at T2. We performed a $\chi^2$ test for association between subgroup assignment at these time points.

## Results

### Community detection analysis

Three distinct subgroups were identified. The modularity index indicated weakly defined communities, Q=0.26. Figure 2.1 depicts subgroup profiles on the cluster variables at T1 (panel A). Table 2.1 presents test statistics for the findings described below.

We refer to the first subgroup ($N_1$=435; 29%) as '*Subgroup A*'. This subgroup had the highest educational level attained, lowest level of physical activity and the highest use of alcohol. These participants experienced fewer negative life events than other subgroups. We labeled the second subgroup ($N_2$=486; 33%) '*Subgroup B*'. This subgroup reported the highest physical activity level and received the lowest levels of emotional and instrumental support. Furthermore, this subgroup experienced the highest number of negative life events compared to the other subgroups. We labeled the third subgroup ($N_3$=557; 38%) '*Subgroup C*'. This subgroup received the highest levels of instrumental and emotional support. This subgroup also reported the lowest sense of mastery.

### Description of subgroups

Subgroups differed from each other on several descriptive measures at T1 (see Table 2.1). Participants in Subgroup A were younger and showed higher scores on fluid intelligence which aligns with this being the highly educated subgroup. Moreover, this subgroup contained more men than women, while the other two subgroups contained more women. Participants in the Subgroup C were older and had lower fluid intelligence scores than the other subgroups. Also, they had the highest ADHD-scores, the smallest household composition and used the highest number of medicines. Moreover, this subgroup included a higher number of participants in widowhood and lower number of married participants compared to the other subgroups, which corresponds





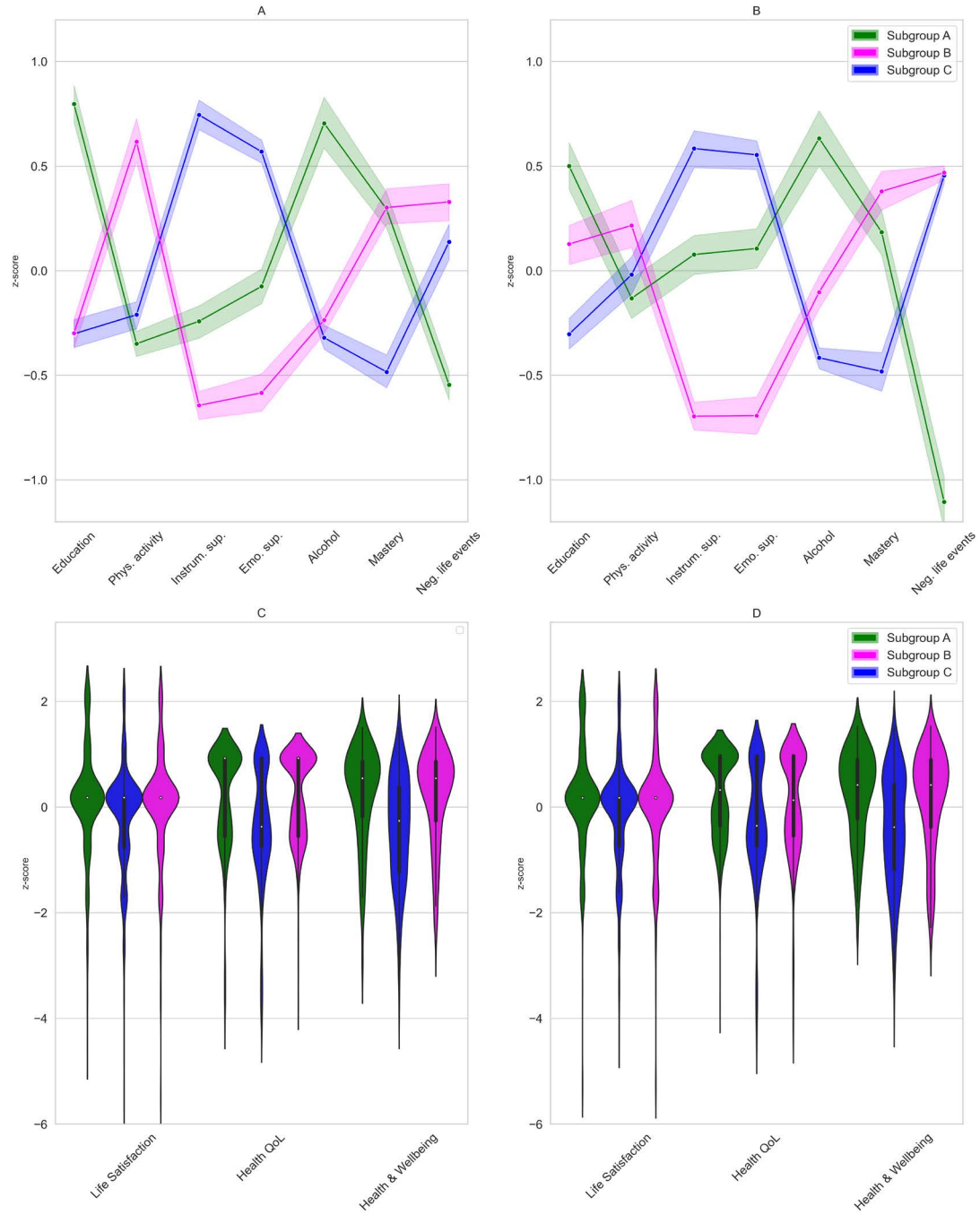


Figure 2.1. A. Subgroup profiles at T1, B. Subgroup profiles at T2, C. External validation (T1), D. Predictive validation (T2)
Note. Scores as shown as z-scores based on the total sample mean. Shaded area represents 95%-confidence interval.

Table 2.1

*Raw cluster variable scores and descriptives for each of the three community detection-based subgroups formed on T1 data (N=1478)*

| | **Subgroup** | | | | | | |
|---|---|---|---|---|---|---|---|
| Variable | Subgroup A N = 435 | Subgroup B N = 486 | Subgroup C N = 557 | test statistic(*df*) | Subgroup C vs. Subgroup B (*Z*) | Subgroup A vs. Sub-group B (*Z*) | Subgroup A vs. Subgroup C (*Z*) |
| **Descriptive variables** | | | | | | | |
| Age *M*(*SD*) | 70.75 (7.58) | 72.30 (8.32) | 75.02 (8.30) | $F(2,1475) = 35.66^{***}$ | 5.54*** | -2.81*** | -8.27*** |
| # household members *M*(*SD*) | 0.80 (0.56) | 0.77 (0.59) | 0.66 (0.63) | $F(2,1446) = 7.08^{***}$ | -3.28*** | 0.82 | 4.03*** |
| # medicines *M*(*SD*) | 2.63 (2.73) | 2.84 (2.66) | 4.16 (3.04) | $F(2,1414) = 42.36^{***}$ | 7.16*** | -1.51 | -8.52*** |
| Raven A-score *M*(*SD*) | 10.58 (2.22) | 10.18 (1.84) | 9.78 (2.55) | $F(2,1414) = 14.94^{***}$ | -1.78 | 5.41*** | 7.31*** |
| Raven B-score *M*(*SD*) | 9.04 (2.90) | 8.29 (2.82) | 7.67 (3.11) | $F(2,1414) = 25.41^{***}$ | -3.12** | 4.78*** | 7.96*** |
| ADHD-score *M*(*SD*) | 0.51 (1.16) | 0.45 (0.96) | 0.79 (1.38) | $F(2,1388) = 11.48^{***}$ | 4.40*** | 0.40 | -3.87*** |
| Gender | | | | $\chi^2(2) = 84.18^{***}$ | | | |
| $N_{male}$ (%) | 276 (63) | 205 (42) | 194 (35) | | | | |
| $N_{female}$ (%) | 159 (37) | 281 (58) | 363 (65) | | | | |
| Country of Origin | | | | $\chi^2(2) = 2.17$ | | | |
| $N_{Netherlands}$ (%) | 431 (99) | 485 (99) | 554 (99) | | | | |
| $N_{Other}$ (%) | 4 (1) | 1 (1) | 3 (1) | | | | |
| Current depression[a] | | | | $\chi^2(2) = 0.52$ | | | |
| $N_{Yes}$ (%) | 3 (6) | 3 (5) | 10 (7) | | | | |
| $N_{No}$ (%) | 49 (94) | 61 (95) | 128 (93) | | | | |
| Lifetime depression[a] | | | | $\chi^2(2) = 3.10$ | | | |
| $N_{Yes}$ (%) | 14 (27) | 9 (14) | 31 (22) | | | | |
| $N_{No}$ (%) | 38 (73) | 55 (86) | 107 (78) | | | | |
| Lifetime anxiety[a] | | | | $\chi^2(2) = 3.46$ | | | |
| $N_{Yes}$ (%) | 10 (20) | 21 (36) | 37 (28) | | | | |
| $N_{No}$ (%) | 41 (60) | 38 (64) | 95 (72) | | | | |
| Medication use | | | | $\chi^2(2) = 47.24^{***}$ | | | |
| $N_{Yes}$ (%) | 308 (74) | 354 (76) | 478 (90) | | | | |
| $N_{No}$ (%) | 111 (26) | 111 (24) | 55 (10) | | | | |
| Marital status | | | | $\chi^2(6) = 52.41^{***}$ | | | |
| $N_{never\ married}$ (%) | 33 (8) | 23 (5) | 17 (3) | | | | |
| $N_{married}$ (%) | 296 (68) | 325 (67) | 308 (55) | | | | |
| $N_{divorced}$ (%) | 35 (8) | 38 (8) | 45 (8) | | | | |
| $N_{widowhood}$ (%) | 71 (16) | 100 (20) | 178 (34) | | | | |
| **Cluster variables** | | | | | | | |
| Phys. activity *M*(*SD*) | 117.22 (71.60) | 212.09 (120.02) | 129.31 (78.69) | $F(2,1465) = 156.70^{***}$ | -12.29*** | -13.96*** | -2.52** |
| Instr. support *M*(*SD*) | 13.95 (5.04) | 11.39 (4.61) | 20.04 (5.25) | $F(2,1475) = 420.40^{***}$ | 22.71*** | 6.41*** | -15.43*** |
| Emo. support *M*(*SD*) | 21.85 (6.71) | 18.02 (7.80) | 26.70 (5.19) | $F(2,1473) = 227.20^{***}$ | 18.25*** | 6.81*** | -10.67*** |
| Alcohol use *M*(*SD*) | 14.23 (12.94) | 5.93 (7.45) | 5.05 (6.98) | $F(2,1410) = 177.30^{***}$ | -1.97* | 13.28*** | 15.64*** |
| Mastery *M*(*SD*) | 25.13 (3.70) | 25.25 (4.00) | 22.03 (3.70) | $F(2,1473) = 123.90^{***}$ | -12.84*** | -0.22 | 12.23*** |
| Neg. events *M*(*SD*) | 0.48 (0.63) | 1.26 (0.93) | 1.09 (0.90) | $F(2,1461) = 109.30^{***}$ | -2.96** | -13.69*** | -11.25*** |
| Education *M*(*SD*) | 11.94 (3.65) | 9.00 (2.77) | 8.99 (2.80) | $F(2,1475) = 246.30^{***}$ | 0.12 | 15.91*** | 16.30*** |

*Note.* * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. [a] Sample sizes are lower for these variables because data are only available for participants who completed a Composite International Diagnostic Interview (CIDI)

Table 2.2
*Scores for external (T1) and predictive (T2) validation measures for each of the three community detection-based subgroups formed on T1 data.*

| | Subgroup | | | | | | |
|---|---|---|---|---|---|---|---|
| Variable | Subgr. A *M*(*SD*) | Subgr. B *M*(*SD*) | Subgr. C *M*(*SD*) | *F*(*df*) | Subgr. C vs. Subgr. B (*Z*) | Subgr. A vs. Subgr. B (*Z*) | Subgr. A. vs. Subgr. C. (*Z*) |
| **External validation** | | | | | | | |
| Life satisfaction (T1) | 0.16 (1.01) | 0.06 (1.01) | -0.18 (0.97) | *F*(2,1376)= 14.16*** | -4.42*** | 1.11 | 5.48*** |
| Health-related QoL (T1) | 0.21 (0.94) | 0.22 (0.80) | -0.34 (1.10) | *F*(2,1362)= 54.63*** | -8.46*** | 0.52 | 8.88*** |
| Functional health & wellbeing (T1) | 0.25 (0.92) | 0.24 (0.88) | -0.41 (1.03) | *F*(2,1211)= 65.53*** | -9.52*** | 0.34 | 9.71*** |
| **Predictive validation** | | | | | | | |
| Life satisfaction (T2) | 0.14 (0.97) | <-0.01 (1.03) | -0.11 (1.00) | *F*(2,1117)= 5.97** | -2.38* | 2.15* | 4.49*** |
| Health-related QoL (T2) | 0.26 (0.79) | -0.06 (1.00) | -0.30 (1.09) | *F*(2,1069)= 30.71*** | -5.01*** | 2.42* | 7.35*** |
| Functional health & wellbeing (T2) | 0.26 (0.85) | 0.17 (0.95) | -0.40 (1.06) | *F*(2,975)= 46.54*** | -7.28*** | 1.00 | 8.17*** |

*Note*. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 2.3
*Scores related to subjective cognitive decline for external (T1) and predictive (T2) validation for each of the three community detection-based subgroups formed on T1 data*

| | | | | 95% CI for Odds Ratio | | |
|---|---|---|---|---|---|---|
| Subgroup comparison | *B* (*SE*) | *df* | *p* | Lower | Odds ratio | Upper |
| **External validation (T1)** | | | | | | |
| Subgr. B vs. Subgr. A | -0.07 (0.15) | 1 | 0.614 | 0.70 | 0.93 | 1.24 |
| Subgr. C vs. Subgr. B | 0.45 (0.13) | 1 | 0.001 | 1.21 | 1.57 | 2.04 |
| Subgr. C vs. Subgr. A | 0.38 (0.14) | 1 | 0.005 | 1.12 | 1.46 | 1.91 |
| **Predictive validation (T2)** | | | | | | |
| Subgr. B vs. Subgr. A | -0.07 (0.15) | 1 | 0.650 | 0.69 | 0.93 | 1.26 |
| Subgr. C vs. Subgr. B | 0.33 (0.14) | 1 | 0.021 | 1.05 | 1.40 | 1.85 |
| Subgr. C vs. Subgr. A | 0.26 (0.15) | 1 | 0.075 | 0.97 | 1.30 | 1.74 |





with the older ages of participants in this subgroup.

**External validation: Strongly supported Subgroup C scored lower than other subgroups**

For external validation, we tested subgroup differences in four preregistered external measures. Results for measures related to wellbeing are presented in Table 2.2. Figure 2.1 (Panel C and D) depicts violin plots of the distribution on variables measuring wellbeing (this is not possible for subjective cognitive decline due to binary response categories).

On all domains related to wellbeing (i.e., life satisfaction, health-related QoL, and functional health), Subgroup C scored significantly lower than Subgroups A and B. There were no differences in wellbeing domains between Subgroups A and B. Table 2.3 presents test statistics related to the findings of subjective cognitive decline. Being a member of Subgroup C compared to Subgroup B, multiplied the odds of experiencing subjective cognitive decline by 1.57. Being a member of Subgroup C compared to Subgroup A, multiplied the odds of subjective cognitive decline by 1.46.

**Longitudinal stability: A small majority remains in the same subgroup**

Community detection analysis was repeated using T2 data (N=1186). There was more drop-out from T1 to T2 in Subgroup C compared to the other two subgroups. Compared to participants that did not drop out, the drop-out group was older, used a higher number of medicines and had lower fluid intelligence scores. Attrition from T1 to T2 is further described in S9.1.4.

Again, we identified three subgroups ($N_1$=351, $N_2$=435, $N_3$=400). Profiles of the subgroups identified at T2 are presented in Figure 2.1 (Panel B). We used the same labelling as for the subgroups formed at T1, since subgroup profiles observed at T2 were highly similar to those observed at T1 (although subgroup differences regarding physical activity were smaller at T2 than at T1). There was a significant association between subgroup membership at T1 and at T2 ($\chi^2(4)$ =229.52, $p < 0.05$). For specific percentages regarding subgroup membership stability, see Figure 2.2[2]. While not preregistered, we explored changes in subgrouping variables for those participants whose subgroup membership was not stable over time (see S9.1.6 for supporting figures). Switches to and from Subgroup A seem to be driven by changes in negative life events. Switches between the Subgroup B and Subgroup C were associated with changes in instrumental and emotional support.

**Predictive validity: All three subgroups differ on external validators at T2**

We used subgroup membership at T1 to predict wellbeing and experience of subjective cognitive decline at T2 to assess the predictive validity (i.e., are the earlier discovered differences on the external validators stable over time). Results are presented in Table 2.2. Figure 2.1 (Panel D) depicts violin plots of scores per subgroup on wellbeing variables at T2. On all wellbeing domains (i.e., life satisfaction, health-related QoL, and functional health), Subgroup C scored significantly lower than Subgroups A and B. Subgroup A scored higher than Subgroup B on life satisfaction and health-related QoL, but these subgroups did not differ on functional health at T2. Table 2.3 presents test statistics related to prediction of experiencing subjective cognitive decline. Being a member of Subgroup C compared to Subgroup B multiplied the odds of experiencing subjective cognitive decline at T2 by 1.40.

## Discussion

In this study, we identified three subgroups of older adults by analysis of protective and vulnerability factors of aging: Subgroup A, characterized by average levels of social support, high alcohol use, low number of experienced negative life events, low physical activity level and high educational level; Subgroup B, characterized by a high physical activity level, low levels of social support, and high number of experienced negative life events; Subgroup C, characterized by high levels of social support and low sense of mastery. We further assessed the validity of these subgroups and their longitudinal stability.

Subgroup C differed from the other subgroups by displaying lower scores on wellbeing and higher odds of experiencing subjective cognitive decline. The other two subgroups were highly similar when focusing on external validators. At the second measurement, Subgroup C was again associated with the most vulnerable profile on the external variables. At this occasion, Subgroup A scored higher on two wellbeing measures than Subgroup B. Repeating the subgrouping analysis at the second measurement occasion yielded the same number and character of subgroups, but just 47-62% of participants retained their subgroup membership over time.

Subgroup C, characterized by high levels of social support, was associated with the lowest cognitive and wellbeing profile at T1 and T2, while social support is often seen as a

[2] Although not preregistered, we exploratively calculated two standardized measures of subgroup similarity (see S9.1.5).





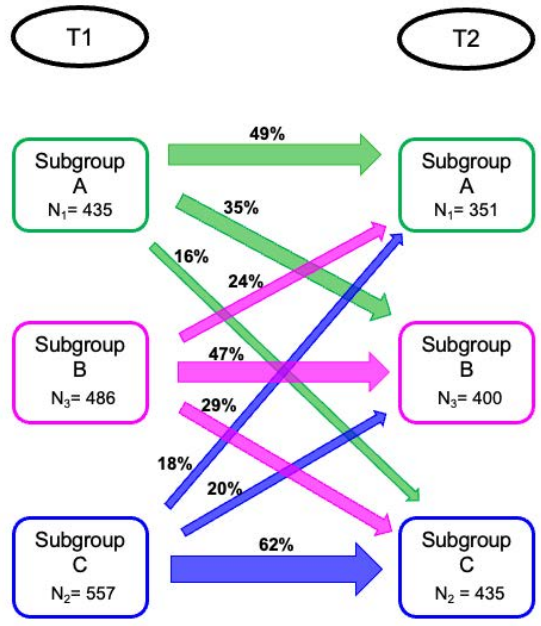


Figure 2.2. Stability of Subgroup Membership from T1 to T2

protective factor for psychological distress (Bøen et al., 2012). The observed low wellbeing and cognitive profile in our study could be explained by necessity of this social support alongside other vulnerabilities adults in this subgroup may experience, such as a low sense of mastery. Since this subgroup also experienced more negative life events, more ADHD symptomatology, and used more medicines, social support may best be seen as a necessity in the face of other vulnerabilities.

Subgroup B, also scoring less favorably on cluster variables (i.e., high number of negative life events), was not associated with a lower wellbeing and memory profile. One explanation for this difference compared to Subgroup C, could be the high sense of mastery experienced by individuals in Subgroup B. If participants in this subgroup feel they are more in control of their lives, they may be more capable to deal with other vulnerabilities, while requiring less social support. This may be associated with a better wellbeing and cognitive profile.

Subgroups seem stable over time, since we identified the same number of subgroups at T2, and subgroup profiles at T1 and T2 were practically identical; although Subgroup B was somewhat less physically active at T2. However, only 47%-62% per subgroup retained their membership at T2. Instability in subgroup memberships over time alongside stable subgroup profiles has been indicated in previous studies using community detection (Blanken et al., 2020; Karalunas et al., 2014). Transitions between subgroups over time are also more likely when modifiable cluster factors are included, as in our study. Future research may address whether these factors can be targeted in (clinical) interventions to ultimately transfer people to a subgroup with a more beneficial outcome

Changes in group membership were primarily driven by changes in negative life events. This may be due to the importance of negative life events, but this variable was also more changeable than other variables because of how it was measured. Participants were asked about negative life events they experienced in the past three years, with three years between measurement occasions, which means that the same negative life events are not counted twice. To illustrate, if a participant experienced the death of a father in the three years prior to T1, this negative life event cannot be experienced again in the three years prior to T2, while for example education is the same between T1 and T2. Therefore, changes in the number of negative life events are more likely than changes in education, and thus are also more likely to drive changes in subgroup membership. Negative life events are perhaps most interesting as they were influential in subgroup membership changes, but may only be indirectly modifiable.

The implication of our results is that aging research should consider investigating these subgroups separately. Broad statements on the relationship between a particular risk





factor, or on a trend of worsening cognitive functioning, may only be true for a third, or two-thirds, of the elderly population. Claiming that a particular result holds for the entire population based on an analysis that does not take into account the individual differences that we explored here may be unnecessarily concerning to those who are unlikely to encounter these problems. Conversely, researchers may be unable to detect effects of certain factors at the level of the population, while the impact may be large within one of the subgroups. In adjusting care, these effects are particularly important, so we do not want these to be overlooked.

Irrespective of the strengths of this study, there are some limitations. Firstly, we asked participants whether they experienced memory complaints ('yes' or 'no'). However, one will have a more comprehensive view of cognitive decline when using a more sensitive measure for subjective cognitive decline like the Cognitive Failures Questionnaire (Broadbent et al., 1982), and/or including a neuropsychological test for objective memory problems. To investigate whether using a neuropsychological test would have changed results, we additionally included data from a verbal learning test (Klaming et al., 2017) to investigate whether subgroups differed in their objective episodic memory as well (not preregistered). They did differ in total recall, both in external validation at the same measurement occasion ($F(2, 1365) = 16.843$, $p < 0.001$)), and in predictive validation at the second measurement occasion, ($F(2, 1123) = 12.632$, $p < 0.001$). Subgroup C again had the worst memory scores. Therefore, the results do not seem to be limited to self-report.

Secondly, while the current attrition rates are congruent with those of other longitudinal studies (Fischer et al., 2001; Young et al., 2006), we cannot exclude the possibility that the drop-out group would form an additional subgroup at T2 when included. Compared to the group that participated at both time points, the drop-out group was older, used more medicines, and had lower fluid intelligence scores. The drop-out group included more participants from the most vulnerable subgroup, associated with the lowest wellbeing and cognitive profile. Therefore, attrition may have been somewhat differential. Thirdly, some might argue that we should have corrected for baseline performance as the majority of the participants belong to the same subgroup at follow-up. However, this is only crucial when one wants to predict change of scores. This was not the central question of the current endeavor, as we were interested whether subgroup differences remained the same at the later measurement occasion. Fourthly, the modularity index indicated weakly defined communities. This has also been reported in other studies using community detection with similar types of data (Blanken et al., 2020; Karalunas et al., 2014). Since community detection and the modularity index are relatively new to psychological research, more methodological research is required into its properties with this type of data.

To our knowledge, the current study was the first to identify community detection-based subgroups in aging by inclusion of modifiable vulnerability and protective factors of aging. The study shows that people differ greatly in modifiable aging factors. Those with a low sense of mastery, high levels of social support, and high number of negative life events also had the lowest wellbeing and memory profile, currently and after three years. However, only a minority of participants belonged to this subgroup. Furthermore, transitions between subgroups are common. Therefore, healthy mental aging may be within reach of many, and even for those at risk, there seems to be considerable potential for improvement.



# Chapter 3

# Finding similarities in differences between autistic adults

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## Abstract

**Purpose**: Autism is heterogeneous, which complicates providing tailored support and future prospects. We aim to identify subgroups in autistic adults with average to high intelligence, to clarify if certain subgroups might need support.

**Methods**: We included 14 questionnaire variables related to aging and/or autism (e.g., demographic, psychological, and lifestyle). Community detection analysis was used for subgroup identification in an original sample of 114 autistic adults with an adulthood diagnosis (Autism) and 58 non-autistic adults as a comparison group (COMP), and a replication sample ($N_{Autism}$ = 261; $N_{COMP}$=287), both aged 30-89 years. Next, we identified subgroups and assessed external validity (for cognitive and psychological difficulties, and quality of life [QoL]) in the autism samples. To test specificity, we repeated the analysis after adding 123 adults with ADHD, aged 30-80 years.

**Results**: As expected, the Autism and COMP groups formed distinct subgroups. Among autistic adults, we identified three subgroups of which two were replicated. One of these subgroups seemed most vulnerable on the cluster variables; this subgroup also reported the most cognitive and psychological difficulties, and lowest QoL. Adding the ADHD group did not alter results.

**Conclusion**: Within autistic adults, one subgroup could especially benefit from support and specialized care, although this must be tested in future studies.






## Introduction

The search for support for people with psychiatric conditions is complicated by interindividual differences in key characteristics, support needs, and prognosis, even between people with the same diagnostic classification. Characteristics of a diagnostic category are not necessarily caused by one specific mechanism (Klahr et al., 2012), and several different combinations of mechanisms may cause the same characteristics (equifinality). Whether differences between people within a diagnostic category are so large that it becomes necessary to establish subgroups for whom different variables are central to experienced challenges and solutions has been debated for decades (Buchanan & Carpenter, 1994; Feczko et al., 2019; Lombardo et al., 2019; Wardenaar & de Jonge, 2013). However, while the overarching category can make sense and subclassifications are not needed for diagnostic purposes, it could be relevant to look for subgroups within a classification to provide better support and more insight in a specific individual's prognosis. In the current study we aim to test whether we can identify such subgroups within the autism spectrum to increase our insight into this heterogeneity to better inform autistic adults and clinicians what being autistic could entail for them. Thus the goal is not to develop new diagnostic categories or to aid the search for a cause of a specific classification, but rather to focus on subgroup identification within an existing diagnostic category that can increase the likelihood of receiving proper support. To reach this goal, we test our results using several validation approaches.

Heterogeneity across those diagnosed with an Autism Spectrum Disorder (ASD) (American Psychiatric Association, 2013) has been widely acknowledged, as large differences exist in the depth, presentation, and causes for the diverse characteristics that define autism (Happé et al., 2006; Masi et al., 2017; Mottron & Bzdok, 2020). Currently, a broad diagnostic label for autism is used in the DSM-5 (American Psychiatric Association, 2013), i.e., Autism Spectrum Disorder, that acknowledges interindividual differences and is more inclusive (Frith & Happé, 2020). The downsides of this broad classification are the difficulty to inform people about the specific prognosis, and there is less guidance in which characteristics are most amenable for providing support

There have been previous studies indicating that subgroups in autism samples can be found, for example in brain structures (H. Chen et al., 2019), inflammation markers (Sacco et al., 2012), and electroencephalography (EEG) (DiStefano et al., 2019). Most of these studies have a fundamentally different goal than the current subgrouping study. These studies inform us about biological differences and are designed to inform about causes and markers. In the long run this might be informative for prognosis, but these studies do not necessarily lead to clinical insights that are directly relevant to support or prognosis. Moreover, previous subgrouping research is often not informative for autistic

adults, because studies (a) mostly focus on children or adolescents, (b) often include small sample sizes, (c) focus on a single outcome, (d) are cross-sectional, and (e) adopt few or no validation or replication techniques. A recent review on subgrouping research in autism indicates that few studies are explicit about when the observed subgroups are considered valid, replicate results in a second sample, or investigate stability of subgroup membership over time (Agelink van Rentergem et al., 2021). Moreover, of the 156 studies included in this review, the majority (89%) focused on children or adolescents, showing a clear need for more research on autistic adults.

Of these studies included in the review, we would like to highlight two studies that identified clinically relevant subgroups in autistic adults. One study identified three subgroups in 180 autistic adults aged 23-60 years using normative outcomes and indicators of quality of life (Bishop-Fitzpatrick et al., 2016). These subgroups differed in their level of dependence (e.g., living independently, semi-independently, or with full-time oversight by staff and/or family), employment status, and physical/mental health. In a different study, five groups were identified in 55 adults with autism and ADHD (mean age 34 years) that differed in employment status, educational level attained, age at diagnosis and need of hospitalization (LaBianca et al., 2018). Although these studies were conducted for different goals, they show that homogeneous subgroups can be identified in autistic adults that are potentially clinically meaningful. However, the replicability and validity of these subgroups were not yet investigated

To increase the likelihood of finding clinically relevant and valid autism subgroups, we took several measures that also distinguish the current study from earlier subgrouping attempts. First, we include multiple self-report measures of autism characteristics and of demographic, psychological, and lifestyle variables as input for our analyses. The variables chosen as input are important for the expected utility of the obtained subgroups. We chose measures based on research literature and discussion with autistic adults, that can be easily administered on a large scale. Also, many of these variables are modifiable in nature. Consequently, we increase the likelihood that our findings will be informative for clinical practice. In addition, these variables are selected based on their relevance to the outcomes of interest (i.e., cognitive difficulties, psychological difficulties, and quality of life (QoL)). Second, for external validation of the observed subgroups, we focus on the aforementioned outcomes as these are important to general aging (Beydoun et al., 2014; S. T. Chen et al., 2014; Goh et al., 2012; Prenderville et al., 2015). Moreover, these variables are clinically relevant and meaningful to autistic adults as well (Howlin & Magiati, 2017). Third, we include two separate samples which together include over 800 adults aged 30 to 89 years to ensure we can perform a direct replication of our results. Fourth, we include both autistic adults and non-autistic adults without ADHD to see whether the observed heterogeneity in autism is distinct from variation we see in





non-autistic adults (i.e., whether the observed variation is better described by diagnostic categories than by a continuum across groups). Fifth, we investigate the specificity of the results to autism by repeating analyses with inclusion of a group of adults with an ADHD diagnosis; a neurodevelopmental condition which has shown strong overlap with autism in characteristics, as is also acknowledged in the DSM-5 (Antshel & Russo, 2019; Lau-Zhu et al., 2019). Thus, we aim to determine whether valid, replicable, and specific autism subgroups can be identified that are informative for potential future support needs as one ages.

## Methods

### Participants

In total, 924 adults participated in this study. Before applying exclusion criteria, the autism group consisted of 509 adults, the comparison (COMP) group of 486 adults and the ADHD group of 124 adults. Please note that we use the term comparison group to indicate non-autistic adults without AD(H)D.

For all groups, we applied the following exclusion criteria: (a) intellectual disability, (b) insufficient understanding of Dutch language required to complete the questionnaires, (c) age lower than 30 years. In the autism group, we only included participants with a clinical DSM-III, DSM-IV of DSM-5 diagnosis of an Autism Spectrum Disorder (American Psychiatric Association, 1987, 2000, 2013). Most of the included autistic adults received their diagnosis relatively late in adulthood (see Table 3.1 for details). For the COMP group, we also excluded participants with (a) a history of more than one psychotic episode, (b) present or past diagnosis of AD(H)D or a score of six or higher on the Dutch version of the ADHD DSM-IV Rating Scale (Kooij et al., 2005), (c) present or past diagnosis of ASD or total score higher than 32 on the Autism Spectrum Quotient (Baron-Cohen et al., 2001), (d) diagnosis of ASD in close family members (i.e., parent(s), child(ren), brother(s), sister(s)), (e) AD(H)D diagnosis in close family members. In the ADHD group, we only included adults with a clinical DSM-IV or DSM-5 diagnosis of AD(H)D and without a clinical ASD diagnosis. All exclusion criteria were checked based on data from self-report questionnaires. Based on the criteria 980 participants could be included (410 Autism, 446 COMP, 124 ADHD). The most prevalent reason for exclusion was a score higher than the cutoff on the ADHD Rating Scale, which only applied to adults in the COMP group (i.e., 40 out of 40 exclusion cases). In total, 843 participant had sufficient data to be included in this study (375 Autism, 345 COMP, 123 ADHD).

We divided our data into two subsets: an original data set of 172 adults and a replication data set of 671 adults (see Table 3.1 for sample characteristics). The original and replication data sets, each with different participants, were collected during two different waves (i.e., Wave 2 and 3) as part of a larger longitudinal study on aging and autism (Chapter 8; Geurts et al., 2021). The original data set (i.e., Cohort 2) was collected during Wave 2, from December 2015 to December 2016. The replication data set (i.e., Cohort 3) was collected during Wave 3, from September 2018 until October 2020.

Part of the sample (346 in total; 165 autism, 148 COMP, 87 ADHD) was tested with two subtests (i.e., Vocabulary and Matrix Reasoning) of the Wechsler Adult Intelligence Scale-IV (WAIS-IV) (Wechsler, 2012). For participants in the autism group, we administered the Autism Diagnostic Observation Schedule - Second Edition (ADOS-2) Module 4 (Lord et al., 2000, 2012).

Autistic and ADHD participants were recruited through mental health institutions in the Netherlands and advertisements placed on client organization websites and social media. COMP participants were recruited via advertisements on social media and within the social environment of the researchers and research assistants of this study. We also consulted our think tank of older/ autistic adults for recruitment strategies.

**Measures**

We included cluster variables considering whether (a) the variable is potentially predictive of cognitive status and/or comorbid psychological difficulties and/or quality of life in autistic adults, (b) there are known individual differences in scores among autistic adults, (c) the variable is easy to measure on a large scale, so it could be implemented in clinical practice, and whether (d) the variable is either directly or indirectly modifiable to ensure clinical applicability. This resulted in 14 cluster variables that were easy to measure and for which at least two of the other aforementioned questions were answered affirmatively. All measures had sufficient psychometric qualities based on the general population, as described below. We tested the psychometric properties for our autism sample, which resulted in acceptable to good internal consistency for most measures (see Supplementary Materials S.9.2.1).

***Cluster variables:***

*Autism characteristics* were measured by the Autism Spectrum Quotient (AQ) (Baron-Cohen et al., 2001; Hoekstra et al., 2008) as AQ scores have previously been related to QoL (Pisula et al., 2015) and scores are diverse among autistic adults. The AQ consists of 50 items rated on a 4-point scale from "definitely agree" to "definitely disagree". The items divide into five subscales with 10 items each. We included subscale scores for





Table 3.1

*Sample characteristics*

| | Autism | COMP | ADHD | Total |
|---|---|---|---|---|
| **Original data** | | | | |
| N | 114 | 58 | - | 172 |
| Sex (M/F) | 72/42 | 33/25 | - | 105/67 |
| Mean (SD; range) | | | | |
| Age | 54.2 (12.1; 31-89) | 56.0 (10.7; 34-79) | - | 54.8 (11.6; 31-89) |
| AQ total | 34.6 (6.8; 14-47) | 12.6 (4.8; 3-24) | - | 27.1 (12.1; 3-47) |
| ADHD Att sum | 10.1 (5.4; 1-25) | 4.2 (3.7; 0-17) | - | 8.1 (5.6; 0-25) |
| ADHD Hyp-Imp sum | 10.6 (6.1; 1-29) | 4.3 (3.7; 0-16) | - | 8.5 (6.2; 0-29) |
| Age of autism diagnosis | 48.0 (12.5;12-81) | - | - | - |
| **Replication data** | | | | |
| N | 261 | 287 | 123[b] | 671 |
| Sex (M/F/Other) | 127/133/1 | 157/130/0 | 74/49/0 | 358/312/1 |
| Mean (SD; range) | | | | |
| Age | 51.2 (12.7; 30-84) | 55.7 (13.9; 30-85) | 51.2 (11.5; 30-80) | 53.1 (13.2; 30-85) |
| AQ total | 34.9 (7.7; 10-48) | 13.6 (5.9; 2-31) | 20.6 (6.8; 6-40) | 23.1 (11.8; 2-48) |
| ADHD Att sum | 12.0 (6.5; 0-30) | 5.4 (3.5; 0-17) | 18.7 (5.8; 2-31) | 10.4 (7.2; 0-33 1) |
| ADHD Hyp-Imp sum | 12.7 (6.3; 0-32) | 6.4 (3.7; 0-23) | 19.0 (6.6; 4-31) | 11.2 (7.2; 0-32) |
| ADOS-2 total[a] | 11.61 (3.6; 4-19) | - | - | - |
| Age of autism diagnosis | 44.9 (13.4; 4-79) | - | - | - |

*Note.* M = male, F = female, AQ total = Autism-Spectrum Quotient total score. ADHD Att sum = ADHD Rating Scale, Attention sum score, ADHD Hyp-Imp sum = ADHD Rating Scale, Hyperactivity Impulsivity sum score, ADOS-2 total = Autism Diagnostic Observation Schedule, Module 4 total score.[a] Sample size is lower for this variable (N=97), since only a subset of participants was administered the ADOS-2. [b] We only included adults with ADHD in the replication data set, because the ADHD data was collected congruently with the replication data.

Social Skills, Attention Switching, Attention to Detail, Communication and Imagination which can vary between 0 and 10 (Baron-Cohen et al., 2001). The internal consistency of the AQ is acceptable with Cronbach's alpha ranging between .63 and .77 for subscale scores (Baron-Cohen et al., 2001; Hoekstra et al., 2008).

*Educational level* was measured by asking participants about the highest educational-degree they obtained, as lower educational attainment is related to memory problems when aging (Beydoun et al., 2014), and there are differences in educational level among autistic adults (Frank et al., 2018). We used the Dutch Verhage scale to classify the educational level (Verhage, 1964). This scale consists of seven categories that range between 1 (i.e., less than six years of primary education) and 7 (i.e., university degree).

*Mastery* —the extent to which we see ourselves as being in control of factors that affect our lives— was assessed with the Pearlin Mastery Scale (Pearlin et al., 1981). Mastery plays a central role in connecting autism traits and depressive symptoms (van Heijst et al., 2020), and autistic adults experience different levels of mastery (Nguyen et al., 2020). The scale consists of seven items rated on a five-point scale from "strongly disagree" to "strongly agree". We calculated a sum score ranging between 7 (low sense of mastery) and 35 (high sense of mastery). This instrument has a reasonable to high reliability with Cronbach's $\alpha$ between 0.67 and 0.80 (Penninx et al., 1997; Peterson, 1999).

*Worries/Fears:* We used a combination of the Worry Scale (Wisocki et al., 1986) and Fear Questionnaire (Marks & Mathews, 1979). Autism and depression are connected through worry symptoms (van Heijst et al., 2020), and autistic adults experience different levels of worries. This questionnaire includes 15 items that are rated on a five-point scale from "never worries me" to "worries me much of the time". We calculated a total score ranging between 15 (low worries/fears) and 75 (high worries/fears). This instrument has a good internal consistency and test-retest reliability (van der Veen et al., 2014).

*Physical Activity:* We used the International Physical Activity Questionnaire (IPAQ) to measure the amount of physical activity (Craig et al., 2003). Physical activity is an important predictor of QoL in autistic adults and differences exist in the physical activity level of autistic adults (Conn et al., 2011; Hamm & Yun, 2019). The IPAQ includes items about the total time spent in four physical activity domains (i.e., occupational, transport, household and leisure-related physical activity). Physical activities included walking, moderate and vigorous activities for at least 10 consecutive minutes. We calculated the total amount of time (in minutes) during which a participant was physically active during the past seven days. The IPAQ has a good test-retest reliability (Spearman correlation coefficients around 0.80) (Craig et al., 2003).





*Negative life events:* We used the List of Threatening Experiences to measure the number of negative life events in the past year (Brugha et al., 1985), as this number varies between autistic adults and they form a risk for psychological difficulties and lower QoL (Bishop-Fitzpatrick et al., 2017; Rumball et al., 2020). Participants were asked to report whether they experienced any of 12 different life events (e.g., death of a close family member or becoming unemployed). We calculated a sum score ranging between 0 (no threatening life events experienced) to 12 (many threatening life events). The questionnaire has a high test-retest reliability (Brugha & Cragg, 1990).

*Emotional support:* The Close Persons Questionnaire (CPQ) measures the amount of emotional support received (Stansfeld & Marmot, 1992), which is a predictor of QoL (Khanna et al., 2014; Mason et al., 2018) and levels of emotional support differ among autistic adults (Alvarez-Fernandez et al., 2017). The CPQ includes questions about one's social network and quality of support representing different categories of support (i.e., informational, emotional, practical, and appraisal). Items are rated on a five-point scale from "never" to "very often". We calculated a sum score based on 12 items related to emotional support, ranging between 12 and 60. Higher scores indicate higher levels of received emotional support. The four subscales show moderate to good reliability (Hanssen et al., 2019).

*Sensory sensitivity:* The Sensory Sensitivity Questionnaire (SSQ) measures the amount of sensory sensitivity (Lever & Geurts, 2013; Minshew & Hobson, 2008), as sensory sensitivities are related to anxiety levels (Syu & Lin, 2018) and autistic adults report different levels of sensory sensitivity (Kuiper et al., 2019). For each of the 13 items, participants indicated whether they experienced the specific sensory sensitivity (i.e., yes or no). We calculated a sum score between 0 and 13. Higher scores indicate a higher sensory sensitivity level. The Dutch version of the SSQ has an acceptable to good reliability, Cronbach's $\alpha$=.77 (Lever & Geurts, 2013).

*Positive and negative affect:* We administered the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988), as negative affect and affective instability have been linked to depression in autistic adults, and scores on affect are diverse among autistic adults (Dallman et al., 2021). Positive Affect (PA) represents the extent to which we feel enthusiastic, alert, and active. Negative Affect (NA) represents subjective distress encompassing a variety of aversive mood states (e.g., fear, anger, disgust). The scale consists of 20 feelings or emotions (i.e., 10 measuring PA and 10 measuring NA) that are rated on a five-point scale from "very slightly or not at all" to "extremely". We calculated subscale scores for PA and NA ranging between 10 and 50. The subscales have a high reliability (Watson et al., 1988).

***Variables for external validation***

We compared the obtained subgroups on cognitive difficulties, psychological difficulties and QoL.

*Cognitive difficulties:* The Cognitive Failures Questionnaire (Broadbent et al., 1982) is a valid and reliable questionnaire to measure the amount of cognitive difficulties (vom Hofe et al., 1998). This questionnaire consists of 25 items rated on a five-point scale from "never" to "very often". The total score ranges between 0 and 100; higher scores indicate more cognitive difficulties. The questionnaire has a good test-retest reliability (Bridger et al., 2013).

*Psychological difficulties:* We used the Symptom Checklist-90-Revised (SCL-90-R) to measure psychological difficulties (Derogatis, 1977). The SCL-90-R consists of 90 items that are rated on a five-point scale. We calculated the total score and scores on nine subscales (i.e., agoraphobia, anxiety, depression, somatization, cognitive performance deficits, interpersonal sensitivity, hostility, sleep difficulties and items not included in any specific factor). A higher score is indicative of more psychological difficulties. The Dutch version of the SCL-90-R has a high reliability (Smits et al., 2015).

*Quality of life:* The World Health Organization Quality of Life Questionnaire-BREF (WHOQoL-BREF) was used to measure QoL (THE WHOQOL GROUP, 1998). This questionnaire has 26 items rated on a five-point scale indicating how someone has felt during the past two weeks. We calculated scores on four subscales (i.e., physical health, psychological, social relationships and environment). Higher scores indicate a higher quality of life. The instrument has good psychometric properties (McConachie et al., 2018).

**Procedure**

For the precise procedure we refer to the published protocol (Chapter 8; Geurts et al., 2021). In short, interested participants were contacted via telephone, e-mail, or written letters. After obtaining written informed consent participants first filled out two sets of questionnaires either online or on paper depending on the participant's preference. Participants required around two hours to complete the questionnaires. Second, a subset of participants was interviewed either online or in person (including questions regarding psychotropic medication use and depending on one's diagnostic category, the ADOS-2) and tested (e.g., shortened WAIS-IV). Neuropsychological testing was also part of the procedure for a subset of participants, but those data were not included here. Participants received €7,50 for filling out the questionnaires and €10,00 for the interview/test session. They also received a maximum of €20,00 for their travel expenses. This study





was approved by the local ethical review board of the department of Psychology of the University of Amsterdam (Wave 2: 2015-BC-4270 and Wave 3: 2018-BC-9285).

**Statistical Analyses**

All analyses were conducted in RStudio version 1.3.1073 (RStudio Team, 2020), using the R-package igraph for subgroup identification (Csardi & Nepusz, 2006). The analysis plans for the original and replication data were preregistered at AsPredicted.org and included in Chapter 8 (AsPredicted #29596 and #34234).

***(1) Missing data***

Within a questionnaire specific items can be missing. At the item level, we considered 10% of missing data per participant appropriate for imputation (Bennett, 2001). The type of imputation depended on the specific measurement instrument. For mastery, autism characteristics, sensory sensitivity, worries/fears, positive and negative affect, and emotional support, we recoded a maximum of 10% of missing values to the median of the participant's other responses on this specific questionnaire. For negative life events and physical activity, we recoded a maximum of 10% of missing values to zero, implying the absence of a negative life event or the absence of a specific physical activity. We did not impute missing values on education. A full questionnaire might also be missing. At the instrument level, participants with no more than one missing value were included and such missing values were not imputed. Hence, for each included individual we had information on at least 13 cluster variables.

***(2) Community detection analysis***

For the community detection analyses, we first transformed scores on all cluster variables to *z*-scores, such that differences in measurement scales of the instruments would not influence the subgrouping results. Please note that this did not involve a normalizing z-transformation, hence the distribution of scores was not impacted by this transformation. We then created a pairwise Pearson correlation matrix, including person-to-person relationships between all pairs of participants in the study sample. A high correlation in this matrix indicates that two participants have similar scoring patterns on the cluster variables (Karalunas et al., 2014).

In the resulting network each node represents a participant and the edges connecting the nodes represent the correlations between scoring patterns of pairs of adults. We aimed to identify communities (or subgroups), which are locally dense connected subgraphs in the larger network (Barabási & Pósfai, 2016). Participants (i.e., nodes) belonging to a community have a higher probability of connecting to other members of that community than to participants of a different community. Different algorithms can be used for a

community detection analysis. The Spinglass algorithm (Reichardt & Bornholdt, 2006) was preferred over others (Chapter 2; Radhoe et al., 2021), because, amongst other things, this algorithm is able to deal with weighted egdes (in this case, correlations). Moreover, it takes both positive and negative correlations into account, which is important since we aimed to avoid inclusion of dissimilar participants (i.e., with opposite scoring patterns) in the same community. Also, with the Spinglass algorithm each participant is assigned to a single community. This ensures that the resulting communities could eventually become informative for clinical practice, where autistic adults could be aided to transfer from one community to another (possibly more favorable) community. The gamma-parameter was set to 1.0 to assign equal importance to present and non-present edges between adults.

In addition to the preregistered analyses, the modularity index *Q* was calculated quantifying the quality of the assignment of participants into communities (Newman & Girvan, 2004). The *Q*-index indicates the differences between (a) the true connections in a network, and (b) the connections that would be expected if the network was randomly wired (Barabási & Pósfai, 2016). Positive *Q*-values suggest that there are more connections than would be expected by chance, representing a potential community structure. A *Q*-value of 0 implies that the connections between nodes are completely random, and negative *Q*-values suggest that the nodes do not form a community. Higher *Q*-values indicate a stronger community structure. In practice, *Q* ranges from 0.3 to 0.7, with a maximum value of 1.

***(3) Direct replication and specificity***

We performed the community detection analysis in different steps. First, we performed the community detection analysis using the original data set (i.e., autism and COMP). Second, a direct replication of our community detection analysis was conducted using the replication data set containing an independent group of autistic and COMP participants. As subgrouping techniques — including community detection — are potentially susceptible to over-fitting and generalization issues, it is important to validate the results using a larger replication sample (Bubeck & von Luxburg, 2007; Horne et al., 2020). The goal was to determine whether the same subgroups could be identified in a second sample, which would support the subgroups' validity. Third, the analyses on the replication data set were repeated while also including participants with ADHD to test the specificity of the observed findings. The subgrouping solution was considered specific for autism if not all participants with ADHD were allocated to the same subgroup as autistic participants, i.e., ADHD participants would form a separate subgroup or participants with ADHD would be allocated to the COMP subgroup.





***(4) External validation***

Subgroups were compared on variables not included in the community detection analyses to determine the validity of the subgrouping results. We considered the results meaningful if the identified subgroups differed significantly on the external variables.

First, an ANOVA or *t*-test (depending on the number of identified subgroups) was used to assess whether the subgroups differ in their experience of cognitive difficulties. Second, we used ten ANOVA's or *t*-tests to assess whether the subgroups differ in reported psychological difficulties (i.e., SCL-90-R total score, and nine subscale scores). Third, differences in QoL between the identified subgroups were assessed with four ANOVA's or *t*-tests. In addition to our preregistered analyses, we performed two MANOVA's with subscale scores as dependent variables for QoL and psychological difficulties. To correct for multiple testing, we divided our threshold for significance by ten, and thus used $p < 0.005$ as the threshold for statistical significance.

**Community involvement**

For this study, and our overall study on aging in autism (Chapter 8; Geurts et al., 2021), we worked together with a group of four older/ autistic adults, also referred to as the "think tank". We met at least three times a year (either online or in person) to discuss, among other things, recruitment strategies, information letters and the interpretation of study results. For this specific study, the think tank also made suggestions for the interpretations of the subgroup findings and decided the naming of the obtained subgroups during two online meetings. The members were paid for their contribution.

## Results

After checking the exclusion criteria and dealing with missing data, the original data set included 172 adults (114 autism, 58 COMP). The replication data set included 671 adults (261 autism, 287 COMP, 123 ADHD). Although there is no formal way of establishing the required sample size for community detection yet, the present sample size seems sufficiently large given (a) simulations described in Chapter 8 (Geurts et al., 2021) and Agelink van Rentergem et al. (2022), and (b) previous studies adopting a community detection approach including similar sample sizes (Blanken et al., 2020; Karalunas et al., 2014; Mostert et al., 2018). The amount of missing data (a) in total, and (b) per cluster variable is described in S.9.2.2. A correlation matrix of the cluster variables can be found in S.9.2.3. The distribution of scores on the cluster variables for the autism and

COMP groups based on the replication data are provided in S.9.2.4.

**Autistic and non-autistic adults form separate subgroups**

We identified two subgroups ($Q$ = 0.41). The subgroups correspond to Autism and COMP as one subgroup (N=81) mainly included COMP participants (i.e., 70%), whereas the other (N=91) mainly included autistic adults (i.e., 99%). Subgroup profiles on the cluster variables are depicted in S.9.2.5. In line with our preregistration, we followed this result up with a separate community detection analysis for the autism group to gain more insight into the heterogeneity within autism.

**Autistic adults form three separate subgroups**

Three distinct autism subgroups were identified ($Q$ = 0.30). Figure 3.1 Panel A depicts subgroup profiles on the cluster variables in the original data. After consulting with our older/autistic think tank, the labels of the subgroups were based on the cluster variables on which the subgroups differed significantly. The first subgroup ($N_1$=49, 43%) was characterized by the highest educational level, highest scores on social skills and communication (i.e., low scores on AQ subscales), highest sense of mastery (i.e., feeling of being in control and having a grip on what is happening in your life) and highest level of positive affect. Our think tank suggested the term "*Feelings of high grip*" (HighGr) for this subgroup, to indicate that people in this subgroup experience more control over what happens in their life, which also corresponds to the higher social skills, positive affect and lower worries these autistic adults report.

The second subgroup ($N_2$=48, 42%) differed from the other subgroups on social domains, mastery, worry, support and affect. This subgroup was characterized by the lowest scores on attention switching, lowest sense of mastery, and highest levels of worries and negative affect. The term "*Feelings of low grip*" (LowGr) was suggested by the think tank, as adults in this subgroup reported less control over what happens in their life, reflected by lower scores on mastery, the social domain, positive affect, and higher scores on worries and negative affect. We labeled the third subgroup ($N_3$=17, 15%) as the "*Feelings of medium grip with high physical activity*" (MediumGr) subgroup. Participants in this subgroup were characterized by the lowest level of education, low scores on communication and social skills, average level of mastery, and the highest level of physical activity.

**Direct replication of separate subgroups autistic and non-autistic adults**

Combining the data of participants with and without autism again resulted in two larger subgroups (and a third subgroup consisting of one person) ($Q$ = 0.43, which is comparable to the $Q$-value found in the original data set). After excluding the third subgroup consisting of one person, the $Q$-value remained similar, i.e., $Q$ = 0.43. Moreover, we replicated the finding that the two remaining subgroups mainly indicated a distinction between Autism and COMP as one subgroup (N=265) mostly included autistic adults (90%), whereas the other subgroup (N=282) mostly included COMP participants (92%) (Figure 3.2, Panel A). As preregistered, we again performed a separate community detection analyses for the autism group to gain insight into the heterogeneity within this group.

**Direct replication of two out of three subgroups of autistic adults**

We replicated our findings by identifying three distinct autism subgroups ($Q$ = 0.28, which is similar to the $Q$-value found in the original data set). However, subgroup profiles of only two out of three subgroups were similar to those obtained in the original data. Subgroup profiles are depicted in Figure 3.1 Panel B. We again identified a "*Feelings of high grip*" subgroup ($N_1$=124, 47%) that was characterized by the highest scores on social skills, attention switching, communication, and positive affect. The "*Feelings of low grip*" subgroup ($N_2$=130, 50%) was also replicated, characterized by the lowest sense of mastery and highest level of negative affect. The third subgroup ($N_3$=7, 3%) was characterized by the highest educational level. The profile of this subgroup did not resemble the third profile identified in the original data set; i.e., we did not replicate the "*Feelings of medium grip with high physical activity*" subgroup. Also, only seven autistic adults were included in this subgroup. Therefore, we did not consider this a separate subgroup and did not include this subgroup in further analyses in the manuscript. Nonetheless, as all group comparisons were preregistered, results (including descriptive statistics) regarding this Rest-subgroup are included in S.9.2.6, but should not be used to draw conclusions about the Rest-subgroup (Stevens, 1996). In addition, we recalculated the modularity index by excluding participants in the third subgroup, which hardly changed the strength of the community structure (i.e., $Q_{old}$ = 0.28 and $Qnew$ = 0.29).

Table 3.2 presents test statistics for differences between the two main autism subgroups. Because test statistics are describing the group differences rather than testing hypotheses, we did not correct these values for multiple testing. The subgroups differed on 11 out of 14 cluster variables, but not on level of education. The subgroups did not differ in age, sex, or IQ, suggesting that subgroup differences were not driven by demographic or IQ differences.

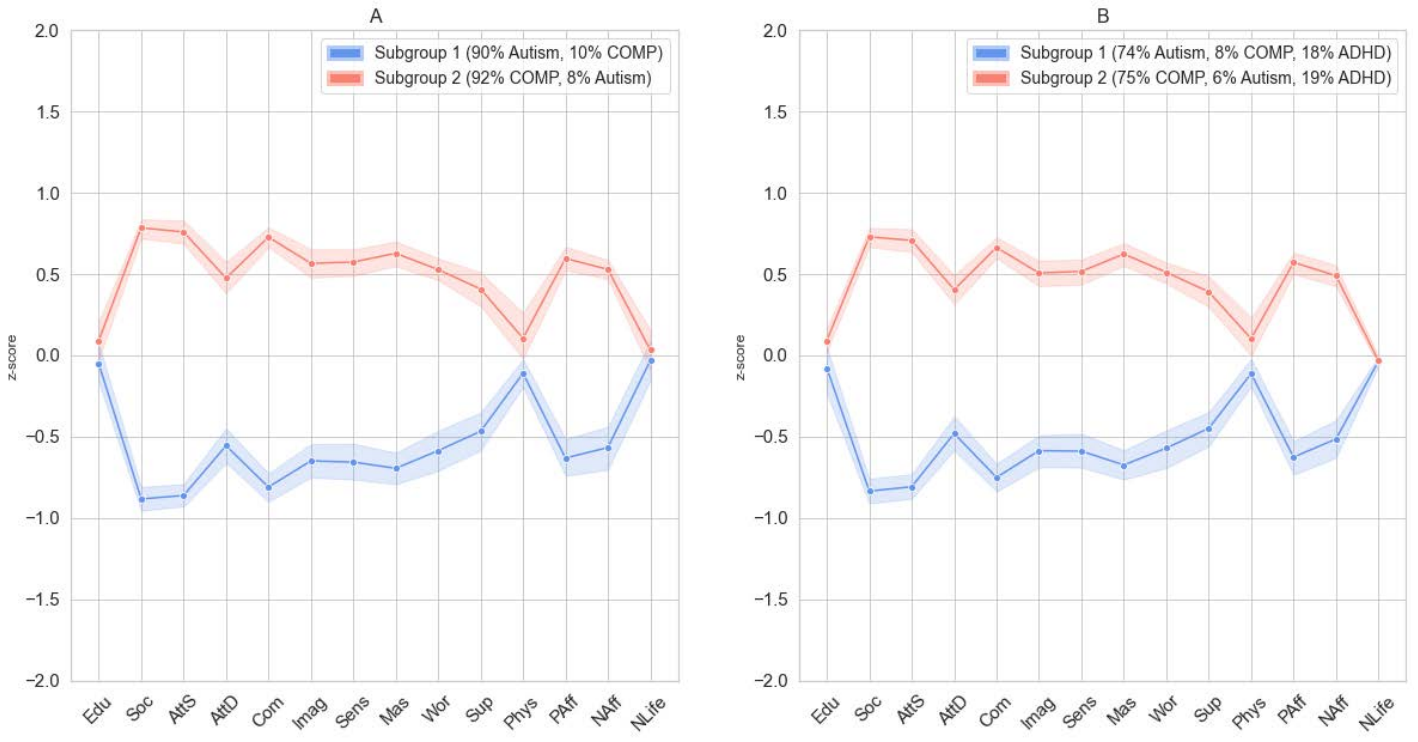


*Figure 3.2.* A. Subgroup profiles based on data from the Autism and COMP groups for each of the two community detection-based subgroups formed on replication data. B. Subgroup profiles based on data from the Autism, COMP, and ADHD groups for each of the two community detection-based subgroups formed on replication data.

*Note*. COMP = comparison. Edu = education, Soc = social skills, AttS = attention switching, AttD = attention to detail, Com = communication, Imag = imagination, Sens = sensory sensitivity, Mas = mastery, Wor = worry, Sup = emotional support, Phys = physical activity, PAff = positive affect, NAff = negative affect, NLife = negative life events. Higher z-scores represent higher scores on Edu, Soc, AttS, AttD, Com, Imag, Mas, Sup, Phys, PAff. Higher z-scores represent better scores on Sens, Wor, Naff, NLife (less sensitivity, less worrying, less negative affect, fewer negative life events). Shaded area represents 95%-confidence interval.

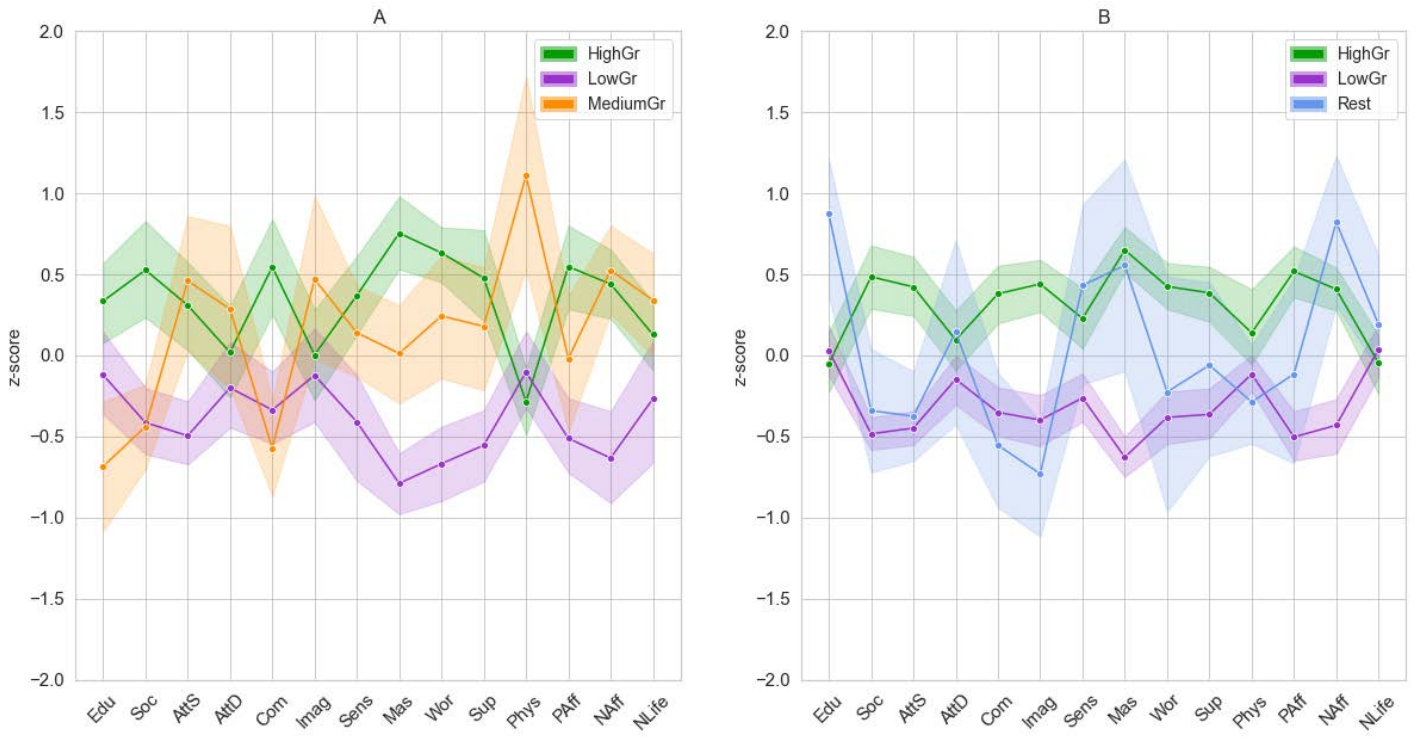


*Figure 3.1.* A. Three autism subgroup profiles based on original data. B. Three autism subgroup profiles based on replication data.

*Note*. HighGr = Feelings of High Grip, LowGr = Feelings of Low Grip, MediumGr = Feelings of Medium Grip with high physical activity. COMP = comparison. Edu = education, Soc = social skills, AttS = attention switching, AttD = attention to detail, Com = communication, Imag = imagination, Sens = sensory sensitivity, Mas = mastery, Wor = worry, Sup = emotional support, Phys = physical activity, PAff = positive affect, NAff = negative affect, NLife = negative life events. Higher z-scores represent higher scores on Edu, Soc, AttS, AttD, Com, Imag, Mas, Sup, Phys, PAff. Higher z-scores represent better scores on Sens, Wor, Naff, NLife (less sensitivity, less worrying, less negative affect, fewer negative life events). Shaded area represents 95%-confidence interval. Since we did not replicate the MediumGr subgroup in the replication data, we labeled the remaining subgroup of N=7 adults as “Rest” in panel B.

Table 3.2
*Raw cluster variable scores and descriptives for the two major autism subgroups formed on replication data (N=254).*

| | **Subgroup** | | | |
|---|---|---|---|---|
| | HighGr | LowGr | | |
| Variable | N = 124<br>*M (SD);* range | N = 130<br>*M (SD);* range | test statistic | Effect size ($\eta^2$) |
| **Cluster variables** | | | | |
| Education[a] | 5.9 (0.9); 2-7 | 6.0 (0.8); 3-7 | $F(1, 249) = 0.4$ | <0.01 |
| AQ social skill | 6.4 (2.5); 0-10 | 8.6 (1.4); 4-10 | $F(1, 252) = 77.6$*** | 0.24 |
| AQ attention switching | 6.9 (2.2); 0-10 | 8.7 (1.3); 4-10 | $F(1, 252) = 61.7$*** | 0.20 |
| AQ attention to detail | 6.4 (2.4); 0-10 | 7.0 (2.0); 2-10 | $F(1, 252) = 3.9$ | 0.02 |
| AQ communication | 5.9 (2.3); 1-10 | 7.6 (1.9); 0-10 | $F(1, 252) = 38.4$*** | 0.13 |
| AQ imagination | 5.0 (2.0); 1-10 | 6.8 (2.0); 1-10 | $F(1, 252) = 55.0$*** | 0.18 |
| Sensory sensitivity | 6.5 (2.8); 0-13 | 7.8 (2.3); 1-13 | $F(1, 247) = 15.6$*** | 0.06 |
| Mastery | 23.2 (4.3); 14-35 | 16.5 (3.8); 7-25 | $F(1, 251) = 172.6$*** | 0.41 |
| Worry | 29.0 (9.6); 15-64 | 38.4 (11.3); 20-69 | $F(1, 252) = 50.5$*** | 0.17 |
| Emotional support | 33.1 (10.7); 12-53 | 24.8 (10.1); 12-54 | $F(1, 245) = 40.0$*** | 0.14 |
| Physical activity[b] | 1314.8 (2028.1); 0-18050 | 908.8 (1022.0); 0-5010 | $F(1, 247) = 4.0$* | 0.02 |
| Positive affect | 32.5 (6.4); 19-49 | 25.0 (6.2); 10-42 | $F(1, 252) = 88.5$*** | 0.26 |
| Negative affect | 18.4 (6.7); 10-40 | 25.5 (8.4); 10-45 | $F(1, 252) = 54.4$*** | 0.18 |
| Negative life events | 0.8 (1.1); 0-5 | 0.7 (1.0); 0-5 | $F(1, 249) = 0.5$ | <0.01 |
| **Descriptive variables** | | | | |
| Age *M*(*SD*), range | 50.6 (13.8), 30-81 | 51.3 (11.6), 30-84 | $F(1, 252) = 0.21$ | <0.01 |
| Biological sex[c] | | | $c^2(2) = 3.0$ | |
| % male | 53 | 44 | | |
| % female | 47 | 55 | | |
| IQ score[d] | 116.7 (17.2) | 113.4 (15.3) | $F(1, 92) = 1.0$ | 0.01 |

*Note.* AQ = Autism-Spectrum Quotient. HighGr = Feelings of high grip. LowGr = Feelings of low grip.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.
[a] Dutch Verhage scale was used to classify the educational level. [b] Physical activity is measured in minutes. [c] The remaining percentage was classified as "other". [d] Sample size (N=165) is lower for this variable because data are only available for participants who completed the interview. Please note that we did not ask participants about race/ethnicity and socioeconomic status, but the majority of the participants was White and had a high educational attainment.

Table 3.3
*External validation measures for the two major autism subgroups based on replication data (N=254).*

| | Subgroup | | | |
|---|---|---|---|---|
| | HighGr N=124 (47%) | LowGr N=130 (50%) | | |
| **Variable** | ***M*(*SD*); range** | ***M*(*SD*); range** | **Test statistic** | **Effect size ($\eta^2$)** |
| Cognitive difficulties | 43.1 (14.8); 12-90 | 51. 8 (13.8); 17-88 | $F(1, 252) = 19.5$* | 0.07 |
| SCL-90 total score | 149.4 (41.0); 93-337 | 199.3 (52.5); 95-397 | $F(1, 249) = 70.3$* | 0.22 |
| SCL-90 anxiety | 15.9 (5.8); 10-43 | 21.6 (7.7); 10-48 | $F(1, 251) = 42.9$* | 0.15 |
| SCL-90 agoraphobia | 9.3 (3.1); 7-24 | 12.9 (5.1); 7-34 | $F(1, 251) = 45.1$* | 0.15 |
| SCL-90 depression | 28.0 (9.1); 16-61 | 40.6 (13.1); 16-76 | $F(1, 251) = 78.3$* | 0.24 |
| SCL-90 somatization | 19.2 (6.6); 12-47 | 22.5 (7.7); 12-51 | $F(1, 249) = 13.3$* | 0.05 |
| SCL-90 cognitive performance deficits | 18.0 (6.2); 9-41 | 23.6 (6.8); 9-41 | $F(1, 251) = 45.8$* | 0.15 |
| SCL-90 interpersonal sensitivity | 30.0 (10.0); 18-80 | 41.1 (13.0); 19-79 | $F(1, 250) = 58.2$* | 0.19 |
| SCL-90 hostility | 8.7 (3.3); 6-29 | 10.4 (4.0); 6-28 | $F(1, 251) = 13.5$* | 0.05 |
| SCL-90 sleep difficulties | 6.6 (2.9); 3-14 | 8.5 (3.5); 3-15 | $F(1, 251) = 22.3$* | 0.08 |
| SCL-90 rest | 13.8 (4.7); 9-40 | 17.7 (5.5); 9-34 | $F(1, 251) = 37.2$* | 0.13 |
| QoL Physical health | 14.3 (2.6); 7-19 | 12.1 (2.6); 6-20 | $F(1, 250) = 45.0$* | 0.15 |
| QoL Psychological | 13.4 (2.3); 9-20 | 10.8 (2.4); 5-19 | $F(1, 251) = 81.0$* | 0.24 |
| QoL Social relationships | 12.9 (2.8); 7-20 | 10.7 (3.2); 4-19 | $F(1, 252) = 34.4$* | 0.12 |
| QoL Environment | 15.8 (2.1); 11-20 | 14.1 (2.4); 8-19 | $F(1, 251) = 38.9$* | 0.13 |
| **Multivariate analyses**[a] | | | | |
| SCL-90 | | | $F(9, 241) = 10.8$[b] | |
| QoL | | | $F(4, 246) = 22.8$[b] | |

*Note.* HighGr = Feelings of high grip. LowGr = Feelings of low grip. SCL-90 = Symptom Checklist. QoL = World Health Organization Quality of Life Questionnaire-BREF.
* $p < 0.005$. [a] Wilks' Lambda. [b] $p < 0.05$



**Two replicated autism subgroups differ on all external validators**

External validation results for the original data are presented in S.9.2.7. The LowGr subgroup indicated significantly more cognitive difficulties and more psychological difficulties when compared to the HighGr subgroup. The LowGr subgroup also scored significantly lower on all measures of QoL.

**Replication of external validation: LowGr subgroup scores less favorable on all external validators**

External validation results are presented in Table 3.3 (and results including the smaller third autism subgroup are presented in S.9.2.8), and are similar to the results obtained from the original data set. The LowGr subgroup again reported significantly more cognitive difficulties than the HighGr subgroup. Moreover, this LowGr subgroup scored significantly higher on all measures of psychological difficulties, and significantly lower on all measures of QoL.

**Testing specificity: Addition of ADHD group does not alter subgrouping solution**

After adding a group of adults with an ADHD diagnosis to investigate specificity, we again detected two subgroups ($Q = 0.42$). Once more a distinction was found between the Autism group and COMP group, as the first subgroup ($N_1$=321) mostly included autistic adults (239/321, 74%) and the second subgroup ($N_2$=346) mostly included non-autistic adults (261/346, 75%). The ADHD group was almost equally distributed among these two subgroups, as 57 (47%) adults with ADHD belonged to the first subgroup and 64 (53%) adults with ADHD belonged to the second subgroup. Inspection of subgroup profiles (Figure 2, Panel B) indicated that the two identified subgroups are identical to the two identified subgroups when adults with ADHD were not included (Figure 3.2, Panel A). Thus, addition of an ADHD group did not alter the earlier observed subgrouping solution.

# Discussion

In this study, we identified subgroups in adults with autism or ADHD, and comparison participants using self-report measures of autism characteristics, and demographic, psychological, and lifestyle variables. Community detection analysis based on data from comparison participants and autistic adults indicated two distinct subgroups: one of comparison adults and one of autistic adults. We replicated these subgroups in a second data set. This indicates that the variation in variables as diverse as education, negative life events, and mastery, is better described by diagnostic category than by continuous variation across people (Abu-Akel et al., 2019; Frazier et al., 2010). When we added ADHD adults to this second data set, half of them grouped together with the Autism subgroup, and half with the COMP subgroup. Community detection analysis of just autistic adults indicated three subgroups: (a) "*Feelings of high grip*", (b) "*Feelings of low grip*", and (c) "*Feelings of medium grip with high physical activity*". Subgroups were particularly distinct in feelings of grip (i.e., mastery), the social domain, and affect. We replicated the profiles of the first two subgroups in our replication data set, and showed that these subgroups differed on the external validators: cognitive difficulties, psychological difficulties, and QoL.

The two autism subgroups we identified and replicated were distinct on most cluster variables. Therefore, it seems that a variety of factors —i.e., not only variables related to self-reported autism characteristics— cause the distinction between subgroups. The "*Feelings of low grip*" subgroup was characterized by a more vulnerable profile on the cluster variables; low scores on the social domain, lowest sense of mastery (i.e., experienced grip on life), and highest level of negative affect. This was also indicated by the external validation, as this subgroup reported more cognitive difficulties, more psychological difficulties and a lower QoL compared to the "*Feelings of high grip*" subgroup.

We replicated two out of three autism subgroups. The third "rest" subgroup that did not replicate only included seven adults in our replication data set. We consider this subgroup an artifact of the Spinglass community detection method, rather than a distinct and valid subgroup. Subgrouping techniques, including community detection, are known for over-fitting or failing to generalize (Bubeck & von Luxburg, 2007; Horne et al., 2020). Consequently, it is worrying how validating one's results in a separate sample is often not included in subgrouping studies in the autism research field (Agelink van Rentergem et al., 2021). The findings of the current study emphasize the importance of a direct replication: Without this validation procedure, we would not have known that this rest subgroup was not a valid subgroup and we could have overinterpreted the findings in the original data set.





The results on the specificity to autism were somewhat inconclusive. We had anticipated several possible results: had adults with ADHD been similar to comparison participants or formed their own subgroup, this would have suggested specificity of the autism subgroup; had they been similar to autistic adults, this would have suggested nonspecificity of the autism subgroup. However, the adults with ADHD were divided equally across both subgroups. One possible explanation for our findings may be related to an overarching condition perspective of autism and ADHD (van der Meer et al., 2012): Those with the fewest ADHD characteristics are indistinguishable from comparison participants, and those with the most ADHD characteristics are indistinguishable from autistic adults. However, critical examination of our inclusion criteria is also warranted. Autistic adults were allowed to have a comorbid ADHD diagnosis, and 20% of our autism sample did. The ADHD group was not screened for reporting too many autism characteristics on the AQ. Therefore, some overlap between ADHD and the other two categories may have been rooted in the design.

The finding that the Autism and COMP subgroups did not differ on education level was unexpected, since the literature often shows that autistic adults attain a lower education level than non-autistic adults (Anderson et al., 2017; Shattuck et al., 2012). There are several possible explanations for this result: (a) we did not include any participants with a diagnosis of intellectual disability, (b) most of the adults in the autism group received a late ASD diagnosis (i.e., 94% in original data and 97% in replication data was diagnosed after age of 18 years), so the included autistic adults might not have encountered as many problems during their education as compared to people diagnosed in childhood, or might have been able to compensate for their difficulties (Livingston et al., 2020), and (c) highly educated people are more likely to participate in scientific studies (Reinwand et al., 2015; Viken et al., 2019).

It is important to consider the representativeness of our autism sample when interpreting our findings. First, autistic participants were selected based on diagnosis rather than ADOS or AQ-scores. Such scores are snapshots of the full behavioral profile and the scores that we report were not obtained throughout the diagnostic process. Hence, we consider it important for the inclusion criteria to follow the clinical diagnosis given the purpose of the current study. Second, most of the adults in the autism group received a late ASD diagnosis. Our knowledge of autism in adulthood is expanding so we are increasingly able to recognize the presentation of autism characteristics in this age group. Nonetheless, we need to be aware that these results may not be generalizable to autistic adults diagnosed in childhood. As indicated by a recent study, there may be differences between autistic adults diagnosed in adulthood and those diagnosed in childhood, especially in co-occurring psychiatric conditions (Jadav & Bal, 2022). Third, our sample was a blend of adults recruited from the community and from mental health

institutions. This recruitment strategy was adopted to ensure an accurate representation of the diverse population of autistic adults. Fourth, we only included autistic adults with average to high intelligence. Inclusion of autistic adults with an intellectual disability (ID) would have likely resulted in two autism subgroups: one subgroup with ID and one subgroup without ID. This implies that our subgroup analysis would merely reflect subgroups across intellectual ability, rather than capturing the heterogeneity across demographic, psychological, and lifestyle factors. Thus, given the goal of the current study, we chose to exclude adults with an ID. Hence, our results are probably not generalizable to autistic adults with an intellectual disability.

Moreover, it should be noted that 12% of participants in the original data set and 6% in the replication data set were excluded due to missing data. Missing data mostly occurred on instruments measuring emotional support, physical activity and negative life events. The questionnaire measuring emotional support (Stansfeld & Marmot, 1992), was administered last in the questionnaire booklets, and may have been skipped more frequently by participants. To measure physical activity, a questionnaire was used that is relatively more demanding to fill out. For different types of physical activity, the participants had to indicate how much time (in minutes) they spent on a specific physical activity, which is relatively more challenging than the other questionnaires. Nonetheless, this measure has been validated in previous research (Craig et al., 2003). Moreover, the questionnaires for physical activity and negative life events both include retrospective questions, that require more time from the participants and may, therefore, have been skipped more often.

This study is unique in its sample (e.g., autistic individuals included, sample size, and age span), included measures, analysis, and validation procedure. First, the sample was large compared to what is typical in the autism subgrouping literature (Agelink van Rentergem et al., 2021). Also, we adopted a wider age range, and included both adults with autism, ADHD, and a comparison group. Second, we designed the study in such a way that we had a multivariate data set, which allowed us to include multiple cluster and external variables across different domains. This is important as the goal of our analysis was to detect differences between subgroups in variables that are meaningful to autistic adults: cognitive and psychological difficulties, and quality of life. This also guided the variable selection procedure. Third, the analysis method, Spinglass community detection, has rarely been used in autism. Fourth, we preregistered most analyses. Fifth, we included several validation strategies to critically evaluate our results and to examine the validity of the subgrouping results (Agelink van Rentergem et al., 2021).





With our external validation procedure, the identified autism subgroups were compared on clinically relevant measures related to the cluster variables, that were not used in the community detection analysis itself: cognitive and psychological difficulties, and QoL. Although these cluster variables and external variables are different constructs, some may wonder whether certain variables used to build and test the subgroups (e.g., negative affect and psychological difficulties) are too closely associated and, therefore, a methodological concern. However, it was a deliberate choice to include both external variables that are more closely related to the cluster variables (i.e., psychological difficulties), and some that are less closely related (i.e., QoL and cognitive difficulties) as they provide different information on the validity of the subgroups. Differences on external variables that are more closely related to the clustering variables suggest that the subgroup differences were structural, i.e., less overfitting of the random noise in the clustering variables in this particular sample. Including QoL and cognitive difficulties demonstrates that subgroup differences also extend to variables less closely related to the cluster variables, highlighting the generalizability of the subgroups.

It is important to note that the use of subgroup labels (e.g., Feelings of high grip) could (mis)guide the interpretation of findings in subgroup research and could potentially affect conclusions. Therefore, we considered it both important and necessary to consult our think tank of older autistic adults for the subgroup labels and conclusions reported in this study. However, even in this case one should be careful not to use the suggested labels outside the context of this study. As our replication sample showed, the subgroups differed on more cluster variables than mastery, so nuances may get lost when using subgroup labels.

Moreover, the labels were based on the mean differences, between the groups, but the assignment of participants to a specific subgroup was not based on the level of the scores, but on the pattern of scores. By calculating the correlations and using this as input, the level of scores is corrected for. Therefore, participants in the same subgroup have a similar pattern of peaks and troughs, even though one participant may have high scores on specific measures, and the other one has low scores on specific measures. Conversely, participants in different subgroups may overall have the same level of scores, but are assigned to different subgroups because there is a double dissociation in where the peaks and troughs in their pattern of scores are (Crawford et al., 2003). To interpret and describe the subgroups, we did examine whether there were level differences in scores as well, and found that these were present on some domains. But because of the way the participants were assigned based on strengths and difficulties, we should not and cannot state that participants in one subgroup show a deficit. The findings of the current study are in line with a categorical difference in autism, rather than a dimensional difference (Abu-Akel et al., 2019; Frazier et al., 2010). For clinical practice, this entails

that to correctly apply these findings, clinicians should not focus on 'severity' by using cut off scores, but instead focus on the pattern of strengths and difficulties to determine subgroup membership.

Furthermore, it remains difficult to evaluate one's subgrouping results, as there is no golden standard on how to determine the robustness of the results. In this study, we adopted several preregistered techniques to confirm the validity of our results, which is more than is usually done in the autism research realm (Agelink van Rentergem et al., 2021). Nonetheless, the modularity index, that was calculated in addition to the preregistered analyses, resulted in Q-values around 0.30. Although positive Q-values are indicative of a potential community structure, the absolute values were relatively low. Even when we ran a community detection analysis including the autism and comparison group — that are known to differ on many cluster variables —the Q-index was relatively low (Q=0.41). Similar values have been reported in different community detection studies analyzing psychological data (Blanken et al., 2020; Karalunas et al., 2014; Chapter 2, Radhoe, Agelink van Rentergem, Kok, et al., 2021). These low values could be due to the inclusion of people in the community detection analysis (as compared to more distinct entities), suggesting that people are overall more similar than different. This could indicate that the modularity index may not be well-suited for psychological data, although this has to be investigated in methodological research.

To be directly applicable to clinical practice, it is important to first assess how these subgroups develop over time. The subgroups did not differ in age, but this only provides cross-sectional evidence for a lack of a developmental effect. Longitudinal data is needed to determine whether the identified subgroups are stable over time and can be used to make clinical predictions. Therefore, we collected follow-up data and aim to assess the temporal stability of the subgroups, and their predictive value for future clinical outcomes (Chapter 8; Geurts et al., 2021). If the subgroups' validity proves robust in these additional validation steps, we can turn towards the development of interventions. For example, future studies could investigate whether the relationship among characteristics differs between the two subgroups. If differences are found in relationships between characteristics, future research may address whether intervening on the characteristics that differ most strongly between the subgroups, results in transitions in subgroup membership, or whether interventions should focus on the relationship between characteristics instead. Moreover, in this study we have focused on self-report questionnaire data; future work could also include proxy or clinician report for a more comprehensive picture. Furthermore, qualitative data can also enrich the interpretation of the current subgroup findings.





In the clinical field, it is recognized that there is a group of autistic adults that reports having feelings of low control, or low sense of mastery. In order to support these autistic adults, in the Netherlands, job coaches or life coaches are often hired to help people gain control over their life. This seems to be useful, but the subgroups formed could also inform us about the level of care needed. In the Netherlands, there is a distinction between general mental health care that is easily accessible for everyone, and specialized mental health care that is directed at specific groups such as those autistic adults for whom their care needs cannot be met within general mental health care. The subgroups that we identified in this study could therefore indicate the distinction between autistic adults who could benefit from this highly specialized care (i.e., the "Feelings of low grip" subgroup) and those that might already be helped via basic mental health care (i.e., the "Feelings of high grip" subgroup) when this is needed. Thus, it should be noted that not every autistic adult is in need of highly specialized care. It is also more likely that in the group with higher quality of life and less cognitive and psychological difficulties, there are autistic people who do not have any support needs, as not every autistic adult is in need of mental health care. Moreover, the current study implies that for autistic adults in the LowGr subgroup, vulnerabilities in one domain (e.g., mastery) are often accompanied by other difficulties (e.g., worries or negative affect). Therefore, if an autistic person reports difficulties in one domain, it may be helpful to screen for vulnerabilities in additional domains as we know these are associated with more cognitive and psychological difficulties, and a lower QoL. A better grasp on the full representation of the challenges someone might experience, may be crucial for tailored support to eventually improve the lives of autistic people.

In conclusion, we not only discovered that autistic adults form a clearly distinct group from adults without an autism diagnosis, but also found subgroups among autistic adults when focusing on autism characteristics and demographic, psychological, and lifestyle factors. While we replicated these findings and showed that these subgroups differ on clinically relevant outcomes (i.e., they are externally valid), these subgroups warrant further research to determine the longitudinal stability. Moreover, with this study we show which largely modifiable variables may distinguish these subgroups, which might be a starting point for an intervention. For example, mastery can successfully be improved with intervention (van der Klink et al., 2001; van der Zanden et al., 2012). Future studies can focus on subgroup replication and validation, but also on the development of interventions for those autistic adults who could benefit from extra support.



# Chapter 4

# Network structure differences between autism subgroups

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## Abstract

**Purpose**: Differences in (autism) characteristics are often reported between autistic and non-autistic adults, but also between autistic adults. We aim to determine whether mean differences correspond to differences in network structure of these characteristics in (a) autistic and non-autistic adults, and (b) two previously identified autism subgroups.

**Methods**: 16 network variables related to demographic and psychological characteristics were included. First, Gaussian Graphical Models were used for network estimation in 261 autistic adults and 384 non-autistic comparisons aged 30-85 years. Second, we repeated this step within two previously identified autism subgroups ($N_1$=124, $N_2$=130). Third, sex differences were explored in the networks of the autism subgroups.

**Results**: The networks of the autism and comparison groups differed on individual edges and visual inspection, although the Network Comparison Test showed no overall differences. The networks of autism subgroups were similar based on visual inspection and statistical comparisons. Sex did not impact the subgroup networks differently.

**Conclusion**: Networks were more similar than different, but observed edge differences could be informative for targeted support. Focusing on mean differences is not sufficient to determine which factors (and associations) are important for autistic people. Thus, network analysis provides a valuable tool beyond assessing mean differences for autistic adults.






## Introduction

The heterogeneity within the autism spectrum is a widely known phenomenon: Autism is characterized by differences in core characteristics between autistic and non-autistic people, but also by large differences between autistic people (Happé et al., 2006; Masi et al., 2017). For example, autistic adults report higher sensory sensitivity (Ben-Sasson et al., 2019; Crane et al., 2009) and more social interaction difficulties than non-autistic adults (Ruzich et al., 2015). However there are also large individual differences between autistic people (Masi et al., 2017). While differences in the level of autism characteristics are informative as a description, they do not inform us about the mechanisms that give rise to these differences, nor do they provide specific leads for support or interventions. In this study we do not focus on the heterogeneity in autism per se, but zoom in on this added level of complexity. Therefore, we focus on the relationship among characteristics instead of the level of characteristics, between autistic adults and non-autistic comparisons, and between autistic people.

A useful tool to gain more insight in the underlying structure of these differences is provided by the network approach. With a network analysis, one can visualize a complex system by identification of its components (i.e., nodes) and the relationships between these components (i.e., edges or links between nodes) (Borsboom & Cramer, 2013). The nodes can represent different types of things (e.g., persons, autism characteristics, cities) and the edges can represent different types of relationships (e.g., (partial) correlations, distances). One could use this method to examine whether there is a direct association between sensory sensitivity and difficulties with social interaction, or whether such an association is indirect (e.g., sensory sensitivity is associated with stress, while stress is associated with social interaction difficulties). An advantage of this method is that it also allows exploration of relationships in data when you do not have a clear hypothesis on how variables are related (Borsboom et al., 2021). In the autism field it is often unknown how different types of characteristics are related, hence this method could provide new insights into where autistic people might encounter difficulties and where autistic people flourish.

Network analyses have already proven insightful in autism. For instance, one study used a network analysis to elucidate risk and success factors for subjective wellbeing in autistic adults (Deserno et al., 2017). The study showed that social satisfaction and contribution to society were highly important for the wellbeing of autistic adults. A different study compared centrality indices in networks of autistic and non-autistic children and indicated that depression symptoms were more central in networks of autistic children (Montazeri et al., 2020), although this study did not involve a statistical comparison of the network structures. To our knowledge, there have not been any studies that included

a formal statistical comparison of the network structures of autistic and non-autistic individuals. To know whether network structures generalize across (diagnostic) groups or whether they differ, formal statistical comparisons are needed. Moreover, the autistic population is marked by heterogeneity. To determine what is best for whom, it could well be that we need to estimate a network for each specific individual. However, to move away from (diagnostic) group level (i.e., one measurement per person), towards individual level (i.e., many measurements per person) is a big leap that requires a vast amount of data. Thus, before we turn towards the individual level, it is useful to take an intermediate step by first focusing on homogeneous subgroups.

Many studies have already focused on subgroup identification in autistic adults (for a review see Agelink van Rentergem et al., 2021), by for example determining autism subgroups based on sensory sensitivity variables (DeBoth & Reynolds, 2017). In our own work described in Chapter 3, we identified two subgroups of autistic adults (Radhoe, Agelink van Rentergem, Torenvliet, et al., 2023): a "Feelings of High Grip" subgroup and a "Feelings of Low Grip" subgroup, that differed on several variables (e.g., sensory sensitivity, social and communication skills, sense of mastery). The "Feelings of Low Grip" subgroup had the most vulnerable profile on the included measures, and scored less favorably on external, clinical outcomes: quality of life, psychological difficulties, and cognitive failures. This shows that subgroups of autistic adults show differences in the level of autism characteristics (i.e., mean differences) and other psychological factors. It is not yet known how the network approach and subgrouping approach which looks at mean differences, could complement one another.

There are different ways in which mean differences could correspond to differences in network structure. It could be that the subgroups differ in the level of certain factors, while the relationship between these factors is comparable within each subgroup. However, it could also be that observed mean differences between subgroups go together with a difference in (causal) relationship between factors. In a given subgroup, subgroup A, there may be a direct relationship between sensory sensitivity and social interaction, i.e., sensitivity to noises (and other sensory stimuli) lead to problems with having conversations in loud environments. In subgroup B, there may be an indirect relationship between sensory sensitivity and social interactions, i.e., sensory sensitivity might lead to avoidance behavior towards social events, leading to more social interaction difficulties. In the latter subgroup, this would imply that sensory sensitivity and social interaction difficulties are conditionally independent given the avoidance behavior (Borsboom & Cramer, 2013). The network approach can be utilized to assess this type of differences between data-driven subgroups.





In this preregistered study (Chapter 8, Aspredicted #49209), we aim to determine how these techniques complement each other by combining our subgrouping approach with the network approach. First, we test at the (diagnostic) group level whether there are differences in network structure between autistic adults and non-autistic comparisons. Second, we zoom in at the subgroup level by testing for differences in networks between the previously identified autism subgroups (Chapter 3; Radhoe, Agelink van Rentergem, Torenvliet, et al., 2023). See Figure 4.1 for an illustration of the relationship between statistical methods. Third, we exploratively assess the impact of biological sex on the networks of the autism subgroups as differences between autistic men and women in behavioral characteristics have often been reported (see for example Baron-Cohen et al., 2014; Werling & Geschwind, 2013). Specifically, we aim to determine whether there are (sub)group differences in (a) the overall network structure, and/or (b) specific relationships between factors (such as between sensory sensitivity and social interaction difficulties). This study will bring to light whether mean differences correspond to differences in network structure in autistic adults and non-autistic comparisons, potentially improving our understanding of mechanisms and targeted support.

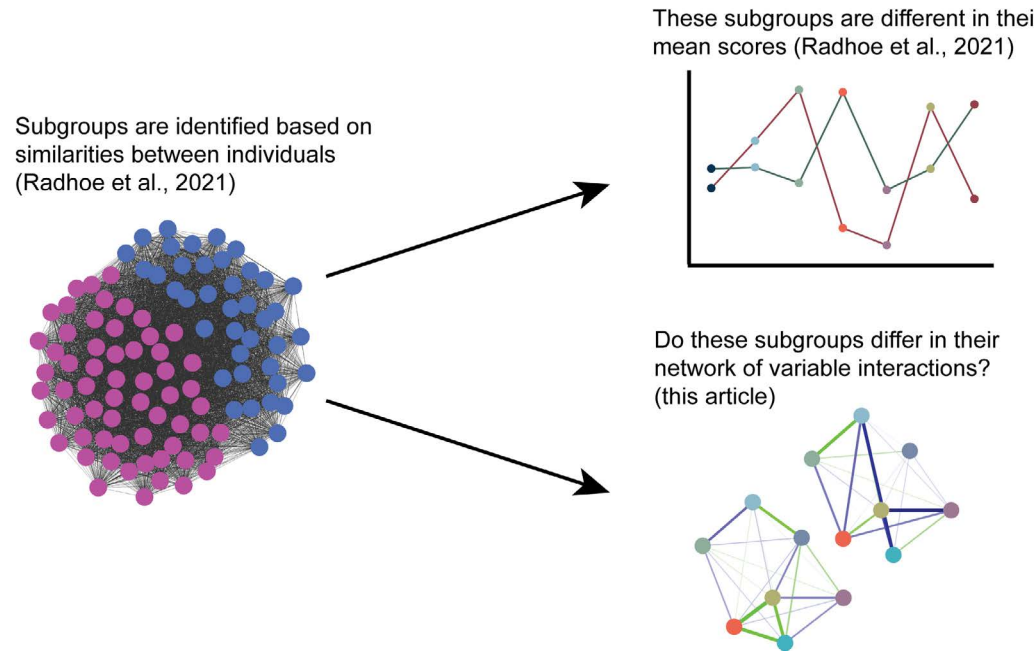



*Figure 4.1.* Illustration of the relationship of this article to previous work.

# Methods

**Participants**

In total, 661 adults participated in this study: There were 261 adults in the autism group (AUT; 133 women, 127 men, 1 other) with a mean age of 51.2 years (SD=12.7, range 30-84), and 384 adults in the comparison group (COMP; 170 women, 214 men) with a mean age of 54.9 years (SD=13.8, range 30-85). We did not ask participants about race/ethnicity and socioeconomic status, but the majority of the participants was White and had a high educational attainment. Please see our earlier work for a more detailed sample description (Chapter 3; Radhoe, Agelink van Rentergem, Torenvliet, et al., 2023).

For both groups, we applied the following exclusion criteria: (1) present or past diagnosis of intellectual disability or an IQ-score below 70, (2) being younger than 30 years, (3) insufficient understanding of Dutch language required to complete the questionnaires. In the autism group, we only included participants with a clinical diagnosis of an autism spectrum disorder (ASD) according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV or DSM-5) (American Psychiatric Association, 2000, 2013). For the comparison group, we also excluded participants with (1) a present or past ASD diagnosis or a total score higher than 32 on the Autism Spectrum Quotient (Baron-Cohen et al., 2001), (2) an ASD diagnosis in close family members (i.e., parent(s), child(ren), sibling(s)), (3) a history of more than one psychotic episode, (4) a present or past diagnosis of AD(H)D or a total score of six or higher on the Dutch version of the ADHD DSM-IV Rating Scale (Kooij et al., 2005), and (5) AD(H)D in close family members.

Participants in the autism group were recruited through mental health institutions in the Netherlands and advertisements placed on social media and client organization and autism advocacy websites. Participants in the comparison group were recruited through advertisements on social media and via the social network of the researchers, research assistants, and students collaborating on this study in the period between 2018 and 2020.

**Autism subgroups**

In our earlier work, we focused on subgroup identification within the autism group (Chapter 3; Radhoe, Agelink van Rentergem, Torenvliet, et al., 2023). We identified two subgroups of autistic adults: a "Feelings of High Grip" subgroup[3] (N=124, mean age=50.6, SD=13.8, range=30-81, 47% women) and a "Feelings of Low Grip" subgroup (N=130, mean age=51.3, SD=11.6, range=30-84, 55% women).

[3] The labels of the subgroups were suggested by our think tank of older/autistic adults and were based on the cluster variables on which the subgroups differed significantly (see for more information Chapter 3, Radhoe et al., 2021). It is important to be aware of the possible impact of using subgroup labels on the interpretation and conclusions drawn. Thus, the suggested labels should not be used outside the context of this study.





In the current study, we proceeded with both (a) the overall diagnostic groups (described above), and (b) the identified autism subgroups.

**Measures**

We included 17 variables in the network analysis. The first eleven variables were previously included in the identification of the subgroups. The last variable, biological sex, is included only in a separate analysis.

***Autism characteristics*** were measured using two instruments. First, the Autism Spectrum Quotient (AQ) (Baron-Cohen et al., 2001) was used by including subscale scores for "Social interaction" (40 items, range 0 to 40) and "Attention to detail" (10 items, range 0 to 10) (Hoekstra et al., 2008). A higher score reflects more autism characteristics. Second, the Sensory Sensitivity Questionnaire (SSQ) (Lever & Geurts, 2013; Minshew & Hobson, 2008) was used to measure sensory sensitivity. A total score was included (13 items, range 0 to 13), where a higher score was indicative of a higher sensory sensitivity level.

***Educational level*** was measured by asking participants about the highest education degree they obtained. We used the Dutch Verhage scale to classify the educational level (Verhage, 1964), consisting of seven categories (i.e., 1 = less than six years of primary education, 7 = university degree).

***Sense of Mastery*** was measured by the Pearlin Mastery Scale (Pearlin et al., 1981). Mastery is the extent to which we consider ourselves as being in control of our lives. We included the sum score (7 items, range 7 -35) where a higher score is indicative of a higher sense of mastery.

***Worries/Fears*** were measured by a combination of the Worry Scale (Wisocki et al., 1986) and Fear Questionnaire (Marks & Mathews, 1979). The total score was included (15 items, range 15-75). A higher score indicates more worries/fears.

***Physical activity*** was assessed using the International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003). We included the total amount of minutes during which a participant was physically active during the past week (11 items, range 0 to the maximum number of minutes per week, i.e., 10080). A higher score reflects more physical activity.

***Negative life events*** were measured using the List of Threatening Experiences (Brugha et al., 1985). Based on 12 different life events, a total score was included (12 items, range

0 (no negative life events) to 12 (many negative life events)).

***Emotional support*** was assessed using the Close Persons Questionnaire (Stansfeld & Marmot, 1992). For emotional support, a total score was included (12 items, range 12 to 60). A higher score indicates a higher level of emotional support people felt that they received.

***Positive and negative affect*** were measured using the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988). We included scores for Positive Affect (PA; 10 items, range 10 to 50) and Negative Affect (NA; 10 items, range 10 to 50). A higher score indicated more positive (or negative) affect.

***Cognitive failures*** were measured using the Cognitive Failures Questionnaire (Broadbent et al., 1982). A total score was included (25 items, range 0 to 100). A higher score indicates more experienced cognitive failures.

***Quality of life*** was measured using the World Health Organization Quality of Life Questionnaire-BREF (WHOQoL-BREF) (THE WHOQOL GROUP, 1998). We included the first question referring to one's overall quality of life perception (one item, range 1 to 5), where a higher score is indicative of a higher quality of life.

***Psychological difficulties*** were assessed using the Symptom Checklist-90 Revised (SCL-90-R) (Derogatis, 1977). A total score was included (90 items, range 90 to 450), where a higher score is representative of more psychological difficulties.

***Number of physical illnesses*** was measured using the Health Interview Questionnaire (Central Bureau of Statistics (CBS), 1989). A total score was included (21 items, range 0 to 21). Like most previous measures, a higher score reflects more reported physical illnesses.

***Age*** was measured by asking participants about their chronological age.

***Biological sex*** was measured by asking participants about their biological sex. Response options were "male", "female" and "other". Therefore, we included this variable as a categorical variable in the network analysis.





**Procedure**

We refer to the published protocol in Chapter 8 for the detailed procedure (Geurts et al., 2021), but below the procedure is described briefly. After receiving written informed consent, participants filled out a set of questionnaires (online or on paper, dependent on the participant's preference). If participants met the inclusion criteria, they filled out a second set of questionnaires. They received €7,50 for completing the questionnaires. This study was approved by the local ethics review board of the department of Psychology of the University of Amsterdam (2018-BC-9285).

**Statistical Analyses**

All analyses were conducted in RStudio version 1.3.1073 (RStudio Team, 2020). We preregistered the analysis plans at AsPredicted.org, included in Chapter 8 (AsPredicted #49209). The analysis can be described in four parts: (1) missing data, (2) network methods, (3) network comparisons, (4) power analysis. We followed the reporting standards for psychological network analyses (Burger et al., 2022).

***(1) Missing data***

We based our dealing with missing data on the simulation studies described below (see also Supplementary Material S9.3.1 for more info). Within a specific questionnaire, we considered 10% of missing data per respondent appropriate for imputation at the item level (Bennett, 2001). The manner of imputation depended on the measurement instrument. For autism characteristics, mastery, worries, emotional support, positive and negative affect, psychological difficulties and cognitive failures we recoded a maximum of 10% of missing values to the median of the participant's other responses on that specific measurement instrument. For negative life events, number of physical illnesses and physical activity, we recoded a maximum of 10% of missing values to zero, which implies the absence of a negative life event, physical illness or physical activity. We did not impute any missing values on education, quality of life, biological sex and age. After our item-level imputation was completed, we removed participants who still had missing values on more than one network variable (out of 16 variables in total) from all analyses. Thus, information was available from each respondent on at least 15 network variables.

As the Network Comparison Test (NCT) does not handle missing data, we excluded participants with any missing observations before we proceeded to the statistical comparison of the networks.

***(2) Network estimation methods***

A network consists of nodes (i.e., variables) connected by edges (statistical relationships between nodes) (Hevey, 2018). In this study, the edges represent partial correlations that indicate the strength of a relationship between two nodes after controlling for the effects of all other associations in the network (Epskamp & Fried, 2018). We used two different models to estimate the networks depending on the specific research question and the type of data. First, we used Gaussian Graphical Models (GGM) when estimating the networks using continuous data (*bootnet* package v1.5; Epskamp et al., 2018). Second, Mixed Graphical Models (MGM) were used when we estimated the networks using both continuous and categorical data (*mgm* package v1.2-12; Haslbeck & Waldorp, 2020). The *qgraph* package was used for network visualization (v1.9.2; Epskamp et al., 2012).

A common problem in network estimation is the existence of spurious edges or false positives (Epskamp & Fried, 2018). This implies that you obtain small partial correlation coefficients, even when two variables are conditionally independent (i.e., two variables are independent after controlling for the effects of all other variables in the network). These spurious edges complicate the interpretation of the network and may lead to failures to replicate estimated networks (Epskamp & Fried, 2018). To limit the number of spurious edges, we applied the *least absolute shrinkage and selection operator* (lasso) as a method of regularization. The lasso only retains the most robust edges by shrinking all estimates, causing some estimates (such as the smaller, spurious edges) to become exactly zero (Deserno et al., 2017). The lasso utilizes a tuning parameter, $\lambda$, to determine the level of sparsity. It is important to select the appropriate value of $\lambda$, such that the number of spurious edges is minimized while the number of true edges is maximized. We used the Extended Bayesian Information Criterion (EBIC) to determine the value of $\lambda$ (for more detail, see Epskamp & Fried, 2018). After estimating the network structure, the accuracy of the edge weights was examined by estimating a 95% confidence interval (CI) around the edge weights (using non-parametric bootstrapping with 2500 bootstrap samples; *bootnet* package v1.5; Epskamp et al., 2018). This procedure allows assessment of the variability in the edge weights, and to compare edges with each other. The wider the bootstrapped CIs, the more difficult it becomes to interpret the strength of an edge.

Four centrality indices were calculated in order to interpret the networks (Costantini et al., 2015; Opsahl et al., 2010; Robinaugh et al., 2016): (1) betweenness (i.e., the importance of a node in the average path between two nodes), (2) closeness (i.e., how well a node indirectly connects to other nodes), (3) strength (i.e., how well a node directly connects to other nodes), (4) expected influence (i.e., the influence of a node on its immediate neighbors). The stability of the centrality indices was assessed using the correlation stability (CS) coefficient (*bootnet* package version 1.5; Epskamp et al., 2018). The





CS-coefficient represents the maximum proportion of participants than can be dropped from the data set, such that (with 95% probability) the correlation between the original centrality indices and those based on the subset is 0.7 or higher. Based on a simulation study, CS-coefficients should not be below 0.25 in order to be considered stable indices (Epskamp et al., 2018).

***(3) Network comparisons***

Three different comparisons were performed based on the research questions. First, to determine whether the network structure generalized across diagnostic groups, a GGM was estimated separately in the full autism and comparison groups. Sixteen variables were included in this analysis (i.e., the variables mentioned under "measures", except for biological sex). After estimating the networks, a Network Comparison Test (NCT) was used to assess differences across diagnostic groups (*NetworkComparisonTest* package v2.2.1; van Borkulo et al., 2022). Two outcomes are of importance for this test: (1) global strength (i.e., is the overall level of connectivity equal across the two networks), (2) difference in network structure (i.e., are the distributions of edge weights comparable across the two networks). Moreover, differences in individual edges between the networks were tested using the NCT. We also explored the results visually.

Second, to gain further insight at the subgroup level, GGMs were estimated in the previously identified autism subgroups using the aforementioned sixteen variables as input. Again, a NCT was used to test for differences between the autism subgroups.

Third, to assess whether biological sex (a categorical variable) had a differential impact on the networks of the subgroups, an MGM was used. Seventeen variables were included, i.e., all variables mentioned under "measures". For this analysis we did not separately consider centrality measures again. Differences between the networks were assessed using a NCT.

***(4) Power analysis***

We performed four simulation studies (*parSim* package v0.1.4.; Epskamp, 2020) to assess whether we had sufficient power to estimate a network with 16 nodes (i.e., the beforementioned variables excluding sex) for each subgroup, and to compare the networks. In these simulations, we varied the sample size, percentage of missing data, and two parameter values that can be used to reduce the number of edges. Please refer to S.9.3.1 for a detailed description of the simulations. The simulations indicated that we were able to estimate and compare networks for 120 participants per subgroup with a maximum of 10% missing data, a sensitivity of 0.50, a specificity of 0.90 and a false discovery rate of 4% (with specific parameter values for reducing the number of edges, namely alp-

ha=0.25, gamma=0).

**Community involvement**

We worked together with a group of older/autistic adults (also referred to as the think tank) for this specific study, and our overall study on aging in autism (Chapter 8; Geurts et al., 2021). We met with the think tank at least three times a year (either online or in person) to discuss the recruitment strategies, information for participants, the interpretation of study results and other study-related matters. For this specific study, the think tank gave their interpretation of important associations in the networks, and differences between the networks during an in-person meeting. The members were paid for their contributions.

## Results

After dealing with missing data (i.e., removing participants who still had missing values on more than one network variable), the autism network included 258 adults and the comparison network included 287 adults. The network of the HighGr subgroup included 123 autistic adults, and for the LowGr subgroup 128 autistic adults were included. The main findings are described below, but please refer to the Supplementary Material for all plots of centrality indices, results of the nonparametric bootstrap analyses and results of the Network Comparison Tests (i.e., Supplementary Material S9.3.2 to S9.3.8).

**Psychological difficulties are central for autism group**

In the autism group, the total amount of psychological difficulties had the highest values on node strength and expected influence measures (please note that we only interpret node strength and expected influence given that these were the two stable centrality measures, i.e., CS > 0.25). Education and age had low values on all centrality indices suggesting that differences in these demographics cannot explain associations between variables.

The autism group network is depicted in Figure 4.2. Psychological difficulties were associated with negative affect and worrying. Quality of Life was not directly related to negative affect, but was positively related to other variables that could be considered aspects of wellbeing, like feelings of mastery and positive affect. Sensory sensitivity was associated with attention to detail, and difficulties with social interactions —these three variables are all autism characteristics. Four of these associations were reliably the strongest in the network (i.e., their bootstrapped confidence intervals did not overlap with those of most other edges): psychological difficulties with negative affect, attention to detail with sensory sensitivity, Quality of Life with mastery, and psychological difficulties with worrying.





**Differences at the edge level between autism and comparison groups**

In the comparison group, the total amount of psychological difficulties also had the highest value on the centrality indices (again, only node strength and expected influence are interpretable as they were stable, i.e., CS > 0.25). The number of negative life events and education scored lowest on all centrality parameters, which indicates that these variables do not explain associations between the other variables.

The comparison group network is displayed in Figure 4.3, panel B. Similar to the autism group, there was a positive association between psychological difficulties and negative affect. The number of physical illnesses was negatively associated with quality of life, and positively with psychological difficulties and age. Thus, more self-reported physical illnesses were associated with lower quality of life, more self-reported psychological difficulties and a higher age. Positive affect was related with most psychological variables in the network: positively related to quality of life, emotional support and mastery, and negatively associated with worrying and psychological difficulties. Three of these associations were reliably the strongest in the network according to the nonparametric bootstrap analysis: psychological difficulties with negative affect, physical illnesses with age, and emotional support with positive affect.

Based on a visual inspection of the autism network (Figure 4.3 panel A) and the comparison network (Figure 4.3 panel B) it seemed that the comparison network was more connected, whereas the autism network included stronger connections. However, a statistical comparison ($N_{autism}$= 233, $N_{comparison}$= 254) showed that there were no significant differences in global strength ($p$=0.36) and in network structure ($p$=0.09). Although there were no overall differences between the networks, testing of individual edges indicated several differences (see highlighted edges in Figure 4.3, panel A and B). As expected, in the autism group, the autism characteristic variables (i.e., attention to detail, social interaction difficulties, and sensory sensitivity) were more strongly connected compared to the comparison group. In the comparison group, the variables related to an autism diagnosis (i.e., attention to detail, social interaction difficulties, and sensory sensitivity) showed more connections to other network variables compared to the autism group.

Also, there were stronger associations between positive affect and (a) emotional support, (b) psychological difficulties, (c) sensory sensitivity, and (d) attention to detail compared to the autism group. Thus, although there are no structural differences between the autism and comparison group, there were differences at the edge level.

**From a network perspective autism subgroups do not structurally differ**

For both autism subgroups (i.e., the "Feelings of High Grip" (HighGr), and "Feelings of Low Grip" (LowGr) subgroups), the total amount of psychological difficulties had the highest value on measures of node strength, as was the case in the total autism group. Physical activity and the number of negative life events had the lowest values on the centrality measures (only node strength and expected influence were interpretable as they were stable, i.e., CS > 0.25).

In both subgroups, there were strong positive associations between (a) psychological difficulties and negative affect, and (b) attention to detail and sensory sensitivity. In the HighGr subgroup, there was an additional strong positive association between psychological difficulties and worrying.

A visual examination indicates that there were more and stronger connections in the HighGr subgroup as compared with the LowGr subgroup. Although statistical comparison ($N_{HighGr}$= 110, $N_{LowGr}$=117) showed that the networks did not differ in global strength (p=0.66) or in network structure (*p*=0.58), a few individual edges differed between the subgroups. In the HighGr subgroup, there was a stronger positive association between psychological difficulties and worrying. In the LowGr subgroup, there was a stronger association between psychological difficulties and negative affect. Moreover, there was a stronger association in the LowGr subgroup between positive affect, and (a) education, and (b) sensory sensitivity. Thus, in the LowGr subgroup, positive affect relates to more variables compared with in the HighGr subgroup. However, overall, as aforementioned, both subgroups do not fundamentally differ from a network perspective.

**Biological sex does not affect the autism subgroup networks differently**

In the HighGr subgroup, adding biological sex (i.e., male versus female) to the network resulted in three additional significant associations. The network is displayed in Figure 4.4, panel A. First, sex was associated with age, indicating that women were younger in this subgroup than men. Second, there was an association between sex and sensory sensitivity, which indicates that women reported higher sensory sensitivity compared with men in this subgroup. After adding sex to the network, there was no longer a significant association between age and sensory sensitivity. Thus, sex mediated this association.





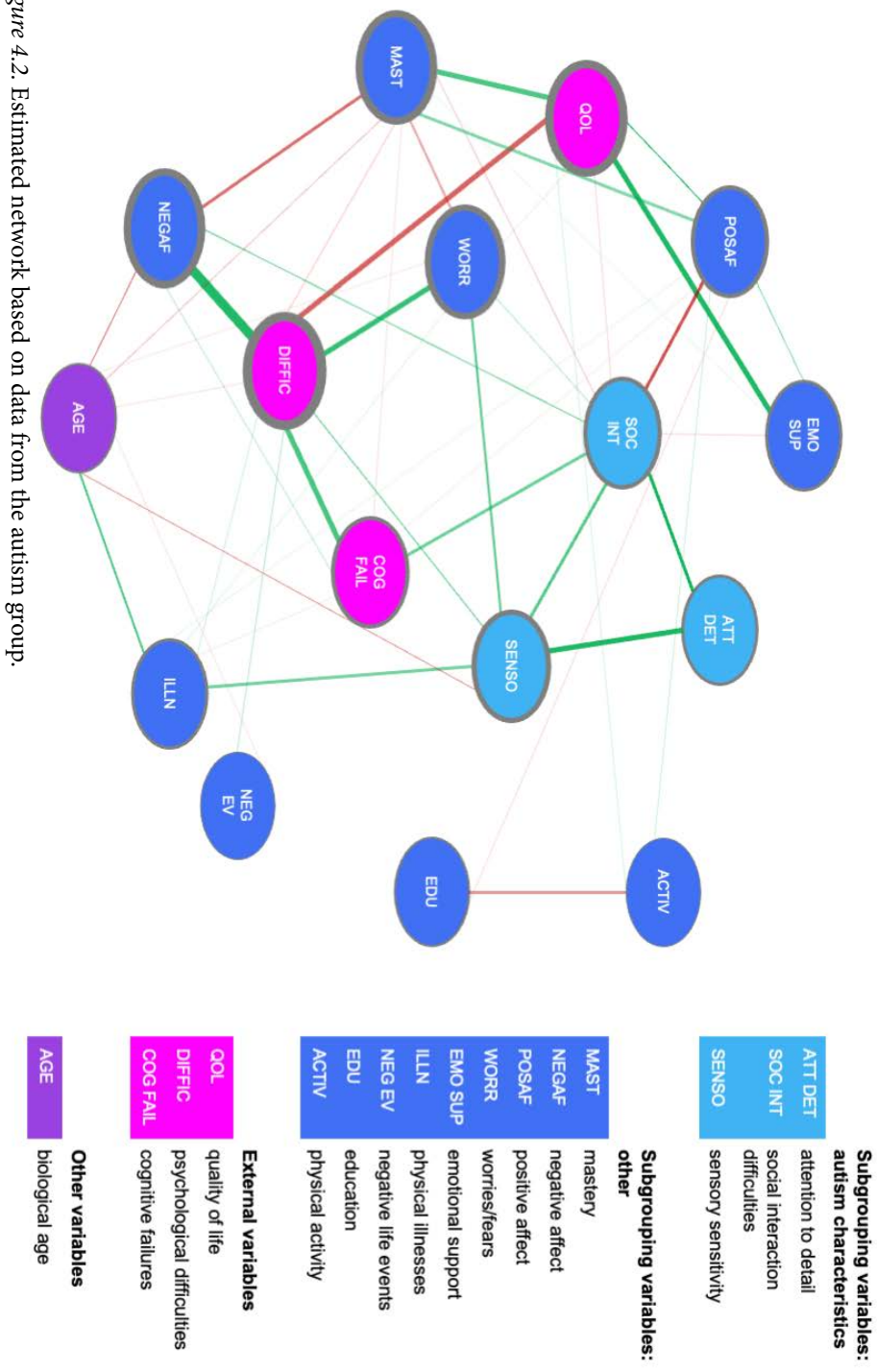



*Figure 4.2.* Estimated network based on data from the autism group.

*Note.* The color of the edge indicates the direction of the association (green for positive associations; red for negative associations). The thickness of the edge indicates the strength of the association: the thicker the edge, the stronger the association. The gray borders around the nodes indicate the strength of the node; the thicker the border, the higher node strength.

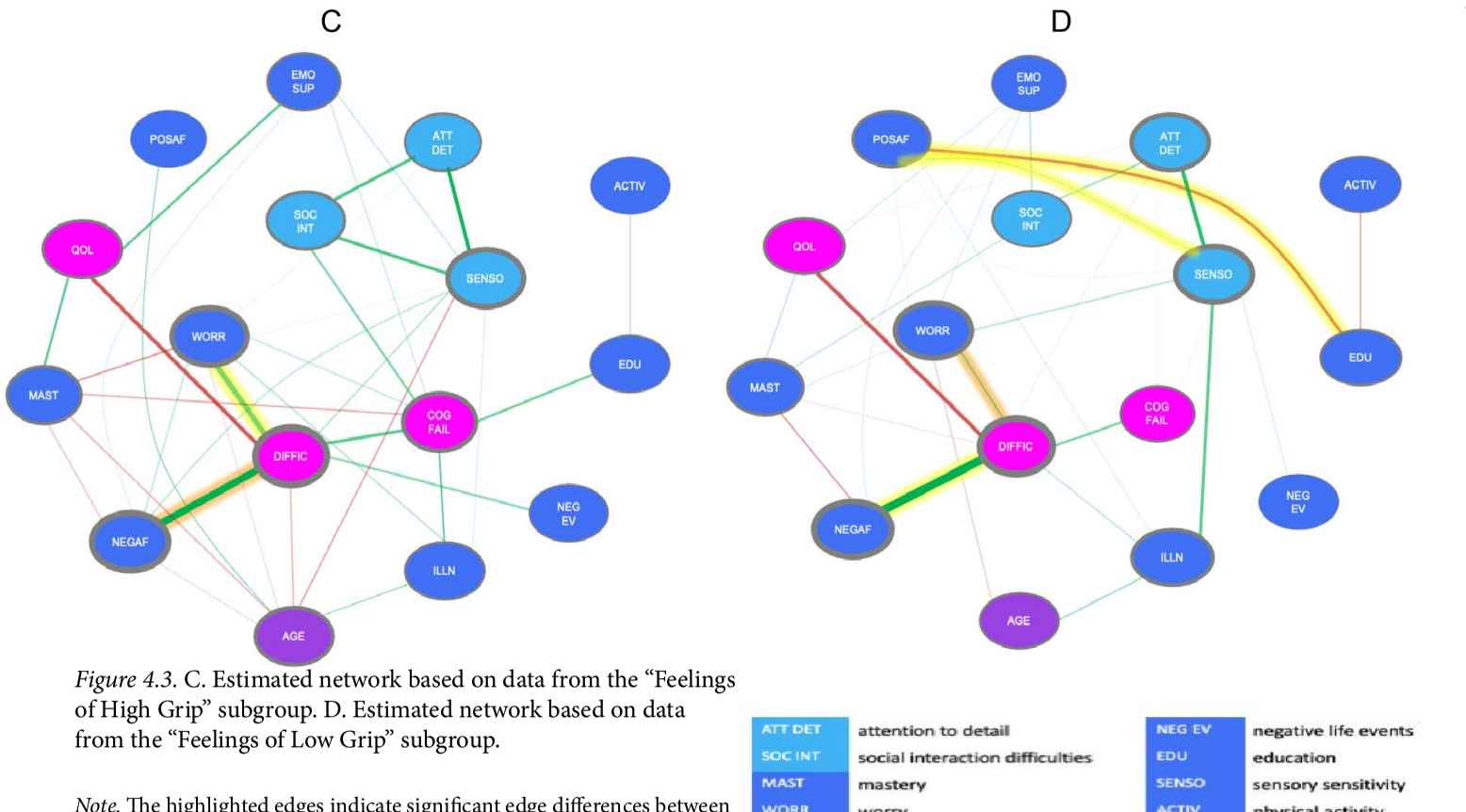



*Figure 4.3.* C. Estimated network based on data from the "Feelings of High Grip" subgroup. D. Estimated network based on data from the "Feelings of Low Grip" subgroup.

*Note.* The highlighted edges indicate significant edge differences between the groups (i.e., HighGr vs. LowGr): yellow indicates a higher value compared to the other group, and orange indicates a lower value compared to the other group. The color of the edge indicates the direction of the association (green for positive associations; red for negative associations). The thickness of the edge indicates the strength of the association: the thicker the edge, the stronger the association. The gray borders around the nodes indicate the strength of the node; the thicker the border, the higher node strength.

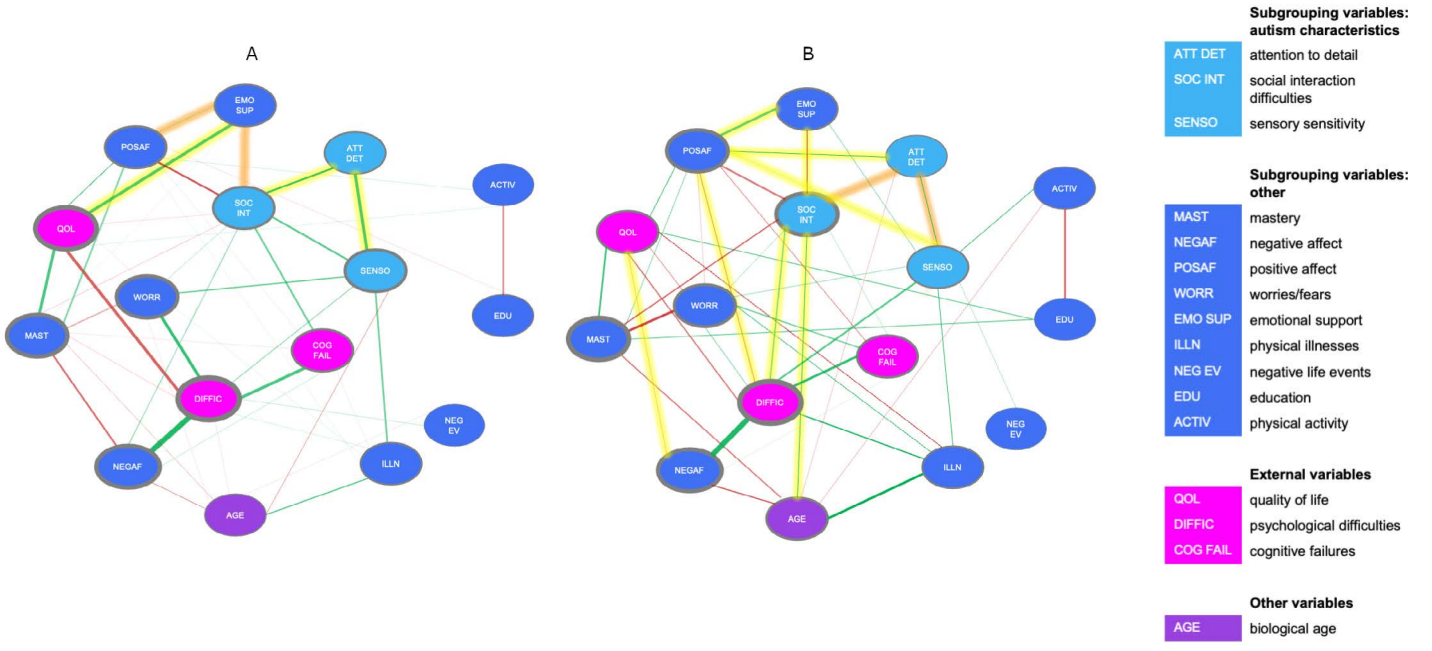



*Figure 4.3.* A. Estimated network based on data from the autism group. B. Estimated network based on data from the comparison group.

*Note.* The highlighted edges indicate significant edge differences between the groups (i.e., autism vs. comparison): yellow indicates a higher value compared to the other group, and orange indicates a lower value compared to the other group. The color of the edge indicates the direction of the association (green for positive associations; red for negative associations). The thickness of the edge indicates the strength of the association: the thicker the edge, the stronger the association. The gray borders around the nodes indicate the strength of the node; the thicker the border, the higher node strength.

Third, sex was related to emotional support, indicating that women experience more emotional support than men. Moreover, after adding sex to the network, the association between sensory sensitivity and emotional support became absent, demonstrating that sex mediated this relationship. In the LowGr subgroup, adding biological sex to the network did not result in any additional associations. The network is depicted in Figure 4.4, panel B.

Thus, while adding sex resulted in several changes in the HighGr subgroup, it did not influence the network of the LowGr subgroup. A statistical comparison did not indicate a significant difference between the two networks with respect to global strength and network structure.

## Discussion

In this study, we focused on network structures to determine whether mean differences between (sub)groups correspond to differences in network structures. When comparing the networks based on data from self-report questionnaires, we found that (a) networks of autistic adults and non-autistic adults did not differ in overall structure, but showed differences in individual edges, and (b) the autism subgroups that showed mean differences in various aspects, hardly differed in their network structure. Moreover, adding biological sex did not impact the networks of the autism subgroups differently. We did observe some subtle differences between the identified subgroups that provide hints for both clinical practice and future research. The LowGr subgroup reported more psychological difficulties and cognitive failures, and a lower quality of life (Chapter 3; Radhoe, Agelink van Rentergem, Torenvliet, et al., 2023). The network of this subgroup showed more associations with positive affect (i.e., with sensory sensitivity and education). Even though we did not find differences in overall network structure, it would be premature to conclude that the networks of the autism subgroups can be merged into a single network.

When comparing the networks of the overall autism and comparison groups, we conclude that these networks differ as (1) the networks seem to differ in connectivity based on visual inspection, and (2) while the NCT indicated no overall differences, there were differences in individual edges. Specifically, in the comparison group, there were both more and stronger connections as compared to the autism group. When comparing the networks of the autism subgroups, we conclude that the networks do not differ as (1) the NCT indicated no significant differences, (2) the networks seem similar based on visual





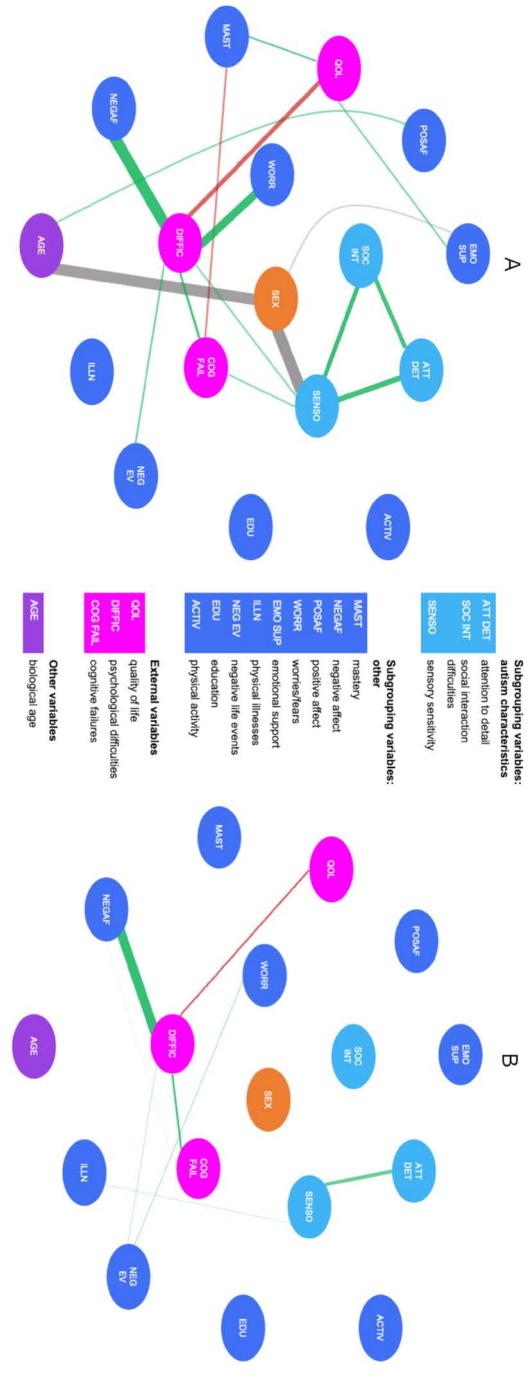



*Figure 4.4.* A. Estimated network (including biological sex) based on data from the "Feelings of High Grip" subgroup. B. Estimated network (including biological sex) based on data from the "Feelings of Low Grip" subgroup.

*Note.* The color of the edge indicates the direction of the association (grey indicates associations with sex, a categorical variable; green indicates positive associations; red indicates negative associations;). The thickness of the edge indicates the strength of the association: the thicker the edge, the stronger the association.

inspection, and (3) there were hardly any differences in individual edges. Thus, networks between an autistic and a non-autistic group show some subtle differences while this is not the case for subgroups within the autism group.

In contrast to what we expected, some of the factors on which the autism subgroups showed large mean differences in our previous study (i.e., social interaction difficulties, mastery, and emotional support), were not the factors that showed differences in connectivity in the current study. This does not imply that these variables are not important for autistic adults. In fact, the opposite may be true: While the connectivity of mastery does not differ between the networks, this factor is connected to many other variables in both subgroups. This stresses the importance of mastery for autistic adults in general (i.e., not dependent on subgroup membership). This has also been indicated in earlier research in autistic adults as mastery was found to be an important node connecting depressive symptoms with autism characteristics (van Heijst et al., 2020).

There were also some variables that showed large mean differences and showed differences in connectivity in the networks (i.e., worrying, positive and negative affect, and sensory sensitivity). Thus, while we initially thought that factors with large mean differences would correspond to either (a) differences in connectivity between the networks (because these factors would be most important), or (b) no differences in connectivity (because the variation in this factor would already be explained by the subgrouping solution), this study indicates that these two aspects are unrelated. Thus, based on mean differences, one cannot make any claims about the relationships of these factors, emphasizing the added value of the network approach.

The current study has several strengths. First, it is a novel approach to test whether the findings of our subgrouping study on autism can be validated when followed by a network comparison. Rather than limiting our conclusions to mean differences between (sub)groups, we gained additional insight by considering the associations between factors. Second, we included a large sample of autistic adults across a wide age span from 30 to 85 years. These adults were recruited from the community and from mental health institutions to obtain an accurate representation of the diverse population of autistic adults (without an intellectual disability) in the Netherlands. Third, we preregistered our analysis plan (Chapter 8; AsPredicted #49209), which is especially important given the exploratory nature of this study. Fourth, we preceded our network analysis by detailed simulations to determine whether we had sufficient statistical power to perform the desired analyses. Fifth, we discussed our findings with our think tank of older/autistic adults to help us interpret our results.

However, there are also several caveats that need to be acknowledged. First, it proved





difficult to interpret subgroup differences, as (1) we did not find any overall differences according to the NCT, and (2) adding biological sex to the subgroup networks had a complex effect. Specifically, biological sex visually seemed to affect the network structure, which shows that adding one additional variable (e.g., biological sex) could impact the associations in the networks. This indicates that one should only make claims based on the variables that are included in the network analysis. Nonetheless, we did find differences in individual edges between the subgroups that could be interesting for clinical practice. Second, the interpretation of psychological networks in general can be challenging, as it is difficult to decide what associations to focus on and to extract their meaning correctly (Bringmann & Eronen, 2018). Hence, we considered it essential to discuss our findings with our think tank of older/autistic adults.

Third, in all estimated networks (i.e., autism, comparison, HighGr, LowGr), we found a strong positive association between negative affect and psychological difficulties. The more negative emotions (e.g., anger, disgust) one has, the more psychological difficulties (e.g., sleep difficulties) or vice versa. Thus, this association is not specific to autism (or to an autism subgroup) but applies to both autistic and non-autistic people. The high correlation between these factors may induce questions regarding the distinctiveness of these concepts. Although these concepts are related, there is a clear difference. Psychological difficulties, measured with the SCL-90-R (Derogatis, 1977), reflects *current* distress (i.e., during the past week), so this is sensitive to fluctuations in mood. In contrast, negative affect, measured with the PANAS (Watson et al., 1988), reflects a *general* dimension of aversive mood states, representing a trait like stability. As an example, one could imagine that losing your job could cause sleep problems and depressive feelings for a while, although this does not mean that you experience these emotions this intensively in general. Thus, one's general state may not be identical to one's current state of distress. Therefore, separate measures are justified.

Some of the edge differences between the autism subgroups could be informative for clinical practice. For example, if an autistic adult from the LowGr subgroup seeks help in clinical practice, it may be wise to be aware of vulnerabilities in positive and negative affect, as these variables are strongly related to other important factors (e.g., worrying, psychological difficulties and sensory sensitivity). The focus on identifying factors that may have a role in the development of (psychological) problems is also in line with the clinical guideline for autistic adults (National Institute for Health and Care Excellence, 2012). However, we do not yet know whether intervening on these factors indeed has the desired impact on the other factors. When the current findings are replicated it could be fruitful to test whether targeting positive/negative affect indeed has an impact on the experience of psychological difficulties.

In conclusion, we showed that network analysis provides a valuable tool beyond looking at mean differences when comparing (sub)groups. While we expected that there was some relationship between mean differences and corresponding network architecture, this study showed that these aspects are unrelated. Thus, to make claims about the importance of certain factors (and the associations between these factors) for autistic people, solely looking at mean differences is not sufficient. Future studies should first focus on replicating these results before moving to intervention, to eventually determine whether distress, cognitive failures and reduced quality of life in autistic adults can be addressed by the provision of tailored support.



# Chapter 5

# The clinical relevance of subgroups of autistic adults

This chapter is submitted as:

Radhoe, T.A., Agelink van Rentergem, J.A., Torenvliet, C., Groenman, A.P., van der Putten, W.J., & Geurts, H.M. (2023). *The clinical relevance of subgroups of autistic adults: Stability and predictive value* [Manuscript under review at Autism Research]. Preprint doi: 10.31234/osf.io/ycp6q

## Abstract

Autism in adulthood is characterized by heterogeneity, complicating the provision of tailored support. In previous work, we aimed to capture this heterogeneity by identification of subgroups of autistic adults that differed in clinical outcomes: cognitive failures, psychological difficulties, and quality of life (QoL).

The current pre-registered study involves a longitudinal extension to determine (a) stability and (b) predictive value of the previously identified two subgroups. Subgroups were identified using community detection based on 14 self-report measures related to demographic, psychological, and lifestyle characteristics in two separate samples (aged 31-86 years): Sample 1 ($N_{Autism}$=80) measured five years after baseline and Sample 2 ($N_{Autism}$=241, $N_{Comparison}$=211) measured two years after baseline. The stability over time was assessed based on (a) the number of subgroups, (b) subgroup profiles, and (c) subgroup membership. Predictive validity was assessed for cognitive failures, psychological difficulties, and QoL.

Results indicated that autistic and non-autistic adults formed distinct subgroups. Within both autism samples, the two previously identified autism subgroups were replicated at follow-up. Subgroup profiles were similar for >50% of the variables at two-year follow-up, and 21% at five-year follow-up. Moreover, ≈79% remained in the same subgroup at two-year follow-up, and 64% after five years. Subgroup membership was predictive of external clinical outcomes up to five years.

Thus, this study demonstrated the stability and predictive value of the autism subgroups. A further focus on their clinical utility might not just increase the aptness of support, but may also provide more insight into the aging process when being autistic.






## Introduction

Autism in adulthood is characterized by heterogeneity at multiple levels ranging from biology to behavior (Masi et al., 2017). At the behavioral level there are differences in the presentation, extent of autism characteristics, and experienced strengths and challenges (Happé et al., 2006; Masi et al., 2017). This heterogeneity complicates provision of tailored support and the search for prognoses. Hence, autistic adults often do not receive the specific support they need and wish (Hwang et al., 2017). Moreover, many autistic adults live with the uncertainty of what to expect as they reach old age (Finch et al., 2022). Therefore, gaining insight into this behavioral heterogeneity is needed to improve support and care for autistic adults.

One promising solution is to determine subgroups within the autism spectrum with predictive power for the adulthood developmental trajectory. Many studies have focused on the identification of subgroups (Agelink van Rentergem et al., 2021), but only a few focused primarily on adulthood (Elwin et al., 2017; Gonthier et al., 2016; Lewis et al., 2008; Lombardo et al., 2016; Ring et al., 2008) of which even fewer included multiple clinically relevant variables or domains (Bishop-Fitzpatrick et al., 2016; LaBianca et al., 2018). Including such variables (like well-being, autonomy, or social satisfaction) is of importance when the goal of subgrouping is not primarily to understand the observed heterogeneity, but also to implement this knowledge into clinical practice.

A crucial additional step in subgrouping research involves the validation of the identified subgroups. If the aim is to utilize the subgroups in practice, it is essential to determine their validity (i.e., to ensure the subgrouping solution is sensible). However, it is remarkable how little attention has been devoted to validation in the subgrouping studies within the autism research field so far (see for review Agelink van Rentergem et al., 2021). Specifically, of the subgrouping studies in autistic adulthood, only one study performed an independent replication (i.e., identified subgroups in an additional, independent sample) (Lombardo et al., 2016). Moreover, none of the studies included longitudinal data to (a) test predictions over time, or (b) assess the temporal stability of the subgroups. This lack of validation leaves the question whether the identified subgroups are genuinely sensible, which would limit the (clinical) applicability of the identified subgroups.

In the autism literature thus far, there have been two subgrouping studies — apart from our own — focusing on clinically relevant measures in adulthood, while also adopting some form of subgroup validation. Bishop-Fitzpatrick and colleagues (2016) focused on QoL and identified three subgroups using normative outcomes and objective QoL. They

assessed the external validity by showing that the subgroups differed on related external measures, such as employment status and independent living. LaBianca and colleagues (2018) aimed to assess need for healthcare across the autism and/or ADHD spectrum. They identified five subgroups and demonstrated the external validity by showing subgroup differences on genetic risk factors. The difference between these findings already shows how the study goal impacts the design choices (in terms of sample and included variables), and which subgroup validation approaches may be most suitable. Thus, the studies focusing on clinically relevant subgroups in autistic adults are (a) still limited in numbers, and (b) difficult to bring together as their goals, approaches, and results are diverse.

Moreover, there have not been any subgrouping studies focusing on clinical predictions throughout autistic adulthood. Even when we zoom out from the subgroup-level, and focus on autism in adulthood in general, it becomes clear how much is still unknown about the developmental process of autistic adults (Tse et al., 2022; Wise, 2020). This is both surprising and alarming, as the evidence shows that autistic adults have a poorer overall quality of life compared to the general population (Ayres et al., 2018) and increased rates of all major psychiatric conditions such as depression and anxiety (Hand et al., 2020; Nylander et al., 2018). The few longitudinal studies that have followed autistic people throughout adulthood show that there is marked heterogeneity in living arrangements, employment, medical, and psychiatric co-occurring conditions (see for review Wise, 2020). Therefore, most autistic adults do not know what to expect as they grow older. This highlights the need for (a) knowledge on the developmental trajectory in adulthood, while (b) considering individual differences between autistic adults.

In our previous work, we have focused on subgroup identification in autistic adults using clinically relevant variables: psychological, demographic, and lifestyle characteristics (Chapter 3; Radhoe, Agelink van Rentergem, Torenvliet, et al., 2023). Our goal was to detect subgroups that might have an impact on clinical practice. Two subgroups were identified that differed in susceptibility to experienced difficulties. As suggested by a group of older/ autistic adults, the subgroups were labeled as "Feelings of High Grip" and "Feelings of Low Grip". We showed that (a) the subgroups can be replicated in an independent sample, and (b) demonstrated the external validity as the subgroups differed on clinically meaningful variables. Specifically, the Feelings of Low Grip subgroup showed the most vulnerable profile on the cluster variables, and was associated with the lowest QoL, most psychological difficulties and cognitive failures. Thus, two autism subgroups were identified of which the validity has been demonstrated in multiple ways. However, while of value in itself, it is yet unknown whether these subgroups are informative for the future prospects of autistic adults.





In this study, we follow up on our earlier work by assessing the prognostic utility of the previously identified subgroups in a longitudinal extension. First, we assess whether the identified subgroups are stable as people age. Second, we determine whether the subgroups can be used to predict clinically relevant outcomes (i.e., QoL, psychological difficulties, and cognitive failures) over time.

## Methods

This study is the longitudinal follow up (data-collection 2020-2022) of our previous cross-sectional study (data collection 2015 to 2020) (Chapter 3; Radhoe, Agelink van Rentergem, Torenvliet, et al., 2023). Therefore, the same exclusion criteria and materials were used. Concise information on each of these elements is provided below, and a detailed description is provided in the cross-sectional study and protocol paper (Chapter 8; Geurts et al., 2021).

### Participants

In total, 592 (348 autistic and 244 non-autistic adults) were screened for inclusion. Autistic participants were recruited via mental health institutions in the Netherlands, and advertisements on client organization websites and social media. Participants in the non-autistic comparison group were recruited through advertisements on social media, and via the social network of researchers and research assistants involved in this study.

As in the cross-sectional study, we applied the following exclusion criteria to all participants: (1) intellectual disability, (2) insufficient understanding of the Dutch language required to complete the self-report questionnaires, (3) age lower than 30 years. For the autism group, we only included adults who received a clinical DSM-III, DSM-IV or DSM-5 diagnosis of an Autism Spectrum Disorder (ASD) (American Psychiatric Association, 1987, 2000, 2013). For the non-autistic comparison (COMP) group, we applied the following additional exclusion criteria: (1) history of more than one psychotic episode, (2) a present or past diagnosis of ASD or a total score higher than 32 on the Autism Spectrum Quotient (Baron-Cohen et al., 2001), (3) a present or past diagnosis of AD(H)D or a score of six or higher on the Dutch translation of the ADHD DSM-IV Rating Scale (Kooij et al., 2005), (4) ASD diagnosis in close family members (i.e., parent(s), child(ren), sibling(s)), (5) AD(H)D diagnosis in close family members. The exclusion criteria were checked based on data from self-report questionnaires. In total, 532 participants met inclusion criteria and had sufficient data to be included: 321 autistic and

Table 5.1
*Participant characteristics for two separate samples at baseline and follow-up after five and two years.*

| | **Baseline** | | | **Follow-up** | | |
|---|---|---|---|---|---|---|
| | Sample 1 (2015-2016) | Sample 2 (2018-2020) | | Sample 1 (after 5 years) | Sample 2 (after 2 years) | |
| | AUT | AUT | COMP | AUT | AUT | COMP |
| N | 114 | 261 | 287 | 80 | 241 | 211 |
| Sex (M/F/Other) | 72/42/0 | 127/133/1 | 157/130/0 | 46/34/0 | 116/124/1 | 116/95/0 |
| Mean (SD; range) | | | | | | |
| Age | 54.2 (12.1; 31-89) | 51.2 (12.7; 30-84) | 55.7 (13.8; 30-85) | 58.2 (10.6; 37-83) | 52.8 (12.4; 32-86) | 58.6 (13.4; 31-86) |
| AQ total | 34.6 (6.8; 14-47) | 34.9 (7.6; 10-48) | 13.6 (5.9; 2-31) | 32.0 (7.0; 13-45) | 34.3 (7.9; 7-49) | 13.6 (5.9; 3-32) |
| ADHD Att | 10.1 (5.4; 1-25) | 12.0 (6.5; 0-30) | 5.4 (3.5; 0-17) | 10.5 (5.1; 0-25) | 11.8 (6.5; 0-32) | 5.9 (3.4; 0-16) |
| ADHD Hyp-Imp[b] | 10.6 (6.1; 1-29) | 12.7 (6.3; 0-32) | 6.4 (3.7; 0-23) | 11.0 (6.1; 0-29) | 13.1 (6.6; 0-34) | 6.3 (3.9; 0-19) |
| ADOS-2 total[a] | - | 11.6 (3.6; 4-19) | - | - | - | - |
| Age autism diagnosis | 48.1 (12.4; 12-81) | 44.9 (13.4; 4-79) | - | 46.6 (11.1; 24-70) | 44.8 (13.2; 4-79) | - |

*Note.* AUT = autism group, COMP = comparison group, M = male, F = female, AQ total = Autism-Spectrum Quotient total score. ADHD Att = ADHD Rating Scale, Attention sum score. ADHD Hyp-Imp= ADHD Rating Scale, Hyperactivity Impulsivity sum score. ADOS-2 total = Autism Diagnostic Observation Schedule, Module 4 total score.
[a]ADOS-2 data is only available for 2018-2020 participants.



211 non-autistic adults. Participant characteristics are described in Table 5.1, and participant numbers and reasons for exclusion are described in more detail in Figure 5.1A.

We divided study participants into two datasets[4] based on the time interval until follow-up: Sample 1 (NAUT=80) with a time interval of five years until follow-up, and Sample 2 (NTotal=452, NAUT=241, NCOMP=211) with a time interval of two years until follow-up. These samples did not overlap in included participants. Please note that Sample 1 (with a smaller sample size, but a longer time interval until follow-up) was included to explore the stability of the autism subgroups over a longer time interval. Therefore, although data was collected from both autistic and non-autistic adults at five-year follow-up, only autistic adults were included in this specific sample. A schematic representation of the data collection timepoints and corresponding samples is depicted in Figure 5.1B.

**Measures**

For a more detailed description, including psychometric properties, of the measures see Chapter 3 (Radhoe, Agelink van Rentergem, Torenvliet, et al., 2023). Below each measure is described briefly.

***Cluster variables:***

*Autism characteristics* were measured using the Autism Spectrum Quotient (Baron-Cohen et al., 2001). Subscale scores for Social Skills, Attention Switching, Attention to Detail, Communication, and Imagination were included (10 items per subscale, range 0-10). Higher scores indicated more autism characteristics.

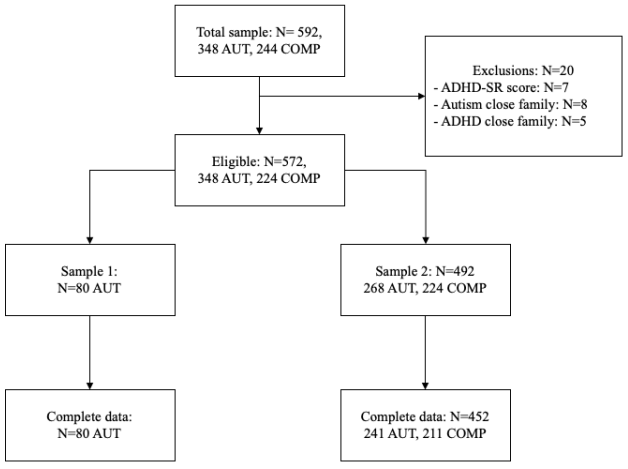
*Educational level* was classified using the Dutch Verhage scale (Verhage, 1964), consisting of seven categories (1 indicating less than six years of primary education, and 7 indicating a university degree).

*Mastery* was measured with the Pearlin Mastery Scale (Pearlin et al., 1981). A sum score was included (7 items, range 7 to 35). A higher score reflected more feelings of being in control.

*Worries/fears* were assessed with a combination of the Worry Scale (Wisocki et al., 1986) and Fear Questionnaire (Marks & Mathews, 1979). A sum score was included, where a higher score indicated more worries (15 items, range 15-75).

[4] The same subsets of participants were used in the cross-sectional study with different labels (Chapter 3; Radhoe, Agelink van Rentergem, Torenvliet, et al., 2023). Sample 1 was referred to as "original sample" (i.e., Cohort 2) and Sample 2 was referred to as "replication sample" (i.e., Cohort 3).

A




B

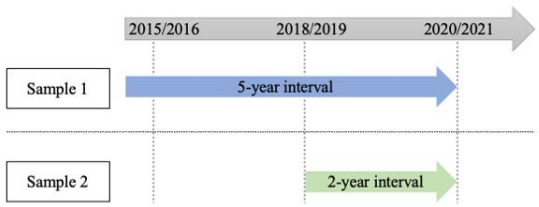



*Figure 5.1.* A. Flow diagram of participant numbers. B. Schematic representation of data collection timepoints per sample.

*Note*. AUT = autism, COMP = comparison.





*Physical activity* was measured with the International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003). The included cluster variable represented the total number of minutes during which someone was physically active during the past seven days.

*Negative life events* were measured with the List of Threatening Experiences (Brugha et al., 1985). A sum score was calculated that indicated the number of negative life events someone has experienced during the past year (12 items, range 0-12).

*Emotional support* was assessed using the Close Persons Questionnaire (Stansfeld & Marmot, 1992). A sum score was included, where higher scores indicated higher levels of received emotional support (12 items, range 12-60).
*Sensory sensitivity* was measured with the Sensory Sensitivity Questionnaire (Lever & Geurts, 2013; Minshew & Hobson, 2008). A sum score was included, where higher scores indicated a higher sensory sensitivity (13 items, range 0-13).

*Positive and negative affect* were assessed with the Positive and Negative Affect Schedule (Watson et al., 1988). Two subscale scores were included, for positive and negative affect (10 items per subscale, range 10-50). Higher scores indicated respectively more positive or negative feelings.

***External validators:***

*Cognitive failures* were measured with the Cognitive Failures Questionnaire (Broadbent et al., 1982). A sum score was calculated, where higher scores indicated more cognitive failures (25 items, range 0-100).

*Psychological difficulties* were assessed with the Symptom Checklist-90 Revised (SCL-90-R) (Derogatis, 1977). The total score (based on 90 items) and nine subscale scores were included: agoraphobia, anxiety, depression, somatization, cognitive performance deficits, interpersonal sensitivity, hostility, sleep difficulties, and items not included in any specific factor. Higher scores represented more psychological difficulties.

*Quality of Life* (QoL) was measured with the World Health Organization Quality of Life Questionnaire-BREF (WHOQoL-BREF) (THE WHOQOL GROUP, 1998). Scores on four subscales were included: physical health, psychological, social relationships, and environment. Higher scores represented a higher QoL.

**Procedure**

For the exact procedure we refer to the cross-sectional study (Chapter 3; Radhoe, Agelink van Rentergem, Torenvliet, et al., 2023) and published protocol (Chapter 8; Geurts

et al., 2021) Briefly, after written informed consent was received, participants filled out questionnaires, either online or on paper. Each participant spent around two hours to complete the questionnaires. A subset of participants was also interviewed (e.g., ADOS-2), either online or in person, and tested using the shortened WAIS-IV (Wechsler, 2012) and the Mini International Psychiatric Interview (MINI ;Van Vliet et al. [2000]). This study was approved by the local ethical review board of the department of Psychology at the University of Amsterdam (2018-BC-9285).

**Statistical Analyses**

The community detection analyses and frequentist analyses were performed in RStudio (RStudio Team, 2020), using the package igraph for subgroup identification (Csardi & Nepusz, 2006). The Bayesian analyses were conducted in JASP (JASP TEAM, 2022). The analysis plan was preregistered at AsPredicted.org (Chapter 8, #77679). The analysis plan consisted of four steps. Step 1 and 2 are an exact replication of our cross-sectional study, and are only described briefly below.

***(1) Missing data on cluster variables***

We distinguished between item-level missingness and instrument-level missingness. At the item level, we imputed a maximum of 10% of missing data per participant for each questionnaire (Bennett, 2001). The manner of imputation was dependent on the instrument: for autism characteristics, mastery, sensory sensitivity, worries/fears, positive and negative affect, and emotional support, a maximum 10% of missing values was recoded to the median of the participant's responses on the specific measurement instrument. For negative life events and physical activity, a maximum of 10% of missingness was recoded to zero, which implied either the absence of a negative life event/ specific physical activity. No missing values were imputed for the education variable.

For the instrument-level missingness, we only included participants with a maximum of one missing value out of the total of 14 cluster variables. Thus, participants with more than one missing value on the cluster variables were excluded from the analyses.

***(2) Community detection: analysis***

The goal of a community detection analysis is to identify communities (/subgroups), which are locally dense connected subgraphs in a larger network. To perform this analysis, the scores on cluster variables were first transformed to z-scores, to ensure that different measurement scales did not affect results. Next, a Pearson correlation matrix was created, that included person-to-person correlations between scores of all participant





pairs in the sample. These correlations represented the similarity between the scores of two participants: The higher the correlation, the more similar the scoring patterns on the cluster variables. This correlation matrix was used as input for the community detection analyses, and the Spinglass algorithm (with $\gamma$=0) was used to identify the communities (Reichardt & Bornholdt, 2006).

The community detection analysis was performed in three different steps in two independent samples. First, the analysis was performed using Sample 2 (two-year follow-up) including autistic and non-autistic participants. Second, the analysis was performed including only the autistic adults from Sample 2. Third, the analysis was repeated for Sample 1 (five-year follow-up) including only autistic participants.

***(3) Stability of autism subgroups over time***

We used three criteria to determine the similarity of the subgroups identified at follow-up to those at baseline. To conclude that the subgroups are stable over time, at least Criteria 1 and 2 or Criteria 1 and 3 had to be met.

*Criterion 1:* The community detection analysis again results in two major autism subgroups at follow-up (i.e., each subgroup should include more than 25% of the sample and should be the largest subgroups identified at follow-up). This involved comparing the number and size of subgroups at both timepoints.

*Criterion 2:* Scores on the individual cluster variables per subgroup are similar between both timepoints (i.e., baseline and follow-up). Bayesian *t*-tests with a standard/flat prior were used for each of the cluster variables. With the Bayesian approach, the likelihood of the data fitting under the null hypothesis (H0: cluster variable scores are similar over time) is contrasted with the likelihood of the data fitting under the alternative hypothesis (H1: cluster variable scores are not similar over time) (Wagenmakers, 2007). The resulting Bayes factor ($BF_{01}$) quantifies the evidence in support of the null hypothesis as compared to the alternative hypothesis (Jarosz & Wiley, 2014; Wagenmakers & Lee, 2014). For example, a $BF_{01}$ of 2 indicates that the data are two times more likely to occur under the null hypothesis than under the alternative hypothesis.

*Criterion 3:* The same participants cluster together in one subgroup at follow-up as they did at baseline. A Bayesian contingency table test (with standard/flat prior) was used to test similarity between subgroup membership at baseline and follow-up. Moreover, two measures were calculated that indicate similarity between subgroup membership at two timepoints (i.e., baseline and two-year follow-up, or baseline and five-year follow-up): (1) the Rand Index (RI; Rand, 1971) and (2) the Hubert-Arabie Adjusted Rand Index ($ARI_{HA}$; Hubert & Arabie, 1985). Values above 0.90 for both measures represent excel-

lent subgroup recovery (i.e., similarity between subgroups identified at two timepoints), while values below 0.65 represent poor recovery (Steinley, 2004).

Next to the pre-registered analyses, a complimentary analysis was performed to determine the stability over time of the mean scores on the cluster variables for the total autism group (see S9.4.4).

***(4) External and predictive validation***

For external and predictive validation, we compared the autism subgroups identified on variables not included in the community detection analysis, i.e., cognitive failures, psychological difficulties, and QoL. The subgroups were considered meaningful if they differed on these external measures (at baseline, external validation; at follow-up, predictive validation). First, ANOVAs were used to assess whether the subgroups differ in the total amount of experienced cognitive failures. Second, ANOVAs were used to assess subgroup differences in psychological difficulties (i.e., total score and scores on nine subscales). Third, subgroup differences in QoL were assessed using an ANOVA for each subscale (i.e., four in total).

**Community involvement**

For this study, and the overarching project, we collaborated with a group of older/ autistic adults. We met at least three times a year (either online or in person), and discussed relevant matters including recruitment strategies, questionnaires, and interpretation of analysis results. All members were paid for their contribution.

## Results

The attrition analyses are described in detail in the Supplementary Materials S9.4.1. Overall, there was more dropout in the comparison group than in the autism group. Between the autism subgroups, there were differences in total AQ score: higher scores for those who dropped out in the "Feelings of High Grip" (HighGr) subgroup compared to the "Feelings of Low Grip" (LowGr) subgroup.

**Two-year follow-up: Autistic and non-autistic adults again form separate groups**

Two subgroups were identified that corresponded to an autistic or non-autistic subgroup. The first subgroup (N=227) mostly included autistic adults (96%), and the second subgroup (N=225) mostly included non-autistic adults (89%). The profiles of the





two subgroups are depicted in S.9.4.2. To obtain more insight into the heterogeneity within the autism group, the community detection analysis was repeated for just the autism group.

**Two-year follow-up: Still three subgroups of autistic adults**

The community detection analysis on data from the autism group again resulted in three subgroups. The profile of the first subgroup (N=109) resembled that of the "Feelings of High Grip" (HighGr) subgroup that was identified at baseline (Chapter 3; Radhoe, Agelink van Rentergem, Torenvliet, et al., 2023). This subgroup was again characterized by a higher score on variables in the social domain, a higher mastery, lower level of worries, more positive affect and less negative affect. The second subgroup (N=122) was similar to the "Feelings of Low Grip" (LowGr) subgroup that was previously identified. This subgroup was again characterized by lower scores on the social domain, lower mastery, more worries, less emotional support, less positive affect and more negative affect. The third subgroup (N=10) did not seem similar to the "rest" subgroup that was previously identified. As this subgroup only included 10 people, we did not consider this a valid separate subgroup, and did not include this subgroup in further analysis. Thus, the HighGr and LowGr subgroups were replicated at follow-up after an interval of two years. Subgroup profiles are depicted in Figure 5.2A. Descriptives and raw cluster variable scores of the subgroups can be found in S9.4.3.

Regarding the stability of subgroup profiles, Bayesian analyses indicated that most scores on the individual cluster variables were similar at follow-up (Figure 5.3, S9.4.5; see S9.4.4 for results of the total autism group). For the HighGr subgroup, there was moderate evidence ($BF_{01}$>3) for eleven out of 14 cluster variables (78%) that the data were in favor of the null hypothesis (i.e., the cluster variable scores were similar over time). For social skills, communication and worries, there was only anecdotal evidence in favor of the null hypothesis. For the LowGr subgroup, most Bayes factors also provided moderate evidence ($BF_{01}$>3) in favor of the null hypothesis, except for attention switching (anecdotal evidence H0), attention to detail (anecdotal evidence H0) and positive affect (anecdotal evidence H1). As the scores on at least 11 cluster variables (out of 14, i.e., 78%) were similar between the two timepoints, we conclude that the subgroup profiles were similar at follow-up.

**Stability of memberships: Most autistic adults remain in the same subgroup after two years**

In both subgroups, the majority of autistic adults retained their subgroup membership at follow-up (Figure 5.2B). Specifically, from the HighGr subgroup 87 adults (79%) remained in this subgroup after two years, whereas 23 (21%) switched to the LowGr sub-

group. From the LowGr subgroup 98 adults (85%) remained in this subgroup, whereas 17 (15%) switched to the HighGr subgroup at follow-up. In both subgroups, the number of participants that were not analyzed at follow-up (due to missing data or drop-out) were similar: 14 from the HighGr subgroup (11%) and 15 from the LowGr subgroup (12%).

A Bayesian test of association produced a Bayes factor > 100 (decisive evidence), in favor of the alternative hypothesis (i.e., there was an association between subgroup membership at both timepoints). Nonetheless, as there were some changes in subgroup membership over time, traditional measures typically used to assess convergence on the same sample showed that recovery was not 100% (RI=0.71, $ARI_{HA}$=0.41).

**Subgroups useful for prediction over time**

Statistics regarding the external and predictive validation can be found in Table 5.2. For external validation, subgroup differences were found on external variables measured at *the same occasion* (i.e., Sample 2; two-year follow-up). The LowGr subgroup reported (a) more cognitive failures, (b) more psychological difficulties, and (c) a lower QoL on all subscales, compared to the HighGr subgroup.

For predictive validation, subgroup differences were found on external variables measured at *a later occasion* (i.e., Sample 2, subgroups identified at baseline; external variables measured at two-year follow-up). Results indicated that the subgroups identified at baseline, scored differently on external outcomes measured at follow-up. Specifically, being a member of the LowGr subgroup at baseline was predictive of (a) more cognitive failures, (b) more psychological difficulties, and (c) a lower QoL when compared to the HighGr subgroup. Thus, subgroup membership at baseline was predictive of future external outcomes.

**Autism subgroups also stable at five-year follow-up**

At five-year follow-up (N=80), we again identified three subgroups of which two profiles were highly similar to those of the HighGr and LowGr subgroups identified at baseline. Subgroup profiles are depicted in Figure 5.2C. Descriptives and raw cluster variable scores of the subgroups can be found in S9.4.3. The HighGr (N=30) and LowGr (N=35) subgroups included most of the autistic adults, whereas the third "Rest"-subgroup (N=15) included a minority.

Bayesian analyses indicated that scores on most cluster variables pointed towards similarity over time (S9.4.6; see S9.4.4 for results of the total autism group). For the HighGr subgroup, there was evidence in favor of the null hypothesis (i.e., similar scores on cluster variables over time) for most cluster variables, although it did not meet the





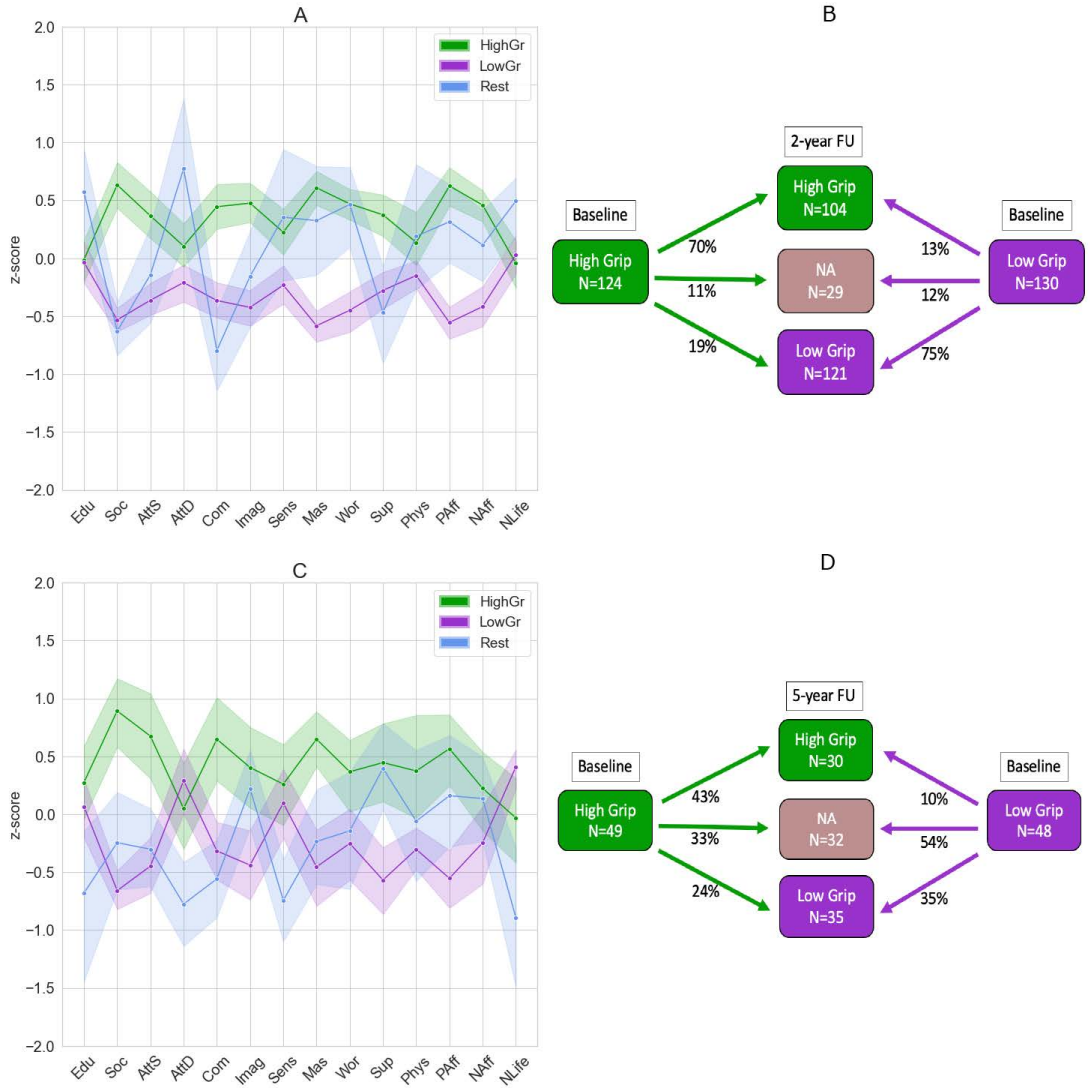



*Figure 5.2.* A. Profiles of the three autism subgroups based on Sample 2 at two-year follow-up. B. Stability of subgroup membership from baseline to two-year follow-up based on Sample 2. C. Profiles of the three autism subgroups based on Sample 1 at five-year follow-up. D. Stability of subgroup membership from baseline to five-year follow-up based on Sample 1.

*Note.* HighGr = Feelings of High Grip. LowGr = Feelings of Low Grip. Edu = education, Soc = social skills. AttS = attention switching. AttD = attention to detail. Com = communication. Imag = imagination. Sens = sensory sensitivity. Mas = mastery. Wor = worry. Sup = emotional support. Phys = physical activity. PAff = positive affect. NAff = negative affect. NLife = negative life events. NA = not analyzed (due to drop-out, missing data, or switches to the Rest subgroup). Higher z-scores represent higher scores on Edu, Soc, AttD, AttS, Com, Imag, Mas, Sup, Phys, PAff. Higher z-scores represent better scores on Sens, Wor, Naff, NLife (i.e., less sensitivity, less worrying, less negative affect, fewer negative life events). Shaded area represents 95%-confidence interval.

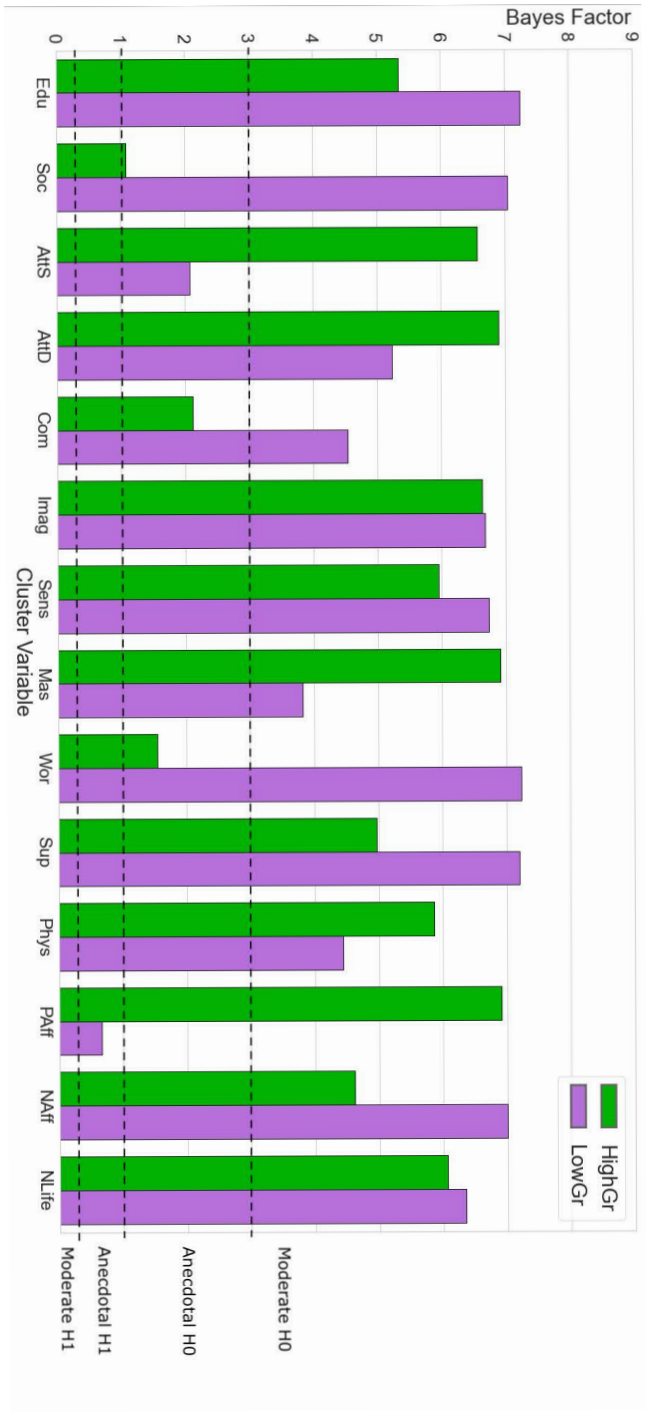



*Figure 5.3.* Bayes Factors (with standard/flat prior) indicating stability of cluster variable scores per subgroup over a two-year interval.

*Note.* Bayes Factors under 1 indicate evidence for a difference over time, a value of 1 represents no evidence, and values above 1 indicate evidence for stability cluster variable scores. HighGr = Feelings of High Grip, LowGr = Feelings of Low Grip, Edu = education, Soc = aocial skills, AttS = attention switching, AttD = attention to detail, Com = communication, Imag = imagination, Sens = sensory sensitivity, Mas = mastery, Wor = worries/fears, Sup = emotional support, Phys = physical activity, PAff = positive affect, NAff= negative affect, NLife = negative life events.





threshold for "moderate evidence". For variables related to autism characteristics, there was evidence in favor of the alternative hypothesis: a decrease in difficulties with social skills, and imagination, and an increase in attention switching. For the LowGr subgroup, there was either anecdotal or moderate evidence in favor of the null hypothesis for eight cluster variables. There was moderate evidence in favor of the alternative hypothesis for mastery (increase), and a decrease in worries, and negative life events.

For the stability of subgroup membership, a Bayesian test of association produced a Bayes factor of 50.8 (very strong evidence) in favor of the alternative hypothesis (i.e., there was an association between subgroup membership at baseline and five-year follow-up). Specifically, from the HighGr subgroup 21 (64%) autistic adults remained in this subgroup, whereas 12 (36%) switched to the LowGr subgroup. From the LowGr subgroup 17 (77%) adults remained in this subgroup, whereas 5 (23%) switched to the HighGr subgroup. Detailed percentages regarding subgroup membership stability can be found in Figure 5.2D. These switches in subgroup membership were also reflected in lower values on other measures (RI=0.57, $ARI_{HA}$=0.13). Thus, after five years (a) the same number of subgroups was identified, (b) scores on less than 50% of the cluster variables were similar (with $BF_{01}$>3) according to Bayesian analyses, (c) stability of subgroup membership over time was at least 64%.

**Five-year follow-up: subgroups still predictive of clinical external outcomes**

Regarding predictive validation, the results were similar to the two-year follow-up. Subgroup membership established at baseline was predictive of external outcomes measured after five years. Specifically, being a member of the LowGr subgroup as compared to the HighGr subgroup was associated with more cognitive failures and psychological difficulties, and a lower QoL at follow-up. Detailed statistics of the predictive validation can be found in S9.4.7.

## Discussion

The goal of this study was to determine the prognostic utility of two previously identified autism subgroups. This study shows that (a) autistic adults and non-autistic adults formed separate subgroups, (b) the LowGr and HighGr autism subgroups were stable up to two to five years after baseline, (c) the subgroups can be used to make clinical predictions over time. When zooming out from the subgroup-level, findings from the overall autism group show that most characteristics remain similar with age, some difficulties decrease (i.e., social interaction, communication and worries), while none seem

Table 5.2

*External and predictive validation measures for the two autism subgroups based on Sample 2 (N=231).*

| | **External validation[a]** | | | | **Predictive validation[b]** | | | |
|---|---|---|---|---|---|---|---|---|
| | Subgroup | | | | Subgroup | | | |
| | HighGr (N=109) | LowGr (N=122) | | | HighGr (N=124) | LowGr (N=130) | | |
| | **M(SD); range** | **M(SD); range** | **Test statistic** | **ES ($\eta^2$)** | **M(SD); range** | **M(SD); range** | **Test statistic** | **ES ($\eta^2$)** |
| **Cognitive failures** | | | | | | | | |
| Total score | 39.9 (13.9); 0-73 | 50.2 (15.5); 18-95 | $F(1,212) = 26.2^{***}$ | 0.11 | 40.3 (14.2); 0-75 | 50.6 (15.6); 18-95 | $F(1,206) = 25.3^{***}$ | 0.11 |
| **Psychological difficulties** | | | | | | | | |
| Total score | 142.7 (38.9); 95-259 | 201.6 (57.5); 103-406 | $F(1,227) = 80.3^{***}$ | 0.26 | 151.0 (45.2); 95-278 | 198.0 (59.3); 103-406 | $F(1,221) = 44.0^{***}$ | 0.17 |
| Anxiety | 15.0 (5.7); 10-36 | 22.3 (8.0); 10-49 | $F(1,229) = 63.1^{***}$ | 0.22 | 16.0 (6.6); 10-39 | 21.8 (8.1); 10-49 | $F(1,223) = 34.9^{***}$ | 0.14 |
| Agoraphobia | 9.0 (2.6); 7-21 | 13.7 (6.0); 7-35 | $F(1,229) = 57.6^{***}$ | 0.20 | 9.3 (3.2); 7-24 | 13.7 (5.9); 7-35 | $F(1,223) = 49.3^{***}$ | 0.18 |
| Depression | 27.3 (9.6); 16-54 | 41.6 (13.8); 19-76 | $F(1,227) = 80.8^{***}$ | 0.27 | 29.8 (11.7); 16-70 | 40.4 (14.0); 17-76 | $F(1,221) = 37.5^{***}$ | 0.15 |
| Somatization | 18.9 (6.4); 12-38 | 23.8 (7.9); 12-51 | $F(1,229) = 27.0^{***}$ | 0.11 | 20.0 (7.0); 12-38 | 23.3 (7.8); 12-51 | $F(1,223) = 11.33^{***}$ | 0.05 |
| Cognitive performance deficits | 16.8 (5.9); 9-35 | 23.8 (7.8); 9-43 | $F(1,229) = 57.4^{***}$ | 0.20 | 17.8 (6.4); 9-35 | 23.5 (8.0); 9-45 | $F(1,223) = 34.1^{***}$ | 0.13 |
| Interpersonal sensitivity | 28.2 (9.1); 18-63 | 39.6 (14.1); 18-84 | $F(1,229) = 52.6^{***}$ | 0.19 | 29.2 (9.7); 18-63 | 39.3 (14.5); 18-84 | $F(1,223) = 37.2^{***}$ | 0.14 |
| Hostility | 8.4 (3.0); 6-24 | 10.0 (3.9); 6-25 | $F(1,229) = 11.8^{***}$ | 0.05 | 8.6 (2.9); 6-22 | 9.9 (4.1); 6-25 | $F(1,223) = 7.6^{**}$ | 0.03 |
| Sleep difficulties | 6.3 (3.0); 3-15 | 8.8 (3.5); 3-15 | $F(1,229) = 33.9^{***}$ | 0.13 | 6.8 (3.2); 3-15 | 8.5 (3.5); 3-15 | $F(1,223) = 15.5^{***}$ | 0.07 |
| Rest | 13.0 (4.0); 9-29 | 17.9 (5.8); 9-39 | $F(1,229) = 54.6^{***}$ | 0.19 | 13.8 (4.2); 9-29 | 17.5 (6.1); 9-39 | $F(1,223) = 28.1^{***}$ | 0.11 |
| **Quality of Life** | | | | | | | | |
| Physical health | 14.4 (2.6); 9-19 | 11.8 (2.9); 5-19 | $F(1,229) = 51.8^{***}$ | 0.18 | 14.1 (2.8); 7-19 | 11.9 (3.0); 5-19 | $F(1,223) = 30.8^{***}$ | 0.12 |
| Psychological | 13.6 (2.3); 8-19 | 10.4 (2.3); 5-17 | $F(1,229) = 118.0^{***}$ | 0.34 | 13.2 (2.5); 7-19 | 10.6 (2.5); 5-17 | $F(1,223) = 62.4^{***}$ | 0.22 |
| Social relationships | 13.3 (3.0); 7-20 | 10.7 (2.8); 4-16 | $F(1,229) = 44.3^{***}$ | 0.16 | 13.0 (3.0); 7-20 | 10.9 (3.1); 4-20 | $F(1,223) = 26.7^{***}$ | 0.11 |
| Environment | 15.9 (2.2); 9-20 | 14.0 (2.7); 6-20 | $F(1,229) = 33.3^{***}$ | 0.13 | 15.8 (2.3); 9-20 | 14.1 (2.8); 6-20 | $F(1,223) = 25.8^{***}$ | 0.10 |

*Note.* HighGr = Feelings of High Grip, LowGr = Feelings of Low Grip, ES = effect size.
[a] Subgroups identified at two-year follow-up based on Sample 2; external variables also measured at two-year follow-up.
[b] Subgroups identified at baseline based on Sample 2; external variables measured at two-year follow-up. *** $p < 0.001$. ** $p < 0.01$

We conclude that the autism subgroups are stable over time based on three pre-registered criteria. First, the community detection analysis again resulted in two major subgroups at two- and five-year follow-up. Second, subgroup profiles (i.e., the average scores on the cluster variables per subgroup) were similar over time on at least half of the cluster variables. Specifically, from baseline to two-year follow-up, scores on 11 out of 14 cluster variables were similar according to Bayesian analyses. From baseline to five-year follow-up, the evidence did not meet the threshold for "moderate evidence", as average scores on only up to four out of fourteen cluster variables were similar. However, the evidence still pointed in the same direction as for the two-year follow-up. Third, subgroup membership was stable from baseline to two- and five-year follow-up according to Bayesian tests of association. This implies that most autistic adults remained in the same subgroup over time.

Although most autistic people retained their subgroup membership over time, this study also shows that switches between subgroups were possible. After two years, 21% switched from the HighGr to the LowGr subgroup, whereas 15% switched from the LowGr to the HighGr subgroup. These percentages were even higher after five years: 36% switched from the HighGr to the LowGr subgroup, and 23% switched from the LowGr to the HighGr subgroup. In the current study, modifiable factors (e.g., physical activity, social skills) were included intentionally, to ensure that changes over time were a possibility. Thus, although the majority of autistic people retained their subgroup membership over time, changes to a subgroup with a more advantageous outcome may occur.

Besides being stable over time, the autism subgroups showed potential utility for clinical practice. Subgroup membership at baseline was predictive of clinically relevant external outcomes (i.e., cognitive failures, psychological difficulties, and QoL) measured after two to five years. Membership of the LowGr subgroup, that was associated with the most vulnerable profile on the cluster variables, was predictive of more cognitive failures, more psychological difficulties and a lower QoL. This was the case even when these outcomes were measured after five years. By considering someone's prognosis based on current subgroup membership, we can focus on intervening on associated vulnerabilities to prevent more cognitive failures, more psychological difficulties and a lower QoL later in life. This study shows which variables —next to autism characteristics — may distinguish these subgroups, namely mastery, worries, emotional support, and affect. As these variables are modifiable in varying degrees, they may be most fruitful for support. Therefore, it may be valuable for future studies to further investigate the potential of these factors for clinical practice.

This study has several strengths. First, a sample of over 300 autistic adults was included, which was large compared to what is commonly reported in the autism subgrouping literature (Agelink van Rentergem et al., 2021). This sample was followed over a period of two to five years, providing valuable longitudinal knowledge on aging with autism, even when we zoom out from the subgroup level. When considering the total group of autistic adults, results indicated that (a) most factors seemed stable over time, (b) some difficulties decreased with age (i.e., worries, and difficulties with social skills and communication), whereas (c) none increased with age. Second, this study included a non-autistic comparison group to assess whether the observed heterogeneity in autism in distinct from variation in non-autistic adults. Third, the validity of the identified subgroups was demonstrated in multiple ways, substantiating the idea that the subgrouping solution was sensible. Fifth, the analysis plan was pre-registered.

There are also some limitations that need to be considered when interpreting the study findings. First, the representativeness of the study sample is restricted to autistic adults with (a) an average to above average intelligence, and (b) an autism diagnosis received in adulthood. Thus, the findings may not generalize to autistic adults with a below average intelligence, or those who received their diagnosis in childhood. Second, the dropout at follow-up may have influenced the results. Compared to the group of autistic adults that was included at follow-up, the dropout group included relatively more men. In the non-autistic comparison group, those who dropped out had an average lower age and IQ score compared to those included at follow-up. Third, it is important to note that the findings of the current study should be interpreted in light of the COVID-19 pandemic that occurred when the follow-up data were collected. As shown by a recent review, the pandemic had a significant impact on the lives of autistic adults (Scheeren et al., 2023). An overall decrease in wellbeing during the pandemic was reported. This potential influence on the current study could explain the finding that there were relatively more people switching from the HighGr subgroup to the LowGr subgroup at follow-up than vice versa. This finding applied to both autism samples (i.e., Sample 1 and 2) and suggests that switches were more likely to occur to the subgroup with more experienced difficulties (i.e., LowGr), which could be expected during a pandemic.

This study highlights the stability of two previously identified subgroups of autistic adults in terms of profiles and memberships, and demonstrates their predictive value for clinical outcomes measured up to five years in time. While subgroup membership seems generally stable over time, switches to a subgroup with a different (perhaps more favorable) outcome were possible. Therefore, even for those autistic adults who are susceptible to more day-to-day difficulties, aging does not inevitably lead to a less favorable outcome. Further considering these autism subgroups and focusing on their potential for clinical practice could be valuable to improve the lives of people on the autism spectrum.



# Chapter 6

# Cognitive aging in autism subgroups

This chapter will be submitted as:

*Radhoe, T.A., *Torenvliet, C., Agelink van Rentergem, J.A., Groenman, A.P., & Geurts, H.M. (2023). *Cognitive aging in autism subgroups: A short report* [Manuscript to be submitted to Autism]. Preprint doi: 10.31234/osf.io/ejszy

* Shared first authorship

## Abstract

**Background**: Research on cognitive aging in autism yielded inconclusive results, which could be due to the heterogeneity among autistic adults. Possibly, some autistic adults are more vulnerable to accelerated cognitive aging than others. We previously identified two subgroups of autistic adults that differed on behavioral (psychological, demographic and lifestyle) characteristics, with one reporting more difficulties in daily life. This study aims to assess whether these subgroups are associated with different patterns of cognitive aging.

**Methods**: Two autism subgroups ($N_1$=65, $N_2$=78) were compared on eleven separate cognitive outcomes, and on their entire cognitive profile. We assessed age-related effects between the subgroups on five cognitive outcomes, cross-sectionally and longitudinally. Next to these pre-registered analyses, the subgroups were compared to a non-autistic comparison group (N=254).

**Results**: The subgroups did not differ significantly on the cognitive outcomes or entire cognitive profile. Moreover, no differences in age-related effects or decline were observed. Differences with the non-autistic comparison group were similar across subgroups.

**Conclusions**: The current results provide evidence for fairly similar cognitive aging across two autism subgroups. Differences in behavioral characteristics between autism subgroups do not necessarily translate to differences in cognition, at least in those with (above) average intellectual abilities and adulthood diagnoses.






## Introduction

In the past decade, the field of aging in autism has evolved rapidly, with many acknowledging the need for research on the psychological, and cognitive consequences of autistic aging (Mason et al., 2021). On cognitive aging specifically, the field developed from the first cross-sectional studies on age-related differences in 2012, to the first longitudinal studies on age-related decline in 2022 (Tse et al., 2022). Most cross-sectional findings indicate evidence for parallel (similar) age-related cognitive effects between autistic and non-autistic adults (Tse et al., 2022). However, longitudinal outcomes yield inconsistent results with some hinting at accelerated aging in autism, yet others observing the same parallel patterns of age-related decline (Pagni et al., 2022; Torenvliet, Groenman, Radhoe, Agelink van Rentergem, Van der Putten, et al., 2022; Walsh et al., 2022). Although these inconsistencies across studies could be attributed to differences in study design or sample size, heterogeneity between autistic individuals may also play a role.

It could be that for some autistic individuals cognitive aging follows a largely similar course to those without autism, yet that others might be vulnerable to accelerated cognitive decline. Cognitive profiles of autistic adults have been shown to vary, hinting at individual differences in cognitive functioning (Torenvliet, Groenman, Radhoe, Agelink van Rentergem, & Geurts, 2022). Therefore, the current study explicitly considers the known heterogeneity within the autism spectrum by examining differences in cognitive functioning between two validated and replicated autism subgroups (Chapter 3; Radhoe, Agelink van Rentergem, Torenvliet, et al., 2023). These subgroups were detected in over 350 autistic adults based on psychological, demographic, and lifestyle characteristics. These subgroups differed both on the measures used to construct the subgroups and external outcomes used for subgroup validation (further referred to as "behavioral characteristics'). The first, labeled as "Feelings of LowGrip" (LowGr), showed a more vulnerable profile, and was associated with more self-reported psychological difficulties, cognitive failures, and a lower quality of life (QoL). The second, "Feelings of HighGrip" (HighGr), showed lower susceptibility for these difficulties alongside a higher QoL. As also argued by others (Mason et al., 2021; Torenvliet et al., 2023), we hypothesize that these characteristics might translate to differences in the pace of cognitive aging.

This pre-registered exploratory study examines whether the previously defined subgroups differ on: 1A) separate domains of cognitive functioning, and 1B) the overall cognitive profile (deviating or not). Further, we explore whether 2A) age-related differences (cross-sectional), and 2B) age-related decline (longitudinal) are different between the two subgroups. Specifically, we expect that the LowGr subgroup has a less favorable cognitive outcome compared to the HighGr subgroup, see for details Figure 6.1.

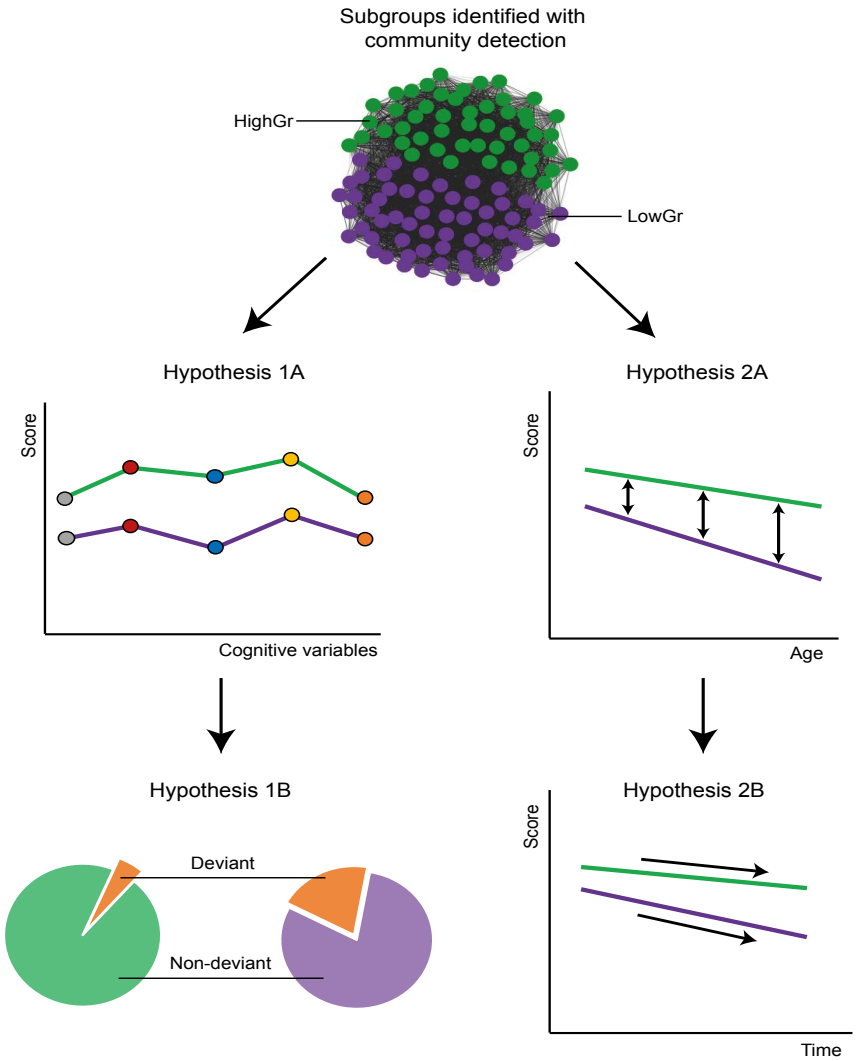



*Figure 6.1.* Overview of our four hypotheses and analysis steps: green representing the "Feelings of High Grip" subgroup and purple representing the "Feelings of Low Grip" subgroup.

*Note.* HighGr = "Feelings of High Grip". LowGr = "Feelings of Low Grip".
Hypothesis 1A: autistic adults in the LowGr subgroup score lower on separate domains of cognitive functioning compared to the HighGr subgroup. Hypothesis 1B: individuals in the LowGr subgroup are more likely to be classified as having a deviating overall cognitive profile compared to the HighGr subgroup. Hypothesis 2A: individuals in the LowGr subgroup show larger negative age effects (cross-sectionally). Hypothesis 2B: individuals in the LowGr subgroup show larger negative age effects over time (longitudinally) compared to the HighGr subgroup.





# Methods

**Participants & Design**

From a larger longitudinal study (Chapter 8; Geurts et al., 2021), a subset (N=143) was selected, consisting of those autistic individuals who completed both questionnaires and cognitive testing. There were 65 autistic adults in the HighGr subgroup and 78 autistic adults in the LowGr subgroup. Participants were between 24 and 85 years of age and had a registered autism diagnosis. Exclusion criteria are described in the Supplementary Materials S9.5.1.

The study design and analysis plans were preregistered at AsPredicted.org, included in Chapter 8 (#114410). When analyses were performed complementary to the pre-registration, this was indicated in the results. This study was part of a larger longitudinal study on aging and autism (Chapter 8; Geurts et al., 2021). A multistage overlapping cohort design was used with two cohorts that were measured at different timepoints. Participants first filled out sets of questionnaires, after which a subsample was administered cognitive measures. We included cognitive data from three waves: Cohort 1 was first included at Wave 1 (2012-2014) and was measured for the second time at Wave 3 (2018-2020). Cohort 2 was first included at Wave 3 and was measured for the second time at Wave 4 (2021-2022). No cognitive data was collected at Wave 2.

**Measures**

***Subgroup membership:*** Participants were assigned to a specific subgroup (out of two) based on the results of a previous community detection analysis using self-report questionnaire data (for more info, see Chapter 3; Radhoe, Agelink van Rentergem, Torenvliet, et al. [2023]). While the subgroups did not differ on all self-reported characteristics, the autistic adults in the first subgroup (HighGr), reported more feelings of control (or mastery), with higher levels of positive affect and social skills. The second subgroup (Low Grip) was characterized by a more vulnerable profile with less feelings of control, and higher levels of worries and negative affect.

***Multivariate Normative Comparisons (MNC) status:*** Participants' cognitive profiles were classified "deviating" versus "non-deviating" as compared to a non-autistic norm group based on eleven cognitive outcomes using a statistical multivariate comparison method (MNC, for more info, see Torenvliet et al. [2022]). "Deviating" indicated a statistical difference on the entire cognitive profile compared to the norm, whereas "non-deviating" implied a non-significant difference in their overall cognitive profile.

***Cognitive outcomes:*** Eleven cognitive variables were included (on six domains) that all had sufficient psychometric properties. All measures were administered in a counter-balanced order and have been used before in aging and/or autism research. Below, the measures are described briefly, more details are provided in S.9.5.2 (see also Torenvliet et al., 2021).
Visual memory involved remembering a set of geometrical figures, replicating the figures directly after presentation (immediate recall: 0-104), after 30 minutes (delayed recall: 0-104), and finally recognizing the figures (recognition: 0-48).

*Visual memory* involved remembering a set of geometrical figures, replicating the figures directly after presentation (immediate recall: 0-104), after 30 minutes (delayed recall: 0-104), and finally recognizing the figures (recognition: 0-48).

*Verbal memory* involved remembering a list of 15 unrelated words (auditory presentation) over five learning trials, recalling the words immediately after each trial (immediate recall: 0-75), after a delay of 30 minutes (delayed recall: 0-15), and finally recognizing the words (recognition: 0-30).

*Verbal fluency* involved listing as many words as possible in one minute that started with a certain letter (D, A, T; total score letter fluency) or were from a certain category (animals, professions; total score category fluency).

*Processing speed* involved a computerized two-choice-response task: pressing a left or right button that corresponded to a colored circle (blue/green) as quickly as possible (mean response time on correct responses).

*Theory of Mind* involved detecting a faux pas in nine stories and answering follow-up questions about the social content of the story (total score: 0-38).

*Visual working memory* involved a computerized visual N-back task with three conditions: first indicating a specific object (0-back), second whether the object was the same as the previous object (1-back) and finally indicating whether the current object was the same as two trials before (2-back; 2/0-back accuracy ratio: -1.0-1.0).





# Results

Descriptives and baseline cognitive performance of the subgroups are provided in Table 6.1. The subgroups did not differ significantly in demographic characteristics, except for a lower estimated IQ in the LowGr subgroup.

**Part 1: No differences in cognitive outcomes between the two subgroups**

Descriptive statistics of the cognitive outcomes in each of the subgroups are provided in Table 6.1. Independent *t*-tests between the two subgroups indicated no significant subgroup differences on nearly all cognitive outcomes, with the majority of Bayes Factors indicating moderate evidence for equal performance across the subgroups. Only on working memory a significant group effect was observed with lower test scores for the LowGr compared to the HighGr subgroup. However, the effect became non-significant after multiple comparison corrections, and the Bayes Factor indicated anecdotal evidence in favor of a subgroup difference. In addition to our pre-registered analyses, the subgroups were compared to a non-autistic comparison group, see S.9.5.3 for details. Scores of both subgroups were comparable to the non-autistic group on most cognitive outcomes. Differences that were observed were similar across subgroups.

A Chi-square test indicated that MNC status (deviating/not deviating) was not significantly different between the two subgroups ($n_{deviating\text{-}HighGr}$=12 (18.5%), $n_{deviating\text{-}LowGr}$ =17 (21.8%), $\chi 2(2)$ =.08, p=.78). In sum, the subgroups differed neither on separate cognitive outcomes nor on an aggregated measure of cognitive functioning.

**Part 2: No age-related cognitive differences between the two subgroups**

Five separate multiple regressions were conducted with age, subgroup, and their interaction as predictors, on each of the pre-registered cognitive outcomes: visual/verbal recall I, letter/category fluency, and processing speed. Statistics are provided in S.9.5.4. None of the age*subgroup interactions reached statistical significance (all uncorrected *p*'s > .07), indicating parallel age-related effects between the HighGr and LowGr subgroups.

Sample characteristics of the longitudinal subsample that participated at follow-up ($n_{tot}$=103, see Torenvliet et al., [2023] for details) are provided in S.9.5.5, and were comparable to the total sample. As this subsample consists of two cohorts ($n_{C1}$=40, $n_{C2}$=63) with varying time-intervals between the two measurements (C1 5-7 years; C2 1.5-2.5 years), we assessed these cohorts separately. Five separate multilevel regressions were conducted with the effects of interval (time between T1-T2), subgroup, and their interactions as predictors, on the same five cognitive outcomes in each of the two cohorts. Statistics are provided in S.9.5.5. None of the interval*subgroup interactions reached statistical significance (all *p*'s>.12) in neither cohort, indicating similar cognitive chan-

ges over time between the two subgroups.

Table 6.1
*Descriptive characteristics and cognitive outcomes in the HighGr and LowGr subgroups.*

| | HighGr (n=65) | LowGr (n=78) | | | |
|---|---|---|---|---|---|
| Sex (M/F, M%) | 43/22, 66% | 48/30, 62% | $\chi^2$=0.57 | | |
| Education[a] | 4/38/23 | 2/50/26 | $\chi^2$=1.32 | | |
| | Mean, SD (min-max) | Mean, SD (min-max) | *t*-value | Cohen's *d* | $BF_{10}$ |
| Age (yrs.) | 52.2, 14.4 (24-79) | 51.7, 14.0 (30-85) | -0.26 | -0.04 | 0.86 |
| Estimated IQ[b] | 119.9, 15.5 (85-153) | 114.2, 15.9 (85-155) | **-2.18*** | -0.37 | 1.56 |
| Visual recall I | 89.9, 10.9 (56-103) | 86.8, 14.0 (26-103) | -1.46 | -0.24 | 0.48 |
| Visual recall II | 74.5, 21.5 (16-103) | 73.9, 21.0 (0-103) | -0.15 | -0.03 | 0.18 |
| Visual recognition | 45.1, 2.5 (37-48) | 44.7, 2.6 (35-48) | -0.99 | -0.17 | 0.28 |
| Verbal recall I | 46.1, 11.4 (20-72) | 46.3, 10.7 (15-68) | 0.07 | 0.01 | 0.18 |
| Verbal recall II | 10.0, 3.2 (3-15) | 9.6, 3.2 (1-15) | -0.65 | -0.11 | 0.22 |
| Verbal recognition | 28.7, 2.9 (10-30) | 28.6, 2.2 (17-30) | -0.23 | -0.04 | 0.19 |
| Theory of Mind | 27.6, 5.1 (13-35) | 26.5, 6.5 (11-38) | -1.12 | -0.18 | 0.32 |
| Letter Fluency | 40.1, 13.3 (16-81) | 38.2, 10.1 (12-60) | -0.97 | -0.17 | 0.28 |
| Category Fluency | 44.6, 10.7 (23-69) | 42.0, 9.7 (13-68) | -1.47 | -0.25 | 0.49 |
| Working memory | 0.9, 0.1 (0.8-1.1) | 0.9, 0.1 (0.8-1.0) | **-2.04*** | -0.35 | 1.20 |
| Processing speed | 418.4, 65.7 (292-595) | 415.3, 64.8 (317-626) | -0.28 | -0.05 | 0.19 |

*Note.* M, male; F, female; yrs., years; $BF_{10}$, Bayes Factor evidence for H1 (group difference); **=*p*<.01; *=*p*<.05.
[a] Level of education was determined by the Verhage coding system, between slashes: junior secondary or practical education / senior secondary education or vocational college / university degree.
[b] IQ was estimated at baseline by using two subtests (matrix reasoning and vocabulary) of the Wechsler Intelligence Scale-III or IV.





# Discussion

The current study explored differences in cognitive functioning between two previously identified autism subgroups. Results indicate no significant differences between subgroups on (a) separate cognitive outcomes, and (b) the entire cognitive profile (MNC deviating/non-deviating). Moreover, there were no age-related cognitive differences between the subgroups when measured cross-sectionally or longitudinally. Therefore, this study provides evidence against differences in cognition or cognitive age-related effects between the two autism subgroups.

Although no evidence was found for differences in cognition, this does not imply that these subgroups are equivalent across domains. As shown in our earlier study, the LowGr subgroup was associated with more vulnerabilities at the behavioral level compared to the HighGr subgroup (Radhoe, Agelink van Rentergem, Torenvliet, et al., 2023). Thus, although it cannot be concluded that the subgroups are overall equivalent, they do seem comparable on measures of objective cognitive functioning. This was also indicated by the comparison with a group of non-autistic adults. On most cognitive outcomes, both subgroups scored similar to the non-autistic comparison group, with differences only occurring on those domains that were previously associated with autism (Fluency, Theory of Mind; [Torenvliet, et al., 2022]). For clinical practice, these findings imply that it may be more fruitful to target modifiable behavioral characteristics related to clinical outcomes, instead of focusing on cognitive training (Dekkers & van der Oord, 2022), to support autistic adults vulnerable to a lower QoL and difficulties in daily life.

The current results also provide further evidence for the previously observed parallel (similar) age-related patterns of autistic cognitive aging. Most importantly, even those autistic individuals with most vulnerabilities at the behavioral level do not seem particularly at risk for accelerated cognitive decline. This seems to indicate that behavioral heterogeneity in autism is not a sufficient explanation for the between study variance on cognitive aging in autism. Possibly, large differences in sample sizes and sample characteristics underlie these inconsistencies. Therefore, replication studies are crucial to gain consensus on cognitive aging in autism.

Given the limited correspondence between behavioral difficulties and cognitive differences, one might even argue that studying cognitive differences in autistic adults is of limited utility. Indeed, it seems that cognitive characteristics do not necessarily "bridge the gap between brain and behavior" (Frith, 2019). The current study included outcomes that are commonly used in neuropsychological practice, for instance, when diagnosing neurodegenerative disorders such as dementia. The tests that were used have been

shown to reliably detect age-related differences, and age-related decline in both autistic and non-autistic adults, providing a reliable judgment on the risks for accelerated aging or age-related cognitive disorders in autism. However, it seems that these tests designed to detect age-related changes are not the ones that best describe autistic and non-autistic differences in cognition. Therefore, future research could focus on designing and validating cognitive measures and/or using computational models in the current tests that accurately capture the strengths and difficulties that autistic adults describe.

Although the current study is exploratory in nature, it is unique in challenging often assumed connections in translational neuroscience between different levels of psychological explanation: the behavioral and cognitive level. Researchers tend to rely on these connections when providing semantic explanations for observed differences in cognitive functioning or the brain. However, as noted by others (Buzsáki, 2020; Nour et al., 2022), these explanations are susceptible to introspective biases, especially when describing diagnostic categories. Such translational neuroscientific explanations are bound by the categories existing in our current reality, while it is unknown whether a biological basis for these categories exists. E.g., over the past decades, researchers have attempted to find biomarkers or biological differences underlying autistic behavior, but to date, no universal biological underpinnings have been identified (Jensen et al., 2022). In this regard, the current findings provide another warning against overinterpreting brain and cognitive differences in neurodivergent groups.

It is important to consider the representativeness of our study sample when interpreting the aforementioned results. Most importantly, the current sample does not represent the full spectrum of autistic adults. Average IQ was higher than that of the general population, and most participants received their diagnosis in adulthood. Although the sample was older and included relatively more women compared to other studies on cognitive aging in autism (Mason et al., 2021), fewer women than men, and few individuals over 80 years of age were included due to difficulties in recruiting these participants. Therefore, caution in generalizing these results across the spectrum is warranted.

This study showed that those autistic people with more experienced difficulties in daily life do not seem especially vulnerable to accelerated cognitive aging. This seems to suggest that difficulties in one domain do not necessarily transfer to another domain. Challenging the assumed connections between behavior and cognitive functioning seems vital to enhance our understanding of autism.



# Chapter 7

# Summary and General discussion

# Summary

Autism in adulthood is characterized by large differences between autistic people (Masi et al., 2017). These interindividual differences are often referred to as heterogeneity (Nunes et al., 2020). As a result of this heterogeneity, autistic people often do not receive the support they need and prefer (Hwang et al., 2017). Moreover, the heterogeneity within the autism spectrum, alongside the limited knowledge on the adulthood developmental trajectory, causes autistic adults to feel uncertain about what to expect as they reach older age (Finch et al., 2022). This PhD thesis aimed to bridge this gap, by advancing our knowledge of aging with autism, and heterogeneity therein. We focused on the identification of subgroups and assessed their validity and potential utility for clinical practice.

For Chapter 2, addressing aging in the general population (i.e., not focusing on autism), data from the Longitudinal Aging Study Amsterdam (Hoogendijk et al., 2016) was analyzed (N=1478). Participants were between 61 and 101 years of age. Intellectual disability was an exclusion criterion. For Chapters 3 to 6, a newly gathered longitudinal data set was used including autistic adults (Nmax=375), non-autistic adults (Nmax=345), and adults with Attention Deficit Hyperactivity Disorder (ADHD; Nmax=123). These participants were between 30 and 89 years of age and, similar to Chapter 2, did not have an intellectual disability. All autistic adults had a DSM diagnosis (American Psychiatric Association, 2000, 2013), and most received their autism diagnosis in adulthood. Chapters 3 and 4 include cross-sectional data, whereas Chapters 5 and 6 also include longitudinal data that was collected two to five years after baseline (see for more info, Geurts et al., 2021). All participants were administered sets of questionnaires (data included in Chapters 3 to 5), whereas a subset was also interviewed and completed neuropsychological tests (data included in Chapter 6). All studies were pre-registered at AsPredicted.org. The studies described in Chapters 3 to 6 were designed and interpreted in collaboration with a group of older/ autistic adults.

In **Chapter 2,** we first addressed subgroup identification in the general aging population. The goal was to evaluate the analytic approach that we planned to use for heterogeneity in autism, by first testing it for heterogeneity in the general aging population. Community detection analysis was conducted on a large sample aged 61 to 101 years from the Longitudinal Aging Study Amsterdam at two measurement occasions (NT1=1478, NT2=1186) with a three-year interval. As input variables, seven well-known vulnerability and protective factors of healthy aging were included, such as alcohol use and physical activity. Community detection analysis was used for subgroup identification, which resulted in three subgroups. These subgroups differed in the cluster variables, but also in external measures relevant to aging: wellbeing and subjective decline. At T2, the same





number of subgroups was identified, and subgroup profiles were practically identical. At least 47% of the adults per subgroup remained in the same subgroup over time. This study showed that the heterogeneity in general aging can be captured by valid subgroups that replicate over time and differ in external measures at current and later measurement occasions. As changes in subgroup membership occurred, transitions to a subgroup with a better outcome were possible.

**Chapter 3** demonstrated that a subgrouping approach was also effective to describe the heterogeneity observed in autism. A large, newly gathered data set including autistic adults (N=375), non-autistic adults (N=345), and adults with ADHD (N=123), aged 30 to 89 years was analyzed. The data set was split into two data sets for validation procedures: an original and replication data set. Fourteen self-report measures of demographic, psychological, and lifestyle variables were included. All variables were related to aging (see also Chapter 2) and/or autism. Again, community detection analyses were used for subgroup identification. Results indicated that autistic and non-autistic adults formed separate subgroups, which is in line with a categorical view of autism (Abu-Akel et al., 2019; Frazier et al., 2010). When adults with ADHD were added to the community detection analysis, it did not alter the subgrouping solution. Specifically, the ADHD group was almost equally distributed among the two earlier observed subgroups, supporting a dimensional view of ADHD and autism (van der Meer et al., 2012). Within the autism group, three autism subgroups were identified, of which two were sufficiently large and were replicated. One of these replicated subgroups, labeled as “Feelings of Low Grip” (LowGr), was susceptible for more difficulties in daily life, compared to the other subgroup (“Feeling of High Grip”, HighGr). The LowGr subgroup was also distinct on external clinical measures: Autistic adults in this subgroup reported more cognitive failures, psychological difficulties, and a lower quality of life (QoL). Hence this study indicated that valid subgroups can be found among autistic adults when including diverse factors, such as autism characteristics, demographic, psychological and lifestyle factors.

In **Chapter 4**, we aimed to get further insight into the differences between the autism subgroups (i.e., LowGr and HighGr) identified in Chapter 3. Specifically, we examined whether mean differences observed on the cluster variables corresponded to differences in network structure. Sixteen network variables were included, related to demographic, psychological and lifestyle characteristics. Networks were estimated using Gaussian Graphical Models, and a Network Comparison Test (NCT) was used for statistical comparison. First, two networks were estimated for the overall groups of autistic adults and non-autistic adults (i.e., comparison group). Second, this step was repeated within the two previously identified autism subgroups (NHighGr=124, NLowGr = 130). Moreover, sex differences were explored in the networks of the autism subgroups. Findings showed that networks of the overall autism and comparison groups showed differences based on

individual edges and visual comparison, although the NCT did not indicate any overall differences. Across the autism subgroups, networks were similar based on visual inspection and statistical comparisons. When sex was added as a network variable, it did not impact the networks differently. This study showed that networks of autism subgroups were more similar than different, although there were differences in individual edges that may be informative for targeted support. Therefore, the mean differences observed in Chapter 3, did not correspond to differences in network structure. This implies that a focus on mean differences is not sufficient when the aim is to determine which factors (and associations between factors) are important for people on the autism spectrum.

**Chapter 5** involved a longitudinal extension of the cross-sectional study described in Chapter 3. The goal was to determine whether the LowGr and HighGr subgroups were stable over time, and predictive of clinical outcomes. Subgroups were identified in two separate samples using community detection: Sample 1 (N=80 autistic adults) measured five years after baseline, and Sample 2 (N=241 autistic adults and 211 non-autistic adults) measured two years after baseline. Participants were aged 31 to 86 years at follow-up. As input for the community detection analysis fourteen variables related to demographic, psychological, and lifestyle factors were included (i.e., the same variables included in Chapter 3). The stability of the subgroups was assessed based on (a) the number of subgroups at baseline and follow-up, (b) subgroup profiles on the cluster variables (>50% had to be similar over time), and (c) subgroup membership. For predictive validity, we assessed whether the subgroups identified at baseline were predictive of clinical outcomes measured at follow-up (i.e., cognitive failures, psychological difficulties and QoL). Results showed that autistic and non-autistic adults formed distinct subgroups. Within both autism samples, the LowGr and HighGr autism subgroups were replicated at follow-up. The subgroup profiles were similar for at least 50% of the cluster variables at two-year follow-up, and for 21% at five-year follow-up. Moreover, the cluster variables that showed changes with age, differed between the two subgroups. After two years, 80% of autistic adults remained in the same subgroup, and 64% after five years. With regard to the predictive validity, subgroup membership identified at baseline was predictive of the external clinical outcomes at both follow-up measurement occasions. Therefore, the stability and predictive value of the autism subgroups was demonstrated, and our preregistered criteria for subgroup similarity were met at both the two-year and five-year follow-up. Moreover, these findings imply that subgroup profiles — while still considered stable — may vary over time, and that transitions to a different subgroup with a different outcome are possible.

The goal of **Chapter 6** was to extend our findings from the behavioral characteristics in Chapters 3 to 5, to the cognitive level. Aging is often accompanied by changes in cognition. Some argue that autistic adults might be more vulnerable to cognitive aging,





reflected by higher risks of neurodegenerative diseases (Croen et al., 2015; Vivanti et al., 2021) and more self-reported cognitive failures (Klein et al., 2022; Lever & Geurts, 2016a). This is one of the factors contributing to the concerns many autistic adults have about their aging process. In this study, we aimed to gain more insight into cognitive aging in autism by considering the identified autism subgroups. Specifically, we explored whether the LowGr and HighGr subgroups differed on (a) individual cognitive measures, (b) overall cognitive profiles (i.e., having an overall deviating or non-deviating cognitive profile), and age-related effects when measured (c) cross-sectionally and (d) longitudinally. The autism subgroups (NHighGr= 65, NLowGr = 78) were compared on 11 cognitive measures in total, encompassing visual/verbal memory, fluency, processing speed, theory of mind, and visual working memory. Both subgroups were also compared to a non-autistic comparison group (N=254). Results indicated no significant differences on the individual cognitive outcomes, or the overall cognitive profile. In addition, no differences were observed in age-related effects or decline. When compared to non-autistic adults, differences in cognition were similar across subgroups. Therefore, this study demonstrates that differences in behavioral characteristics (i.e., demographic, psychological, and lifestyle characteristics) between the autism subgroups do not necessarily translate to differences in cognition. Moreover, it shows that autistic adults who seem vulnerable to daily life difficulties (i.e., the LowGr subgroup), do not appear particularly vulnerable to accelerated cognitive aging.

# General discussion

## Insights into aging

This PhD thesis advances our knowledge on aging in the general population, and aging in autism, in several ways. At the general population level (Chapter 2), it shows that a subgrouping approach can effectively capture the variability seen in general aging. This implies that broad statements made on the associations between a risk factor, or a trend of cognitive decline with age, may only apply to a portion of the elderly population. Moreover, these findings could explain why researchers may struggle to detect differences at the population level (Ferrucci & Kuchel, 2021), while zooming in at the subgroup level may provide a less ambiguous picture. Hence, even in non-clinical populations, studying heterogeneity may be insightful.

As our knowledge on aging in autism is still very limited (Tse et al., 2022; Wise, 2020), the studies in this thesis add valuable knowledge on what happens as autistic adults reach older age. When considering the overall autism group (i.e., zooming out from the subgroup-level), our findings from Chapter 5 show that most behavioral characteristics remain similar up to two years in time: mastery, some autism characteristics, physical activity, negative affect, negative life events, and education. After five years, this still applied to around half of the characteristics: education, sensory sensitivity, emotional support, physical activity, positive affect, and negative life events. Moreover, the longitudinal findings also show that some difficulties appear to decrease with age (i.e., difficulties with social interaction and communication, and worries), while none seem to increase with age. Hence these results show that aging in autism is not inevitably associated with increased behavioral difficulties, as most characteristics seem stable over time and some even improve.

However, when we consider the heterogeneity in autism and focus on the subgroup level instead, this stability over time appears even stronger. Within subgroups, almost all behavioral characteristics were similar up to two years in time. These numbers were lower at five-year follow-up. Nonetheless, even after five years, scores on most cluster variables point towards similarity over time according to Bayesian analyses. Interestingly — and supporting the validity of the subgrouping approach — the cluster variables that changed over time, differed between the autism subgroups. The HighGr subgroup was characterized by fewer difficulties with social skills and imagination, and more difficulties with attention switching over time. The LowGr subgroup showed an increase in mastery, and a decrease in worries and negative life events over time. These differential findings provide further evidence for the importance of considering subgroups within the autism spectrum.





While this thesis mostly included information at the behavioral level (i.e., demographic, psychological, and lifestyle characteristics), we also extended our findings to the cognitive level. This is unique compared to the autism research literature so far, and it provides valuable insights. While studies often mention behavioral heterogeneity in autism as a possible explanation for their findings on other levels of psychological explanation (e.g., cognitive level, genetic level), most studies do not directly test the validity of this explanation. Our findings from Chapter 6 show that the autism subgroups, that differed on many behavioral characteristics, did not differ on the cognitive level. As follows, this study suggests that caution in overinterpreting differences across psychological levels of explanation is called-for. It also suggests that including information at different levels (e.g., behavior, cognition, genetics) may be important and valuable for future studies investigating autism.

## Clinical insights

The goal of this PhD thesis was to focus on the identification of autism subgroups and to assess their potential for clinical practice. In this section, specific choices in study design, the clinical relevance of our results, and suggestions for future research from a clinical point of view are addressed.

Several measures were taken to increase the likelihood that we would detect clinically relevant subgroups. As input variables for the community detection analysis (also referred to as cluster variables), we included self-report measures of autism characteristics, psychological, and lifestyle variables. These measures can be easily administered on a large scale, and they are modifiable in nature, to varying extents. These input variables were selected based on their relevance for the clinical outcomes of interest for autism as well as aging: cognitive failures, psychological difficulties, and QoL. Thus, even when a data-driven statistical method — such as community detection — is used, one can still adopt a theory-driven approach to determine which factors are relevant to consider with this statistical approach. This combined approach may be even more promising to result in meaningful study results compared to a fully theory-driven or fully data-driven approach.

Our choices in design resulted in two autism subgroups that differed in their susceptibility for difficulties in daily life, as described in Chapter 3. The external validity of the subgroups was demonstrated, as the subgroups differed on the external clinical variables that were measured at the same measurement occasion. Specifically, the LowGr subgroup reported more cognitive failures, psychological difficulties and a lower QoL

compared to the HighGr subgroup. In Chapter 5, the prognostic utility of the autism subgroups was demonstrated. Subgroups identified at baseline were predictive of clinically relevant external outcomes measured up to five years in time. When measured longitudinally, the LowGr subgroup was still associated with the most vulnerable profile on the external measures: more cognitive failures, psychological difficulties, and a lower QoL. Consequently, differences in external clinical outcomes — measured both at the same measurement occasion and five years in time — can be effectively described by the identified autism subgroups.

For clinical practice, these findings suggest that it may be wise to consider a diverse range of factors, rather than merely focusing on the level of autism characteristics, when aiming to understand someone's clinical profile (i.e., cognitive and psychological difficulties, and QoL). As follows, these results are in line with the clinical guidelines for autistic adults (National Institute for Health and Care Excellence, 2012; Werkgroep Multidisciplinaire Richtlijn Autismespectrumstoornissen bij Volwassenen, 2013), which recommend developing tools to deal with one's experienced challenges rather than targeting the core features of autism. Moreover, our studies show which variables, in addition to autism characteristics, may distinguish these subgroups, namely mastery, worry, emotional support, and affect. As these factors are modifiable in varying degrees, they might be a starting point for an intervention. Possibly, mastery could be a promising target, as earlier research has demonstrated the importance of mastery in connecting depressive symptoms to autism characteristics (van Heijst et al., 2020). Improving mastery (van der Klink et al., 2001; van der Zanden et al., 2012), could result in a different profile on the cluster variables, which may be effective to transfer someone from the LowGr to the HighGr subgroup. Therefore, the potential effects of intervening on the cluster variables may be a promising pathway for future research.

Another avenue for future research may be to address whether the same subgroups can be identified using different variables that are theoretically equivalent to the variables that were used to construct the subgroups in Chapter 3 and Chapter 5 (i.e., parallel validation; Agelink van Rentergem et al., 2021). This would be a valuable additional validation step, as clinical institutions often make use of different measurement instruments, that aim to measure the same underlying constructs (e.g., different instruments are used to measure autism characteristics). To ensure that the instruments used in a given clinic are appropriate to determine to which subgroup someone belongs, assessing the parallel validity is a crucial additional step.

Furthermore, future research may investigate what causes may underlie the observed differences between the autism subgroups. In contrast to expectations, the network analysis approach adopted in Chapter 4 indicated that the networks of the HighGr and





LowGr subgroups were more similar than different. Hence, underlying differences in associations between variables do not seem to explain why the subgroups differ on the cluster variables. As follows, it has been established that the subgroups differ on behavioral characteristics, but it is still unknown why these differences occur. Future studies may focus on qualitative data, for example by asking autistic adults from the HighGr subgroup how they deal with challenges in daily life, and comparing these responses to those reported by autistic adults from the LowGr subgroup. This may produce insights on the causal mechanisms of the observed differences between the subgroups, which could in turn be informative for developing (clinical) interventions.

## Theoretical insights

In addition to focusing on subgroup identification, an important objective of this PhD thesis was to extensively evaluate the validity of the identified subgroups. In the autism literature thus far, validation procedures are often not adopted after subgroup identification (Agelink van Rentergem et al., 2021). In absence of these validation procedures, it remains unresolved whether subgroups are genuinely sensible, which in turn limits their potential for clinical practice. As the goal of this thesis was to identify subgroups that could inform clinical practice, extensive validation procedures were crucial. The validity of the autism subgroups was demonstrated in four ways. First, the subgroups were identified in two separate samples (i.e., direct replication in Chapter 3). Second, differences between subgroups were established on external clinically relevant variables that were not used in the construction of the subgroups (i.e., external validation in Chapters 3 and 5): cognitive failures, psychological difficulties and QoL. Third, the temporal stability was shown in Chapter 5 as the subgroups formed at baseline were established again after two years and after five years. Finally, the predictive validity was shown in Chapter 5 as subgroups identified at baseline were predictive of external clinically relevant variables when measured after five years. This extensive evaluation of the subgroups' validity was not only unique for the autism literature so far, but it also allowed us to draw more robust conclusions about the results of our studies.

Throughout this thesis, community detection — a relatively novel subgrouping method — was used to identify the subgroups. Participants were clustered together based on correlations between their pattern of scores on the cluster variables. We specifically chose this clustering method, as the interest was in identifying patterns that might make someone more vulnerable to experience difficulties in daily life. One could imagine that a combination of relatively low support, low sense of control, and high level of worries might be such a pattern. Hence the correlations used as input for this analysis are different from more traditional subgrouping techniques that include the level of scores as input (e.g., Latent Profile Analysis [LPA], K-means clustering, Hierarchical clustering). Although community detection seemed most appropriate given the goal of this thesis,

some may wonder whether different methods would have resulted in different autism subgroups (Agelink van Rentergem et al., 2022). In fact, testing whether the same subgroups can be identified with different subgrouping methods, is another technique that can be used to assess the subgroups' validity (Agelink van Rentergem et al., 2021). Although this "cross-method replication" was not included in this thesis, we performed post hoc analyses and compared three additional clustering methods to our subgrouping results: LPA, K-means, and Hierarchical clustering. Although some differences occurred, the number of subgroups and their scoring profiles were mostly similar to those obtained with community detection, especially for K-means and Hierarchical clustering (see Supplementary Materials S9.6.1 for results). Thus, although the most suitable subgrouping technique depends on the specific study goal, we established that different techniques — that use different kinds of information — still result in similar subgroups. This further highlights the validity of the autism subgroups that were identified.

Further elaboration is warranted on the specific goal of subgrouping studies, and the consequences related to interpretation. As indicated throughout this thesis, our goal was to identify subgroups in autistic adults, and to determine their validity and potential utility for clinical practice. Hence, as aforementioned, our goal guided our design choices, for example in terms of subgrouping techniques, selection of variables, and validation procedures. As follows, other subgrouping studies may have different goals, leading to different choices in design and suitable subgroup validation procedures. This suggests that there is no gold standard on how to conduct a subgrouping study, as the most suitable approach is context-dependent. A clear communication about the study goal and expectations (for example, by means of a preregistration) are, therefore, highly valuable for subgrouping studies. One should also be mindful when referring to subgroup labels as the use of such labels (e.g., Feelings of High Grip) may (mis)guide the interpretation of study results. Nuances may get lost when using labels. Therefore, one should be careful not to use the suggested labels outside the context of our studies.

For most studies described in this thesis, and for our overall study on aging in autism (Geurts et al., 2021), we collaborated with a group of four older/ autistic adults. This collaboration included discussing the study design, information letters, questionnaires, and study results. We started this collaboration in 2018, before the third wave of data collection of our overall study on aging in autism. The involvement of this stakeholder group proved valuable. This did not only apply to specific parts of our study (such as discussing the interpretation of study results), but also for communicating our thoughts and findings in an unambiguous, respectful manner. Yet there are certain aspects that should be kept in mind when engaging in participatory research. For example, it should be explicit at the early stages of the project on what aspects the collaboration is feasible, and what aspects may be more fixed, to manage expectations of everyone involved in





the project. For example, in our case, complete co-design was not feasible because of the longitudinal study design. However, as this was clearly discussed from the start (during the application procedure), this did not cause obstacles and our collaboration still turned out to be fruitful. This necessary flexibility in participatory research depending on the specific research project has also been noted by others (Pickard et al., 2022). Moreover, there should be sufficient time scheduled for this collaboration at all stages of the project. Although this may require extra time, it is valuable and important to connect to what autistic people feel and want from research to advance our collective understanding of autism.

Apart from the methodological considerations, there were several unique aspects to the study sample. Subgrouping studies in the autism research field are characterized by large variability in sample sizes (Agelink van Rentergem et al., 2021). While some studies included less than 20 participants (Lewis et al., 2008), others collected data from over 20.000 autistic people (Lingren et al., 2016). What is often overlooked when we merely focus on participant numbers, is the type of data that is collected and what type of information this produces. Because the goal of this thesis was to gain insight in the firsthand experiences of autistic people across major aspects of life, we collected a large amount of information per participant. We administered over 800 questionnaires, and conducted interview sessions and neuropsychological testing of autistic and non-autistic participants, taking up hundreds of hours of data collection. This type of research is demanding for both participants and researchers, but it resulted in a rich data set including the experiences of many autistic and non-autistic people. Hence it includes different information than biological studies, or studies that were fully conducted online. For instance, the diagnostic confirmation (using the Autism Diagnostic Observation Schedule – Second Edition [Lord et al., 2012], and the Dutch Interview for assessment of autism spectrum disorders in adults [Vuijk et al., 2022]) in a subset of our autistic participants is a considerable strength over many existing studies that primarily focus on self-reported information. Consequently, rather than exclusively focusing on participant numbers, one should critically examine the goal of the study, and the unique or relevant knowledge the study yields.

Compared to the autism research literature (Agelink van Rentergem et al., 2021; Tse et al., 2022; Wise, 2020), the studies described in this thesis (a) included a large sample of autistic adults, (b) covered a wide age range from 30 to 89 years, and (c) comprised a relatively large number of women. Aside from these strengths, it is essential to consider the challenges regarding the representativeness of our study sample.

First, we only included autistic adults with an average to high intelligence. Consequently, our results possibly do not generalize to autistic adults with an intellectual disability

(ID). However, it is worth noting that inclusion of autistic adults with an ID would have likely resulted in two larger autism subgroups: one with ID and one without ID. Therefore, our community detection analysis would have probably only captured the heterogeneity in intellectual ability, rather than the diverse demographic, psychological, and lifestyle characteristics, which we aimed to capture. Nonetheless, a large part of autistic adults also has an ID, and this group is underexposed in this thesis, and also in autism research in general (Russell et al., 2019). Although data collection from autistic adults with an ID poses extra challenges (Maes et al., 2021), it would be fundamental for future studies to consider the full autism spectrum by also including people with an ID. For instance, a potential road for future research could be to assess whether the same subgroups can be identified in a sample that only consists of autistic adults with an ID. This could elucidate whether our findings generalize across the full autism spectrum.

Second, most autistic adults in the studies included in this thesis received their autism diagnosis in adulthood. Studies have indicated that there may be differences between autistic adults diagnosed in adulthood, and those diagnosed in childhood (Jadav & Bal, 2022). Specifically, autistic people diagnosed in adulthood were more likely to have psychiatric conditions than those diagnosed earlier in life. This implies that it is necessary to consider age of diagnosis in autism research. Therefore, the findings of this thesis may not be generalizable to those who received their autism diagnosis in childhood.

Third, although we did not specifically inquire about race or ethnicity, we should point out that our sample mostly included White individuals. While this is the group of people we mostly encounter in clinical practice in the Netherlands, it does highlight the selectivity of our study results. It demonstrates that people from a different ethnic background are under exposed in both the clinic and academic research in the Netherlands. This is alarming, as there have been studies indicating a higher prevalence of autism in minority ethnic groups (Pham et al., 2022; Roman-Urrestarazu et al., 2021). To eventually include groups with varying ethnic backgrounds in academic research, it is vital to understand that there may be barriers to getting a diagnosis for these groups, and to engage in research. Cultural or societal factors may play a role here (Memon et al., 2016). This is further complicated by the frequent inadequate recognition of mental health difficulties in minority ethnic populations by healthcare professionals (Memon et al., 2016). To ensure equal opportunities for healthcare and support, future studies should consider these issues relevant to diagnosis. This does not only apply to receiving an autism diagnosis, but also to psychiatric conditions in general (McGuire & Miranda, 2008).





## Conclusions

The findings of the studies described in this thesis indicate that heterogeneity in specific aspects of aging can be effectively captured by a subgrouping approach. For aging in the general population, we demonstrated that statements on risk factors associated with aging may only apply to a part of the elderly population. For aging in the overall autism group, our findings indicated that there is stability or improvement in behavioral characteristics with age, while there seems no indication of worsening of difficulties over time. The importance of considering a subgrouping approach in autism was emphasized: Two autism subgroup were identified, which showed even more stability over time in behavioral characteristics compared to the overall autism group. The subgroups differed on their vulnerability to daily life difficulties, and were predictive of clinical outcomes: experienced cognitive and psychological difficulties, and quality of life. The inclusion of factors that can be modified (for example, with intervention) allowed for changes in subgroup membership over time. Consequently, even for those autistic adults who may seem vulnerable to difficulties in daily life, aging does not necessarily go together with more experienced cognitive and psychological difficulties, and a lower quality of life. The findings described in this thesis produce various avenues for future research, to work towards improvement of the lives of people on the autism spectrum.



# Chapter 8

# Preregistrations

# Overview

All preregistrations are included in this chapter. In addition, the links to the preregistrations and the study protocol are provided below.

**Links to preregistrations:**

Chapter 2: https://aspredicted.org/7np2t.pdf

Chapter 3A: https://aspredicted.org/SUM_UCD

Chapter 3B: https://aspredicted.org/PKR_EZH

Chapter 4: https://aspredicted.org/ISU_KHS

Chapter 5: https://aspredicted.org/X8J_3L2

Chapter 6: https://aspredicted.org/blind.php?x=TSW_ZNJ

**Link to study protocol:**

10.1136/bmjopen-2020-040943





# Chapter 2

## Community detection on LASA data

This preregistration was uploaded at AsPredicted.org (#27409) on September 3rd, 2019.

**1. Have any data been collected for this study already?**

It's complicated. We have already collected some data but explain in Question 8 why readers may consider this a valid preregistration nevertheless.

**2. What's the main question being asked or hypothesis being tested in this study?**

Our hypothesis is that subgroups are distinguishable within the typical aging population (H1) by investigation of self-report measures of demographic, psychological and physical variables (pilot analyses indicated existence of three subgroups). We hypothesise that these subgroups differ in cognitive outcome and wellbeing both at current measurement occasion (H2) and three years later (H3). We hypothesise that the number of subgroups identified at T1 wil be equal to the number of subgroups at T1 (H4). Furthermore, we expect that subgroup membership will be stable between T1 and T2 (H5).

**3. Describe the key dependent variable(s) specifying how they will be measured.**

In subgrouping analyses, we will use the following variables that are measured by means of self- report: (1) educational level attained (in years), (2) sum score of Pearlin Mastery Scale, (3) total physical activity according to LASA Physical Activity Questionnaire, (4) sum score of shortened Life Event Inventory, (5) emotional support received, (6) instrumental support received, (7) alcohol use (number of alcoholic drinks per week).
For the external validation (H2) and prediction (H3) we will use experience of memory complaints and quality of life.

**4. How many and which conditions will participants be assigned to?**

Conditions are not defined a priori, but will be determined as a result of subgroup analyses.

**5. Specify exactly which analyses you will conduct to examine the main question/ hypothesis.**

Subgroups will be identified by means of a community detection analysis with application of the Spinglass algorithm with 50 spins. A correlation matrix with both positive and negative correlations (with equal importance) will be used as input.
H2 and H3 will be investigated by either an independent t-test or ANOVA, depending

on the number of subgroups identified by the community detection analysis (t-test in case of two subgroups, ANOVA in case of more than two subgroups). H4 will involve counting the number of subgroups at T1 and T2. H5 will be investigated by a cross-tabulation of subgroup membership at T1 and T2 with the addition of a chi-square test.

**6. Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.**

There are no demographic exclusion criteria involved in the current study. We will not exclude participant based on outlying observations. If participants have missing values on two or more of the subgrouping variables, they will be excluded from all analyses. We will consider 10% an acceptable amount of missing data for imputation. The type of imputation will depend on the specific measurement instrument:

- Negative Life Events: 10% missing = one NA-value, will be recoded to 0, which means that the negative life event has not occurred in the past three years.
- Support received: missing values will not be imputed.
- Mastery: 10% missing = one NA-value, will be recoded to the median of a respondent's other mastery responses.
- Number of alcoholic drinks per week: missing values will not be imputed.
- Total physical activity: missing values will be imputed using the default syntax from overarching study (Longitudinal Aging Study Amsterdam).
- Educational level attained: missing values will not be imputed.

**7. How many observations will be collected or what will determine sample size?**

Pilot analyses were performed on N=301 participants, which were randomly selected from the full data set. The full data set for definitive analyses at T1 will include 1601 participants (including pilot data), before missing values are either removed or imputed.

**8. Anything else you would like to preregister?**

The current study involves secondary analyses in order to answer a research question by statistical means that were not part of the initial data collection set-up. Furthermore, the authors involved in the conception of the current study are not involved in the LASA data collection. Also, apart from the subset of N=301 participants for the pilot analyses, these authors did not see the LASA data. The combination of variables specified in the current subgroup analysis has not been included in a subgrouping analysis of this data set before. Finally, a community detection approach has not been applied to the LASA data before. Therefore, we consider this a valid preregistration.





# Chapter 3A

## Community detection on "Aging in Autism" original data

This preregistration was uploaded at AsPredicted.org (#29596) on October 22nd, 2019.

**1. Have any data been collected for this study already?**

It's complicated. We have already collected some data but explain in Question 8 why readers may consider this a valid preregistration nevertheless.

**2. What's the main question being asked or hypothesis being tested in this study?**

Our hypothesis is that (H1) subgroups are distinguishable within the population of autistic adults by investigation of self-report measures of demographic, psychological and lifestyle variables. We hypothesise that (H2) these subgroups differ in the experience of cognitive failures, comorbid psychological complaints and wellbeing at the current measurement occasion.

**3. Describe the key dependent variable(s) specifying how they will be measured.**

In subgrouping analysis, we will use the following variables measured by self-report: (1) five scores belonging to subscales of Autism Spectrum Quotient, (2) educational level attained, (3) sum score of Pearlin Mastery Scale, (4) sum score of Worry Scale/Fear Questionnaire, (5) total physical activity in minutes according to the International Physical Activity Questionnaire, (6) sum score of the List of Threatening Experiences, (7) emotional support received according to Close Persons Questionnaire, (8) sum score of the Sensory Sensitivity Questionnaire, (9) positive and negative affect scores according to PANAS. For the external validation (H2) we will use experience of cognitive failures (CFQ), psychological complaints (SCL-90), and quality of life (WHO-QoL BREF).

**4. How many and which conditions will participants be assigned to?**

Conditions are not defined a priori, but will be determined as a result of subgroup analyses.

**5. Specify exactly which analyses you will conduct to examine the main question/ hypothesis.**

H1 will be investigated by means of a community detection analysis with application of the Spinglass algorithm with 50 spins. A correlation matrix with both positive and negative correlations (with equal importance) will be used as input.
H2 will be investigated by either an independent t-test or ANOVA, depending on the

number of subgroups identified by the community detection analysis. If we find two subgroups in our community detection analysis, this could indicate a distinction between our ASD and control groups (i.e. a group that mostly contains ASD participants and a group that mostly contains controls). In this case, we will perform a separate community detection analysis for the ASD group.

**6. Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.**

The following exclusion criteria are applied in the current study:

- A present/past diagnosis of intellectual disability and/or IQ-score below 70.
- Insufficient understanding of Dutch language in order to complete the questionnaires.

For participants in the control group, we additionally apply the following exclusion criteria:

- A history of more than one psychotic episode.
- A present/past diagnosis of AD(H)D or a total score of six of higher on the ADHD-SR.
- A present/past diagnosis of ASD or a total score higher than 32 on the AQ.
- Autism spectrum in close family (i.e. parent(s), child(ren), brother(s), sister(s)).
- AD(H)D in close family (i.e. parent(s), child(ren), brother(s), sister(s)).

We will consider 10% an acceptable amount of missing data for imputation. The type of imputation will depend on the specific measurement instrument: For mastery, autism symptoms, sensory sensitivity, worries/fears, emotional support, positive and negative affect, we will recode a maximum of 10% of missing values to the median of the participant's other responses on that specific questionnaire.
For negative life events and physical activity, we will recode a maximum of 10% of missing values to zero, implying the absence of a negative life event or the absence of a specific physical activity.
Missing values on education will not be imputed.
After our imputation procedure has been completed, we will exclude participants from all analyses if they have missing values on more than one of the subgrouping variables.





**7. How many observations will be collected or what will determine sample size?**

The original data set will consist of at least 190 participants (i.e., 130 ASD, 60 controls)

**8. Anything else you would like to preregister?**

We have already collected data of the original data set and a large part of the data of the replication data set. We think this is a valid preregistration, since the data collection has not yet been completed and since the authors involved in this study did not analyze the data graphically or statistically. We will validate our results by analysis of a replication data set, but we will create a different AsPredicted regarding this specific research question.

# Chapter 3B

## Community detection on "Aging in Autism" replication data

This preregistration was uploaded at AsPredicted.org (#34324) on January 21st, 2020.

**1. Have any data been collected for this study already?**

It's complicated. We have already collected some data but explain in Question 8 why readers may consider this a valid preregistration nevertheless.

**2. What's the main question being asked or hypothesis being tested in this study?**

Our hypothesis is that (H1) subgroups are distinguishable within the population of autistic adults by investigation of self-report measures of demographic, psychological and lifestyle variables. We hypothesise that (H2) these subgroups differ in the experience of cognitive failures, comorbid psychological complaints and wellbeing.

**3. Describe the key dependent variable(s) specifying how they will be measured.**

In subgrouping analysis (H1), we will use the following variables measured by self-report: (1) five scores belonging to the subscales of the Autism Spectrum Quotient, (2) educational level attained, (3) sum score of Pearlin Mastery Scale, (4) sum score of Worry Scale/Fear Questionnaire, (5) total physical activity in minutes according to the International Physical Activity Questionnaire, (6) sum score of the List of Threatening Experiences, (7) emotional support received according to Close Persons Questionnaire, (8) sum score of the Sensory Sensitivity Questionnaire, (9) positive and negative affect scores according to Positive and Negative Affect Schedule.
For the external validation (H2) we will use the sum score of the experience of cognitive failures (CFQ), sum score and subscale scores of psychological complaints (SCL-90), and subscale scores of quality of life (WHO-QoL BREF).

**4. How many and which conditions will participants be assigned to?**

Conditions are not defined a priori, but will be determined as a result of subgroup analyses.

**5. Specify exactly which analyses you will conduct to examine the main question/ hypothesis.**

Step 1: H1 will be investigated by means of a community detection analysis with application of the Spinglass algorithm with 50 spins. A correlation matrix, containing correlations between all individuals across the measures mentioned in 3, with both positive and negative correlations (with equal importance) will be used as input.
Step 2: If we find two subgroups in our community detection analysis, this could indicate a distinction between our ASC (autism spectrum condition) and control groups (i.e., a group that mostly contains ASC participants and a group that mostly contains controls). If this is the case, we will perform a separate community detection analysis for the ASC group.

Step 3: H2 will be investigated by either independent t-tests or ANOVA, depending on the number of subgroups identified by the community detection analysis. If the data violate assumptions of normality, we will try to transform the data to achieve a normal distribution. Otherwise, we will assess the data using a Mann-Whitney test or Kruskal-Wallis test, depending on the number of subgroups.
Step 4: All analyses (i.e. Step 1, 3 and if needed Step 2) will be repeated with the addition of an AD(H)D group to examine the specificity of the ASC results.

**6. Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.**

The following exclusion criteria are applied in the current study:

- A present/past diagnosis of intellectual disability and/or IQ-score below 70.
- Insufficient understanding of Dutch language in order to complete the questionnaires.

For participants in the control group, we additionally apply the following exclusion criteria:

- A history of more than one psychotic episode.
- A present/past diagnosis of AD(H)D or a total score of six of higher on the ADHD-SR.
- A present/past diagnosis of an ASC or a total score higher than 32 on the AQ.
- Autism spectrum in close family (i.e. parent(s), child(ren), brother(s), sister(s)).
- AD(H)D in close family (i.e. parent(s), child(ren), brother(s), sister(s)).
- Age lower than 30 years or higher than 90 years.

For participants in the ASC group, we will apply the following exclusion criteria:

- Age between 30 and 90 years.
- Clinical DSM-diagnosis of an ASC.

For participants in the AD(H)D group, we will apply the following exclusion criteria:

- Age between 30 and 90 years.
- Clinical DSM-diagnosis of AD(H)D.

We will not exclude participants based on outlying observations.

We will consider 10% an acceptable amount of missing data for imputation. The type of imputation will depend on the specific measurement instrument: For mastery, autism symptoms, sensory sensitivity, worries/fears, emotional support, positive and negative affect, we will recode a maximum of 10% of missing values to the median of the participant's other responses on that specific questionnaire.
For negative life events and physical activity, we will recode a maximum of 10% of missing values to zero, implying the absence of a negative life event or the absence of a specific physical activity.
Missing values on education will not be imputed.
After our imputation procedure has been completed, we will exclude participants from all analyses if they have missing values on more than one of the subgrouping variables.

**7. How many observations will be collected or what will determine sample size?**

The replication data set will consist of at least 555 participants (i.e., 245 ASC, 45 AD(H)D, and 265 controls).

**8. Anything else you would like to preregister?**

We have already collected a large part of the data of replication data set. We think this is a valid preregistration, since the data collection has not yet been completed and since the authors involved in this study did not analyze the data graphically or statistically.
We aim to validate our results by analysis of a longitudinal data set, but we will create a different AsPredicted regarding this specific research question.





# Chapter 4

## Networks within autism subgroups

This preregistration was uploaded at AsPredicted.org (#49209) on October 8th, 2020.

**1. Have any data been collected for this study already?**

It's complicated. We have already collected some data but explain in Question 8 why readers may consider this a valid preregistration nevertheless.

**2. What's the main question being asked or hypothesis being tested in this study?**

In pre-registration #34234 (https://aspredicted.org/blind.php?x=hu4ey6), we described our analysis plan to identify subgroups within the population of adults with Autism Spectrum Conditions (ASC) and non-autistic adults (COMP). In this study, we aim to test whether the previously identified subgroups differ in the interactions between vulnerability and protective factors of (cognitive) aging. We hypothesise that these subgroups differ in their underlying network structure of the variables included (see 3), but we have no specific hypothesis concerning specific differences in the exact networks. Differences are the most likely to occur between the ASC and COMP groups and potentially also within the ASC group.

**3. Describe the key dependent variable(s) specifying how they will be measured.**

We will use variables measured by self-report as nodes in the network analyses. There are three subsets of variables:

- A: (1 and 2) two scores belonging to "Social Interaction" and "Attention to detail" scales from the Autism Spectrum Quotient, (3) educational level attained, (4) sum score of Pearlin Mastery Scale, (5) sum score of Worry Scale/Fear Questionnaire, (6) total physical activity in minutes according to the International Physical Activity Questionnaire, (7) sum score of the List of Threatening Experiences, (8) emotional support received according to the Close Persons Questionnaire, (9) sum score of the Sensory Sensitivity Questionnaire, (10 and 11) positive and negative affect scores according to Positive and Negative Affect Schedule.
- B: (12) sum score of the experience of cognitive failures (CFQ), (13) total score of psychological complaints (SCL-90), (14) overall quality of life perception, (15) number of physical illnesses measured by the Health Questionnaire, (16) biological age.
- C: (17) biological sex.

**4. How many and which conditions will participants be assigned to?**

Conditions are not defined a priori. Participants will be assigned to subgroups based on the results of the community detection analyses in preregistration #34234 (hereafter referred to as "the identified subgroups").

**5. Specify exactly which analyses you will conduct to examine the main question/ hypothesis.**

Step 1: We estimate the network structure in ASC adults and comparisons separately. Subsets A+B will be included to estimate two Gaussian Graphical Models (GGM). We apply the LASSO as regularization and we determine the value of the LASSO tuning parameter using the Extended Bayesian Information Criterion (EBIC).

Step 2a: We estimate the network structure separately in the identified subgroups using GGMs with LASSO regularization (subsets A+B). The number of estimated networks depends on the number of identified subgroups. For network interpretation, we will focus on the following centrality indices: Betweenness, closeness and strength. To assess the accuracy of the estimated networks, we will apply the following methods:

- The variability of edge weights will be assessed by estimating a 95% confidence interval by non-parametric bootstrapping.
- Stability of the centrality indices will be assessed by the correlation stability coefficient. This represents the maximum proportion of cases that we can drop from our data set such that with 95% probability the correlation between the original centrality indices and those from the subsets is 0.7 or higher. This coefficient should not be below 0.25 (i.e., the centrality indices are not stable under subsetting cases), and preferably above 0.5.

The estimation of a GGM with LASSO regularization does not allow inclusion of missing values. Therefore, we will estimate additional GGMs using the Full Information Maximum Likelihood estimator, to estimate the influence of missing data.

Step 2b: To assess differences between the networks across subgroups, we perform a network comparison test (NCT). NCTs allow for pairwise comparisons, therefore if more than two subgroups are detected we will perform multiple NCTs. A multiple comparison correction (α (.05) / # tests) will be applied. We consider two p-values resulting from the NCT:

- Global strength: sum of the absolute values of all edges (i.e., the connectivity). This test explores whether the overall level of connectivity is equal across two networks.
- Maximum difference in edge weights: This test explores whether the maximum difference in any of the partial correlations of the observed networks differ significantly.





Step 3: To investigate the influence of biological sex on the networks, we estimate Mixed Graphical Models (MGMs), with subsets A+B+C. The number of networks to be estimated again depends on the number of identified subgroups. By inclusion of 17 network variables, the centrality indices may become less reliable. Therefore, we will only inspect the results of this additional exploratory analysis visually.

**6. Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.**

The following exclusion criteria are applied to all participants in the current study:

- A present/past diagnosis of intellectual disability and/or IQ-score below 70.
- Insufficient understanding of Dutch language in order to complete the questionnaires.
- Age lower than 30 years or higher than 90 years.

For the COMP group, we will apply the following exclusion criteria:

- A history of more than one psychotic episode.
- A present/past diagnosis of AD(H)D or a total score of six of higher on the ADHD-SR.
- A present/past diagnosis of an ASC or a total score higher than 32 on the AQ.
- ASC in close family members (i.e. parent(s), child(ren), brother(s), sister(s)).
- AD(H)D in close family members (i.e. parent(s), child(ren), brother(s), sister(s)).

For the ASC group, we will apply the following inclusion criteria:

- Clinical DSM-diagnosis of an ASC.

The following criteria will be applied to include variables in the network analyses:

- There should be individual differences in the manifestation of the variable in autistic adults.
- If one variable from study #34234 (i.e., cluster variable or external variable) does not show any variation within all subgroups, we will not include this variable in the network analysis. For network estimation, it is important that the included variables show variation within subgroups.

We will not exclude participants based on outlying observations.

We will not include any missing observations in analysis steps 1 to 3 using LASSO regularization. However, for the analyses using the Full Information Maximum Likelihood estimator (see step 2a), we consider 10% an acceptable amount of missing data within questionnaires for imputation. The type of imputation will depend on the specific measurement instrument:

For mastery, autism symptoms, sensory sensitivity, worries/fears, emotional support, positive and negative affect, psychological complaints, cognitive failures, we will recode a maximum of 10% of missing values to the median of the participant's other responses on that specific questionnaire. For negative life events, physical illness, and physical activity, we will recode a maximum of 10% to zero, implying the absence of a negative life event, physical illness, or physical activity. We will not impute missing values on education, overall quality of life perception, biological sex and age. After our imputation procedure has been completed, we will exclude participants from all analyses if they have missing values on more than one of the variables in subsets A and B.

**7. How many observations will be collected or what will determine sample size?**

We will collect data from approximately 395 autistic adults and 370 controls. Based on the first analyses of study #34234 and existing literature, we expect to identify two to four ASC subgroups. Since we will collect data from around 400 autistic participants, it is likely that we will have 100 to 200 participants per autism subgroup. Based on simulation studies we performed (wherein we adjusted parameter values to balance sensitivity and specificity, selecting alpha = 0.25 and gamma = 0), we are able to compare networks with medium power and acceptable false discovery rate with as few as 80 participants per subgroup.

**8. Anything else you would like to preregister?**

We have already collected a large part of the data. We think this is a valid pre-registration, since the data collection has not yet been completed.

Please note that all analyses specified in this pre-registration are exploratory and will not be used to test specific hypotheses.





# Chapter 5

## Longitudinal validation of autism subgroups

This preregistration was uploaded at AsPredicted.org (#77679) on October 22nd, 2021.

**1. Have any data been collected for this study already?**

It's complicated. We have already collected some data but explain in Question 8 why readers may consider this a valid preregistration nevertheless.

**2. What's the main question being asked or hypothesis being tested in this study?**

In our earlier pre-registrations (#29596, https://aspredicted.org/SUM_UCD; #34234, https://aspredicted.org/PKR_EZH), we described our analysis plan to identify subgroups within the population of adults with Autism Spectrum Conditions (ASC) and non-autistic adults (COMP). In our recently submitted paper (Radhoe et al., 2021; https://psyarxiv.com/hs4bx/), we identified two subgroups in a combined sample of ASC + COMP, and three subgroups in the ASC sample, of which the third was small and not replicable. The two replicated ASC subgroups were named (1) "High Social High Grip" and (2) "Low Social Low Grip". In this study, we aim to test whether the previously identified subgroups are (a) stable over time, and are (b) predictive of future outcomes.

Ad a) Stability. We will perform a community detection analysis on data collected at T2 (see for cohort description Geurts et al., 2021). We hypothesize that (H1) combining data of autistic adults and non-autistic comparisons will again yield a distinction between autistic and non-autistic subgroups. We expect (H2) the following outcomes: (1) community detection analysis on data of autistic adults will result in two major ASC subgroups at T2 (i.e., the two major subgroups should each include more than 25% of the sample, and should be the largest subgroups identified at T2), and/or (2) we expect to find similar subgroup profiles as the two ASC subgroups identified at T1, and/or (3) the same participants will cluster together in one subgroup at T2 as they did at T1. We have no specific hypothesis concerning the third ASC subgroup. We conclude that the T1 subgroups are stable if at least criteria 1 and 2 are met, or if at least criteria 1 and 3 are met.

Ad b) Predictive validity: We will also test whether the ASC subgroups identified at T1 differ in the experience of cognitive failures, quality of life, and psychological difficulties measured at T2 (i.e., predictive validation). We hypothesize that (H3) the ASC subgroups identified at T1 will indeed differ on these external measures at T2 (thus we

expect the Low Social Low Grip subgroup to perform worse than the High Social High Grip subgroup).

H1 will be tested across one time interval (i.e., two years after T1), whereas H2 and H3 will be tested across two time intervals (i.e., two years and three to five years after T1).

**3. Describe the key dependent variable(s) specifying how they will be measured.**

Please note that by definition we will use the same measures as those used in (Radhoe et al., 2021). Thus in subgrouping analysis (H1 and H2), we will use the following variables measured by self-report: (1) five scores belonging to the subscales of the Autism Spectrum Quotient, (2) educational level attained, (3) sum score of Pearlin Mastery Scale, (4) sum score of Worry Scale/Fear Questionnaire, (5) total physical activity in minutes according to the International Physical Activity Questionnaire, (6) sum score of the List of Threatening Experiences, (7) emotional support received according to Close Persons Questionnaire, (8) sum score of the Sensory Sensitivity Questionnaire, (9) positive and negative affect scores according to Positive and Negative Affect Schedule. For the predictive validation (H3) we will use the sum score of the experience of cognitive failures (CFQ), sum score and subscale scores of psychological complaints (SCL-90), and subscale scores of quality of life (WHO- QoL BREF) measured at T2.

**4. How many and which conditions will participants be assigned to?**

Participants will not be assigned to conditions.

**5. Specify exactly which analyses you will conduct to examine the main question/ hypothesis.**

The following analyses will be performed for the longitudinal data collected two years after T1:

**Stability**

- Step 1: H1 will be investigated by means of a community detection analysis with application of the Spinglass algorithm with 50 spins for the ASC and COMP groups (the same procedure as our earlier preregistered T1 analysis). A correlation matrix containing correlations between all individuals mentioned in 3, with both positive and negative correlations (with equal importance) will be used as input. Even if we do not find a distinction between autistic and non-autistic subgroups, we will continue with Step 2.
- Step 2: We will perform a separate community detection analysis for the ASC group (H2). We will count the number of subgroups, and inspect subgroup profiles by performing Bayesian Independent Samples T-tests (with standard/flat prior) for each of the cluster variables measured at T1 and T2 to test for similarity. We conclude that subgroup profiles are similar if at least 50% of the cluster variable scores are similar between T1 and T2 (with BF01 > 3).
- Step 3: We will create a cross-tabulation of subgroup membership at T1 and T2 with the addition of a Bayesian contingency table test (with standard/flat prior). We will also calculate two measures of how subgroup membership between the subgroups identified at T1 and T2 has changed/remained the same. First, we will calculate the Rand Index that ranges between 0 and 1. Second, we will calculate the Hubert-Arabie Adjusted Rand Index that ranges between -1 and 1. For both measures, values greater than 0.90 are indicative of excellent subgroup recovery (i.e., similarity between subgroups at T1 and T2), and values less than 0.65 reflect poor recovery. We do not expect excellent recovery, as some intraindividual changes in subgroup membership over time are expected at the current intervals.

**Predictive validity**

- Step 4: H3 will be investigated by either Byesian Independent Samples T-tests or-Bayesian ANOVAs (with standard/flat prior), depending on the number of subgroups identified by the community detection analysis.

For exploratory purposes, we will repeat the analyses mentioned in Step 2, 3 and 4 for a smaller, separate longitudinal data set measured three to five years after T1, that only includes autistic adults.

**6. Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.**

The following exclusion criteria are applied in the current study:

- A present/past diagnosis of intellectual disability and/or IQ-score below 70.
- Insufficient understanding of Dutch language in order to complete the questionnaires.

For participants in the control group, we additionally apply the following exclusion criteria:

- A history of more than one psychotic episode.
- A present/past diagnosis of AD(H)D or a total score of six of higher on the ADHD-SR.
- A present/past diagnosis of an ASC or a total score higher than 32 on the AQ.
- Autism spectrum in close family (i.e. parent(s), child(ren), brother(s), sister(s)).
- AD(H)D in close family (i.e. parent(s), child(ren), brother(s), sister(s)).
- Age lower than 30 years.

For participants in the ASC group, we will apply the following inclusion criteria:
- Age 30 years or older.
- Clinical DSM-diagnosis of an ASC.

We will not exclude participants based on outlying observations.

We will consider 10% an acceptable amount of missing data for imputation. The type of imputation will depend on the specific measurement instrument: For mastery, autism traits, sensory sensitivity, worries/fears, emotional support, positive and negative affect, we will recode a maximum of 10% of missing values to the median of the participant's other responses on that specific questionnaire. For negative life events and physical activity, we will recode a maximum of 10% of missing values to zero, implying the absence of a negative life event or the absence of a specific physical activity. Missing values on education will not be imputed. After our imputation procedure has been completed, we will exclude participants from all analyses if they have missing values on more than one of the subgrouping variables.

**7. How many observations will be collected or what will determine sample size?**
- To test both stability and predictive validity, we use a data set with a two-year time interval: $N_{ASC}$=228, $N_{COMP}$=207.
- To explore whether similar findings will be found with respect to stability and predictive validity with a longer time interval, we will use a data set with a three to five- year interval: $N_{ASC}$=92.

**8. Anything else you would like to preregister?**
We have already collected a large part of the longitudinal data set. We think this is a valid preregistration, since the data collection has not yet been completed and since the authors involved in this study did not analyze the data graphically or statistically.





# Chapter 6

## Cognitive aging in autism subgroups

This preregistration was uploaded at AsPredicted.org (#114410) on November 28th, 2022.

**1. Have any data been collected for this study already?**
It's complicated. We have already collected some data but explain in Question 8 why readers may consider this a valid pre-registration nevertheless.

**2. What's the main question being asked or hypothesis being tested in this study?**
In our previous work (#34234, https://aspredicted.org/PKR_EZH), we identified subgroups in a large sample of autistic adults. Moreover, in a subsample we assessed (a) cognitive functioning, and age-related cognitive effects (#28816, https://aspredicted.org/k9dx6.pdf), (b) identified a subgroup with deviant cognitive profiles (https://aspredicted.org/JEH_ORB; #4009), and (c) assessed age-related changes in cognitive functioning (#80808, https://aspredicted.org/VVZ_MHZ). However, the described cognitive studies have mainly focused on differences between autistic and non-autistic adults, whereas the subgroup analyses indicate large individual differences between autistic adults. In this follow-up study, we aim to test how the previously identified autism subgroups (i.e., Feelings of High Grip (HighGr) and Feelings of Low Grip (LowGr)) relate to cognitive functioning, the subgroups of cognitive deviancy (deviant/not deviant), age-related cognitive effects, and cognitive change. We hypothesize that:

H1: The previously identified autism subgroups provide information on cognitive differences within the autism population. Specifically, we expect (a) the LowGr subgroup to score lower on the included cognitive measures compared to the HighGr subgroup, and (b) that individuals in the LowGr subgroup are more likely to be classified as having a cognitively deviant profile compared to individuals in the HighGr subgroup, and vice versa (individuals with a deviant cognitive profile as indicated by MNC are more likely to be in the LowGr subgroup).

H2: The previously identified autism subgroups provide information on the extent of age- related cognitive effects within the autism population, estimated either cross-sectionally, or longitudinally. Specifically, we expect a significant interaction between subgroup membership and age, with larger negative age-effects for the LowGr subgroup (a) on a single timepoint (cross-sectional), and (b) over time (longitudinal) compared to

the HighGr subgroup.

**3. Describe the key dependent variable(s) specifying how they will be measured.**

For H2a and H2b we will use the following key dependent cognitive variables (k=5):

- Wechsler Memory Scale-III (WMS-III) visual reproduction:
  1. Learning: sum score recall 1
- Rey Auditory Verbal Learning Task (RAVLT):
  2. Learning: sum score trial 1-5
- Controlled Oral Word Association Test (COWAT)
  3. Phonemic fluency: sum score D, A and T
- Groninger Intelligence Test (GIT):
  4. Semantic fluency: sum score "Animals" and "Professions"
- Choice Response Time Task (CRT task)
  5. Psychomotor speed: mean response time on correct trials

For H1a and H1b we will use the following additional cognitive variables (k=6, 11 in total):

- Wechsler Memory Scale-III (WMS-III) visual reproduction:
  6. Retrieval: sum score recall 2
  7. Recognition: sum score
- Rey Auditory Verbal Learning Task (RAVLT):
  8. Retrieval: sum score recall 2
  9. Recognition: sum score
- Faux-pas test:
  10. Theory of mind: sum score
- N-back:
  11. Working memory: 2-back/0-back accuracy difference score

Test scores on all 11 variables are used separately to test H1a, and combined to obtain a measure of "cognitive deviancy" to test H1b. For H2a and H2b we chose measures which were most sensitive to age-related cognitive effects (cross-sectional, AsPredicted #28816) or age-related cognitive decline (longitudinal, AsPredicted #80808).

**4. How many and which conditions will participants be assigned to?**

Participants are assigned to autism subgroups (i.e., HighGr or LowGr) based on the results of the community detection analysis in AsPredicted #34234. Participants are assigned to either a "deviating" or "non-deviating cognitive profile" group based on the





results of the multivariate normative comparisons in AsPredicted #28816.

**5. Specify exactly which analyses you will conduct to examine the main question/ hypothesis.**

H1a will be investigated by independent t-tests with subgroup membership (HighGr or LowGr) as independent variable, and the separate cognitive test scores as dependent variables. We will report both corrected and uncorrected p-values, using Bonferonni-Holm corrections (k=11).
H1b will be investigated by a chi-square test using subgroup membership (HighGr or LowGr) and cognitive deviancy (i.e., deviating, or non-deviating) as variables in a cross-tabulation.

H2a will be investigated by conducting multiple regressions in the cross-sectional data with the effects of age, subgroup, and age*subgroup as predictors, on each cognitive outcome. We report both corrected, and uncorrected p-values using Bonferroni-Holm corrections (k=5). H2b will be investigated in the longitudinal data by conducting multilevel regressions with the effects of interval (time between measurement 1 and 2), subgroup (LowGr/ HighGr), and interval*subgroup interactions as predictors, on each cognitive outcome. Changes over time are freely estimated in each participant (random intercepts and slopes). Analyses will be performed separately in cohorts with long (Cohort 1), and short (Cohort 2) average time intervals (see AsPredicted #80808). We report both corrected, and uncorrected p-values using Bonferroni-Holm corrections (k=5).

**6. Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.**

Participants had a registered diagnosis of autism according to the DSM (III, IV or 5). Diagnoses were verified by the ADOS (-2) and AQ. Participants were excluded if they scored below the cut-off on both instruments.
Additional exclusion criteria are:

- Insufficient understanding of Dutch language to complete the questionnaires.
- Age below 30 years.
- A history of neurological disorder (e.g., epilepsy, stroke, MS).
- A history of schizophrenia or having experienced more than one psychosis.
- Current alcohol or drug dependency.

**7. How many observations will be collected or what will determine sample size?**

No need to justify decision, but be precise about exactly how the number will be determined.
Sample size is determined by the data available for the specific analyses. This results in $N_{max}$=145 ($N_{HighGr}$=66, $N_{LowGr}$=79) for H1a, H1b, and H2a, and $N_{cohort1\_max}$=41 ($N_{HighGr}$=25,

$N_{LowGr}$=15 ) and $N_{cohort2\_max}$=64 ($N_{HighGr}$=24, $N_{LowGr}$=40) for H2b.

**8. Anything else you would like to preregister?**

The hypotheses and analyses described in this pre-registration are informed by previous analyses performed on these data. However, since we have not yet analyzed the combined data sets of the subgroups and cognitive test data, we consider this a valid preregistration. Exploratory analyses: whenever significant subgroup differences are observed on H1a, H2a and H2b, we will assess the magnitude of these cognitive differences by comparing them to a non-autistic comparison sample ($N_{max}$=254 for H1a and H2a, $N_{max}$=112 for H2b).

NB. Please note that the first two authors are shared first author on this project.



# Chapter 9

# Supplementary Materials

# Chapter 2

**Table of content**



## S9.1.1 Data files obtained from the Longitudinal Aging Study Amsterdam

From measurement cycles G and H, the following data files were obtained from LASA for the current study: LASA021, LASA335, LASA135, LASA110, LASA036, LASA113, LASA313, LASA602, LASA702, LASA035, LASA235, LASA133, LASA333, LASA533, LASA025, LASA225, LASA026, LASA226, Z008, LASA027, LASA046, LASA272, LASA047, LASA247, LASA153, Z010, LASA011, LASA016, LASAd10, LASAd11, LASAd12, LASAd13, LASA152, LASA352, LASA179, LASA379.
From measurement cycle 2B, the following data files were requested: Z004, LASA022, LASA222.

## S9.1.2 Measurement instruments for cluster variables and external validators

***Negative life events***

We evaluated negative life events with a selection of questions derived from the life event inventory (Tennant & Andrews, 1976). Participants reported whether they had experienced the following events in the past three years: a) death of a parent, sibling, child, or grandchild, b) illness of partner or other relative, c) being a victim of crime, d) having severe conflict, or e) having financial problems. This resulted in 12 variables, corresponding to each negative life event. A score of 1 indicated that the event had not occurred in the three years prior to the interview, and a score of 2 indicated that the event had occurred. These scores were recoded, such that 0 meant that the event had not occurred and 1 meant that the event had occurred. A sum score for these variables was calculated that ranged between 0 and 12. A lower score implied that the respondent experienced few of these negative life events and a higher score implied that he/she experienced more negative life events. Negative life events have strong associations with depressive symptoms and lower wellbeing (Kraaij et al., 2002). Although the number of experienced negative life events is not directly modifiable, its effect can be modified through interventions. In addition, modifiable resources such as social network, education and health status are negatively associated with the experience of negative life events later in life (Jopp & Schmitt, 2010).





***Alcohol use***

We asked respondents about the amount of days per week on which they drink alcohol and the number of alcoholic consumptions they drink each time. Responses on these two questions were multiplied, which resulted in an indication of the number of alcoholic consumptions per week. This value ranged between 0 and 77 (or more). A higher value indicates a higher number of alcoholic drinks per week (Comijs et al., 2012; Pluijm et al., 2006). Alcohol use is related to memory problems and can be targeted in interventions (Heffernan, 2008; Mintzer, 2007; Platt et al., 2016).

***Physical activity***

Physical activity was assessed during an interview using the LASA Physical Activity Questionnaire (LAPAQ) (Stel et al., 2004). Participants reported how often and for how long they performed certain physical activities during the two weeks prior to the interview. These activities included walking outdoors, biking, gardening, light household activities and the two sport activities that were most frequently performed by the respondent. We calculated the total time (in minutes) during which a respondent was physically active during the past two weeks. In LASA, MET scores are often used to obtain an intensity-weighted total physical activity score (Caspersen et al., 1991). MET scores are calculated by including the type of activity, activity duration, but also a person's body weight and biological sex. In the current study, we aim to reduce the influence of external variables on the variables we include for clustering. Therefore, we decided to include total physical activity in minutes rather than MET scores. Physical activity is associated with less cognitive decline and predicts wellbeing in older adults (Beydoun et al., 2014; Kadariya et al., 2019; McAuley et al., 2000) . Also, physical activity levels can be increased through interventions (Greaves et al., 2011; Müller-Riemenschneider et al., 2008).

***Sense of mastery***

Mastery refers to the extent to which respondents view themselves as being in control of the forces that affect their lifes in important ways (Pearlin et al., 1981). Mastery was assessed by the Pearlin Mastery Scale, which consists of seven items that were rated on a five-point scale that ranged from 'strongly disagree' to 'strongly agree' (Pearlin & Schooler, 1978). The instrument contains five questions that are negatively phrased and two positively phrased items. The negatively phrased items were reverse coded. We created a sum score that varied between 7 and 35, such that higher ratings corresponded to more feelings of mastery. The instrument's reliability has shown to be reasonable to high with Cronbach's α between 0.67 and 0.80 (Penninx et al., 1997; Peterson, 1999). In this study, the reliability was acceptable ($\alpha = 0.72$). A high level of mastery, or stronger internal

locus of control, is related to a better memory performance and higher wellbeing (Amrhein et al., 1999; Robinson & Lachman, 2017; Verhaeghen et al., 2000).

***Emotional and instrumental support received***
A domain-specific network delineation is employed that encompasses a detailed classification of personal relationships: household members, children and their partners, other family members, neighbors, contacts through work and school, members of associations, and other nonkin relationships (van Tilburg, 1998). For each of these domains, respondents were asked to 'Name the people you have frequent contact with and who are also important to you'.
For the nine relationships with the highest contact frequency, four questions about support exchanges were asked. The question for emotional support given was 'How often in the last year did…tell you about his/her personal experiences and feelings?' The question on received emotional support was '…did you tell…about your personal experiences and feelings?' For instrumental support, the question was about help with daily chores in and around the house, such as preparing meals, cleaning the house, transportation, small repairs, and filling out forms. The answer categories were 'never,' 'seldom,' 'sometimes,' or 'often'. Sum scores for emotional support received and instrumental support received were calculated that varied between 0 (low level of support) and 36 (high level of support). Leading a socially active life and receiving sufficient social support are related to a higher wellbeing later in life (Gerstorf et al., 2016; Yaffe et al., 2009). Interventions for social support can be effective in increasing one's perceived level of social support (Hogan et al., 2002).

***Subjective wellbeing***
Subjective wellbeing is measured with three different questionnaires. First of all, satisfaction with life was measured by two questions defined by (van Zonneveld, 1961). The first question asks participants about satisfaction with current life, and the second one about satisfaction with life as a whole. Both questions have five response categories that range from 'very dissatisfied' to 'very satisfied'. A sum score was calculated that ranged from 2 (i.e. low satisfaction with life) to 10 (i.e. high satisfaction).

Second, the EuroQoL (EQ-5D) measures health-related quality of life (Brooks, 1996). The questionnaire consists of five questions and a visual analog scale. Each question represents one the following domains: mobility, self-care, usual activities, pain/discomfort, and anxiety and depression. Response categories vary according to the specific question, but they can roughly be characterized as having 'no problems', 'some problems', and 'extreme problems'. The responses on these items were converted into a weighted health state index according to the Time Trade OFF method (Dolan, 1997). An index score of 0 indicates death and a score of 1 indicates perfect health. The internal consistency of the





EQ-5D is acceptable with Cronbach's α ranging between 0.63 and 0.73 (De Smedt et al., 2013; Khanna et al., 2013), and the test-retest reliability is moderate (intraclass correlation coefficient = 0.6) (Sonntag et al., 2013). In the current study, the internal consistency was acceptable (α = 0.78).

Third, we measured functional health and wellbeing by the Short Form 12 (SF-12) health survey, which is a subset of the larger SF-36 (Ware et al., 1996). This instrument was used to measure the following eight health aspects: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. Sum scores were calculated for two summary scales of the SF-12, the Physical Component Summary (PCS) and the Mental Component Summary (MCS). These summary scales have a mean value of 50 and a standard deviation of 10. The test-retest reliability of the instrument is high, with r = 0.760 to 0.864, and the internal consistencies of the MSC and PCS are high with Cronbach's α higher than 0.80 (Hayes et al., 2017). In the current study, the internal consistency of MSC and PCS was questionable (α = 0.55).

**S9.1.3 Measurement instruments and corresponding descriptive analyses of subgroups identified by community detection analysis**
***Age:*** In order to better characterize the identified subgroups, we checked whether there was a significant mean age difference between the subgroups by performing an ANOVA with subgroup membership as the independent variable and age as the dependent variable.
***Gender:*** To investigate whether the distribution of males and females differed across subgroups, we used a Pearson's chi-square test with gender (two categories) and subgroup membership as categorical variables.
***Country of origin:*** Differences in country of origin across subgroups were also investigated by means of a Pearson's chi-square test with country of origin (Netherlands versus 'other') and subgroup membership as categorical variables.
***Medication use:*** Differences between subgroups in the number of individuals who use medication was investigated by a Pearson's chi-square test in which medication use (i.e. yes or no) and subgroup membership were entered as variables. Furthermore, differences in medication use were analyzed by an ANOVA in which the number of medicines used was the dependent variable and subgroup membership the independent variable.
***Marital status:*** We checked whether subgroups differed in marital status by a Pearson's chi-square test with marital status (i.e. unmarried, married, divorced, widowed) and subgroup membership as categorical variables.
***Household composition:*** To assess whether household composition (i.e. number of other persons in household) differed across subgroups, we performed an ANOVA with subgroup membership as independent variable.

***Depression diagnosis:*** The Composite International Diagnostic Interview (CIDI) (Robins et al., 1988) was used to assess diagnoses of mental disorders based on Diagnostic and Statistical Manual of Mental Disorders-IV (American Psychiatric Association, 2000). Subgroup differences in depression diagnosis were investigated by a Pearson's chi-square test. Differences in depression or anxiety diagnoses were investigated by two Pearson's chi-square tests. It should be noted that the CIDI was only administered to a subsample of participants (N=266), which caused a relatively high number of missing values in these analyses.

***Anxiety diagnosis:*** Anxiety diagnosis was also assessed by the CIDI (Robins et al., 1988). Subgroup differences in anxiety diagnoses were investigated by a Pearson's chi-square test.

***ADHD-score:*** ADHD symptoms were assessed by the ADHD screening list (Barkley et al., 2007). This questionnaire consists of seven items with two response categories (i.e., 'yes' or 'no'). We used an ANOVA to investigate differences in total scores on the ADHD screening list between subgroups.

***Fluid intelligence:*** The Raven Coloured Progressive Matrices (RCPM) were used to assess fluid intelligence (Raven, 1995). The RCPM consists of three sections, namely A, Ab and B. Each subset consists of 12 items. The items consist of a matrix from which one section is missing. The respondent has to select the missing section among six alternatives that are printed below the matrix. A correct response is scored as one point, which results in a score ranging between 0 and 12 per subset. In LASA, only subset A and B were administered. Differences in fluid intelligence scores across subgroups were analyzed by an ANOVA with Raven sum scores for subset A and B separately, as dependent variables and subgroup membership as independent variable.

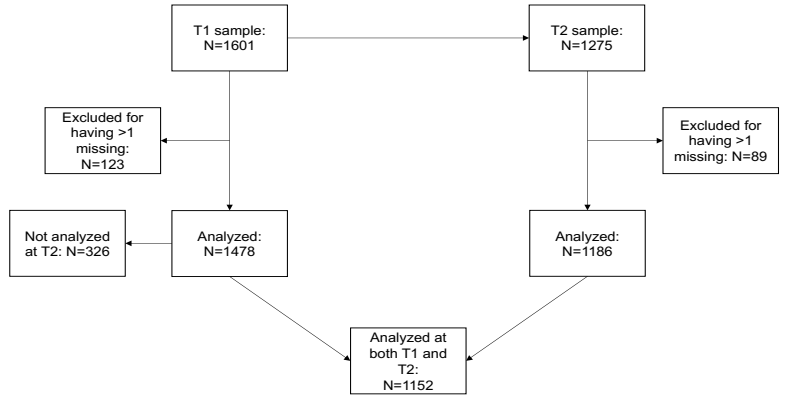
### S9.1.4 Attrition analyses

The attrition from T1 to T2 is depicted in sFigure 9.1.1. We performed six ANOVAs and six Pearson's chi-square tests on descriptive variables to compare differences between the group not analyzed at T2 (N=326) and the group analyzed at both T1 and T2 (N=1152). Results are presented in sTable 9.1.1.

The group of participants who dropped out and were, therefore, not analyzed at T2 (i.e., attrition group), was older than the group that was measured at T1 and T2 (i.e., included group). An explanation for this difference is that older age is more likely to be associated with drop-out due to fluctuating health status or death. The attrition group also had fewer household members, took a higher number of medicines and had lower scores both Raven subtests as compared to the included group. Also, this attrition group reported more medication use, and had fewer married participants that the group who participated at both T1 and T2. Furthermore, the attrition group, contained more participants from the 'Strongly supported with low education' subgroup (45%), and fewer participants from the 'Highly educated with personal vulnerabilities' and 'Physically active with low support and low education' subgroups (i.e., 26% and 29%, respectively).








*sFigure 9.1.1.* Attrition from T1 to T2

sTable 9.1.1

*Raw scores on descriptive variables at T1 for the group that was not analyzed at T2 (attrition group; N=326) and the group that was analyzed at both T1 and T2 (included group; N=1152).*

| | Group | | |
|---|---|---|---|
| | Not analyzed at T2 (attrition) | Analyzed at T1 and T2 (included) | |
| Variable | N = 326 | N = 1152 | test statistic(*df*) |
| **Descriptive variables** | | | |
| Age *M*(*SD*) | 77.71 (9.06) | 71.50 (7.52) | $F(1,1476) = 157.60^{***}$ |
| # household members *M*(*SD*) | 0.61 (0.57) | 0.77 (0.60) | $F(1,1447) = 17.30^{***}$ |
| # medicines *M*(*SD*) | 4.43 (3.20) | 2.98 (2.76) | $F(1,1415) = 59.89^{***}$ |
| Raven A-score *M*(*SD*) | 9.17 (3.02) | 10.40 (1.94) | $F(1,1415) = 72.36^{***}$ |
| Raven B-score *M*(*SD*) | 6.57 (3.40) | 8.72 (2.73) | $F(2,1415) = 129.10^{***}$ |
| ADHD-score *M*(*SD*) | 0.64 (1.17) | 0.58 (1.21) | $F<1$ |
| Gender | | | $\chi^2(1) = 0.03$ |
| $N_{male}$ (%) | 147 (45) | 528 (46) | |
| $N_{female}$ (%) | 179 (55) | 624 (54) | |
| Country of Origin | | | $\chi^2(1) = 0.40$ |
| $N_{Netherlands}$ (%) | 323 (99) | 1147 (100) | |
| $N_{Other}$ (%) | 3 (1) | 5 (0) | |
| Current depression | | | $\chi^2(1) = 0.72$ |
| $N_{Yes}$ (%) | 2 (25) | 20 (9) | |
| $N_{No}$ (%) | 6 (75) | 193 (91) | |
| Lifetime depression | | | $\chi^2(1) < 0.01$ |
| $N_{Yes}$ (%) | 2 (25) | 49 (23) | |
| $N_{No}$ (%) | 6 (75) | 164 (77) | |
| Lifetime anxiety | | | $\chi^2(1) = 0.24$ |
| $N_{Yes}$ (%) | 1 (14) | 57 (30) | |
| $N_{No}$ (%) | 6 (86) | 131 (70) | |
| Medication use | | | $\chi^2(1) = 14.83^{***}$ |
| $N_{Yes}$ (%) | 257 (89) | 883 (78) | |
| $N_{No}$ (%) | 33 (11) | 244 (22) | |
| Marital status | | | $\chi^2(3) = 35.80^{***}$ |
| $N_{never\ married}$ (%) | 11 (3) | 62 (5) | |
| $N_{married}$ (%) | 168 (52) | 761 (66) | |
| $N_{divorced}$ (%) | 29 (9) | 89 (8) | |
| $N_{widowhood}$ (%) | 118 (36) | 240 (21) | |
| Subgroup membership at T1 | | | $\chi^2(2) = 9.83^{**}$ |
| $N_{HighlyEd.}$ (%) | 83 (26) | 352 (30) | |
| $N_{StronglySup.}$ (%) | 147 (45) | 410 (36) | |
| $N_{PhysAct.}$ (%) | 96 (29) | 390 (34) | |

*Note.* PhysAct. = Physically active with low support and low education. HighlyEd. = Highly educated with personal vulnerabilities. StronglySup.= Strongly supported with low education. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$



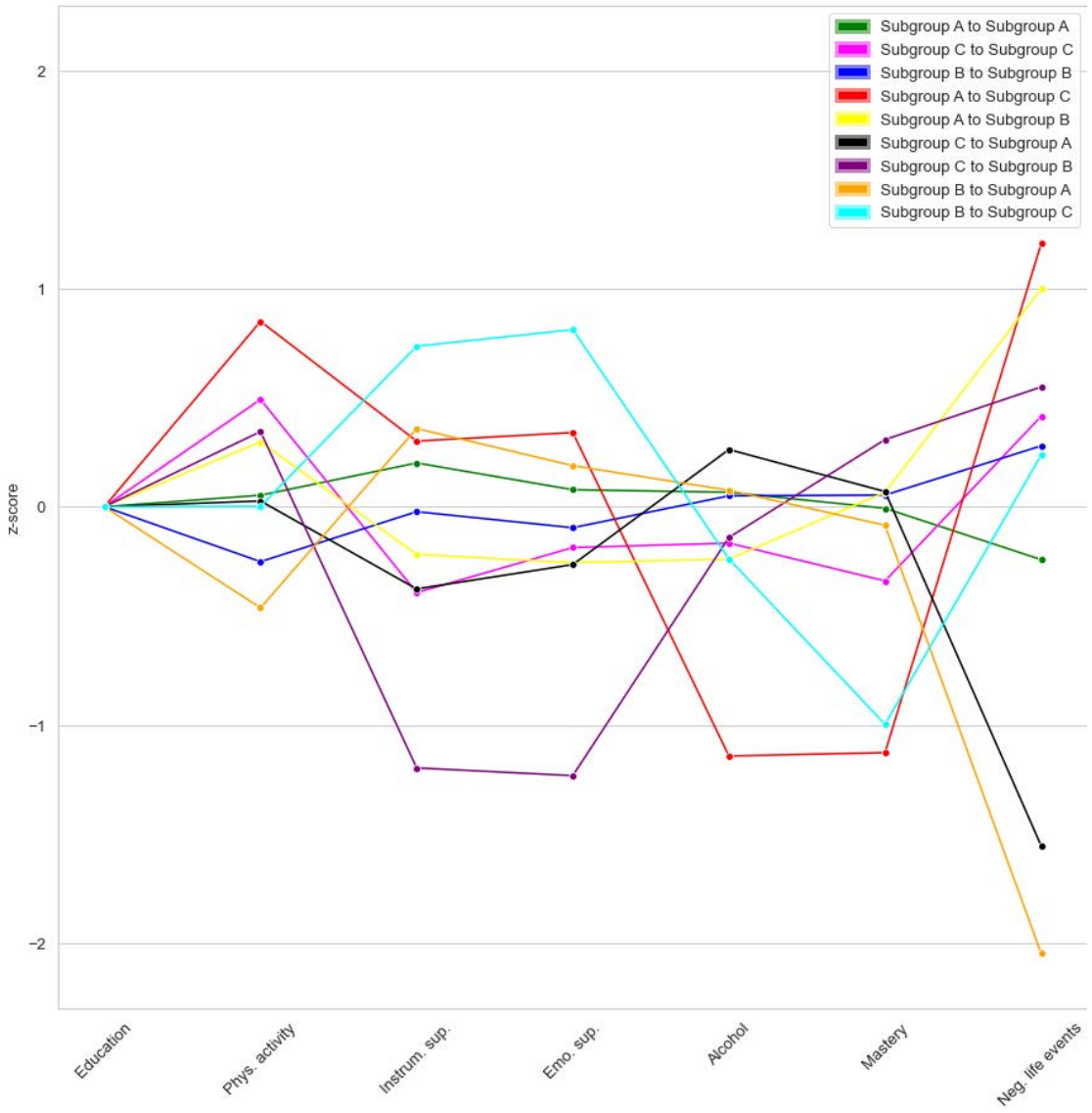


### S9.1.5 Standardized measures of subgroup similarity

Although not preregistered, we exploratively calculated two measures of subgroup similarity between the subgroups identified at T1 and T2. First, we calculated the Rand Index (RI) that ranges between 0 and 1 (Rand, 1971). Second, we calculated the Hubert-Arabie Adjusted Rand Index (Hubert & Arabie, 1985), which ranges between -1 and 1. For both measures, values greater than 0.90 can be interpreted as excellent subgroup recovery (i.e. similarity between subgroups at T1 and T2) and values less than 0.65 reflect poor recovery (Steinley, 2004).

In the current study, results indicated a poor recovery of subgroups from T1 to T2 (RI = 0.60, $ARI_{HA}$ = 0.10). However, it should be noted that a perfect similarity between subgroups at two measurement occasions is unlikely, since individuals are subject to change. A perfect recovery would imply that there are no transitions between subgroups (i.e., people do not change at all over time), which is not likely or clinically desirable. These measures are less applicable to the current study, and therefore, one should consider the underlying profiles of subgroups across measurement occasions as well.

### S9.1.6 Changes in cluster variable scores from T1 to T2




*Note.* HighlyEd. = Highly educated with personal vulnerabilities. PhysAct. = Physically active with low support and low education. StronglySup.= Strongly supported with low education. Scores as shown as z-scores based on the total sample mean. A z-score above 0 indicates an increase from T1 to T2, whereas a z-score below 0 indicates a decrease. A z-score of 0 indicates absence of change.





# Chapter 3

**Table of content**



### S9.2.1 Internal consistency for measures based on autism group in replication data

sTable 9.2.1
*Internal consistency (Cronbach's a) for the measures included as cluster variables, based on the autism group in the replication data.*

| Measure[a] | Cronbach's α |
|---|---|
| AQ total | 0.85 |
| - Social skills | 0.72 |
| - Attention switching | 0.66 |
| - Attention to detail | 0.66 |
| - Communication | 0.66 |
| - Imagination | 0.59 |
| Sensory sensitivity | 0.62 |
| Mastery | 0.80 |
| Worry | 0.88 |
| Emotional support | 0.86 |
| Positive affect | 0.86 |
| Negative affect | 0.90 |

*Note.* [a] Cronbach's alpha was not calculated for education, negative life events and physical activity, as these instruments are better described as formative measures rather than reflective of a latent trait.

### S9.2.2 Missing data

In the original data set there was 4.38% of missing data in total (i.e., 128 missing values out of 2925). In the replication data set, there was 1.96% of missing data in total (i.e., 201 missing values out of 10272). The percentage of missing data per cluster variable can be found in sTable 9.2.2.

On the item level, a maximum of 10% of missing data was recoded to the median of the participant's other responses on this specific questionnaire. Afterwards, sum scores were calculated that resulted in scores on 14 cluster variables per participant. At the instrument level, we only included participants with no more than one missing value (i.e., at least 13 non-missing values on 14 cluster variables), and no imputation was performed.

After imputation of missing data at item level, and removal of cases who still had more than one missing value on instrument level, there were 172 cases in the original data set (i.e., 23 were excluded, 12%). Of these cases, there were 23 cases who still had a missing value on one of the cluster variables: four on education, one on imagination, one on sensory sensitivity, seven on emotional support, eight on physical activity, one on negative affect, and one on negative life events.

After imputation of missing data at item level, and removal of cases who still had more than one missing value on instrument level, there were 548 cases in the replication data set (i.e., 32 were excluded, 6%). Of these cases, there were 52 who still had a missing value on one of the cluster variables: five on education, five on sensory sensitivity, one on mastery, one on worry, 19 on emotional support, 14 on physical activity and seven on negative life events."





sTable 9.2.2

*Number and percentages of missing data for each of the cluster variables in the original and replication data.*

| **Cluster variable** | **Data set** | |
|---|---|---|
| | Original | Replication |
| | Percentage of missing values (%) | |
| Education | 2.05 | 1.25 |
| AQ social skill | 1.03 | 0.62 |
| AQ attention switching | 1.03 | 0.62 |
| AQ attention to detail | 1.54 | 0.62 |
| AQ communication | 1.54 | 0.62 |
| AQ imagination | 1.54 | 0.78 |
| Sensory sensitivity | 1.54 | 1.09 |
| Mastery | 0.51 | 0.62 |
| Worry | 0.51 | 0.47 |
| Emotional support | 13.33 | 3.58 |
| Physical activity | 13.33 | 6.70 |
| Positive affect | 8.71 | 4.36 |
| Negative affect | 9.23 | 4.36 |
| Negative life events | 9.74 | 5.60 |

### S9.2.3 Cluster variable correlation matrix based on training data of autistic and non-autistic adults

sTable 9.2.3

*Correlation matrix of cluster variables based on training data of autistic and non-autistic adults*

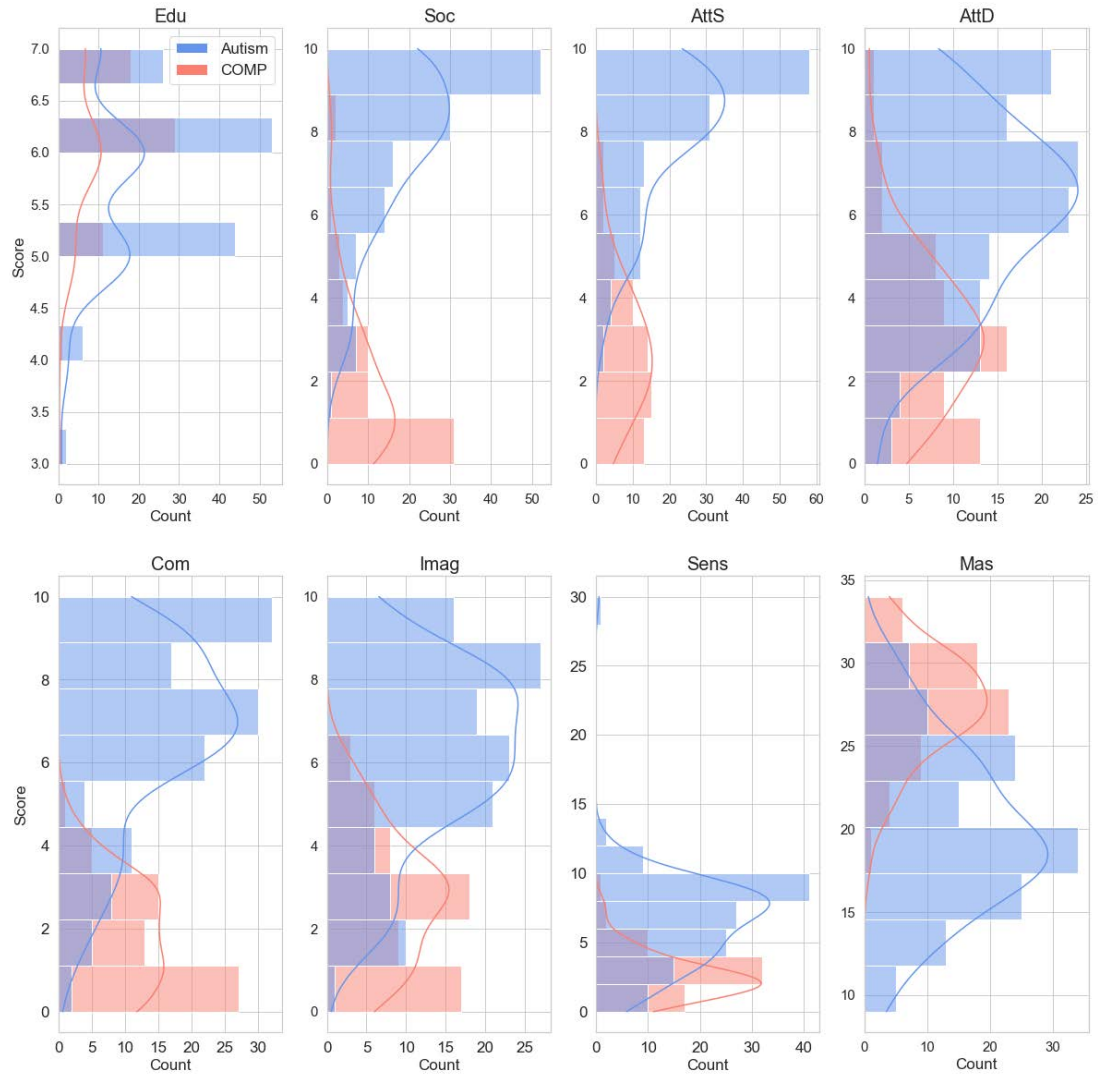
| | Edu | Soc | AttS | AttD | Com | Imag | Sens | Mas | Wor | Sup | Phys | NAff | PAff | Nlife |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Edu** | 1.00 | | | | | | | | | | | | | |
| **Soc** | -0.16 | 1.00 | | | | | | | | | | | | |
| **AttS** | -0.17 | 0.78 | 1.00 | | | | | | | | | | | |
| **AttD** | -0.05 | 0.47 | 0.55 | 1.00 | | | | | | | | | | |
| **Com** | -0.18 | 0.81 | 0.70 | 0.52 | 1.00 | | | | | | | | | |
| **Imag** | -0.10 | 0.59 | 0.66 | 0.45 | 0.60 | 1.00 | | | | | | | | |
| **Sens** | -0.30 | 0.48 | 0.54 | 0.46 | 0.52 | 0.37 | 1.00 | | | | | | | |
| **Mas** | 0.09 | -0.65 | -0.66 | -0.45 | -0.62 | -0.49 | -0.50 | 1.00 | | | | | | |
| **Wor** | -0.06 | 0.45 | 0.48 | 0.34 | 0.48 | 0.26 | 0.46 | -0.68 | 1.00 | | | | | |
| **Sup** | 0.13 | -0.33 | -0.31 | -0.14 | -0.25 | -0.25 | -0.15 | 0.29 | -0.22 | 1.00 | | | | |
| **Phys** | 0.01 | -0.17 | -0.24 | -0.15 | -0.11 | -0.23 | -0.08 | 0.13 | -0.10 | 0.14 | 1.00 | | | |
| **PAff** | 0.17 | -0.48 | -0.50 | -0.15 | -0.36 | -0.37 | -0.21 | 0.54 | -0.36 | 0.36 | 0.28 | 1.00 | | |
| **NAff** | 0.01 | 0.42 | 0.49 | 0.37 | 0.38 | 0.37 | 0.39 | -0.63 | 0.68 | -0.19 | -0.17 | -0.28 | 1.00 | |
| **Nlife** | 0.02 | -0.05 | 0.04 | 0.18 | -0.03 | -0.01 | 0.02 | -0.04 | 0.19 | -0.02 | -0.01 | <-0.01 | 0.21 | 1.00 |

*Note.* Edu = education, Soc = social skills, AttS = attention switching, AttD = attention to detail, Com = communication, Imag = imagination, Sens = sensory sensitivity, Mas = mastery, Wor = worry, Sup = emotional support, Phys = physical activity, PAff = positive affect, NAff = negative affect, NLife = negative life events.



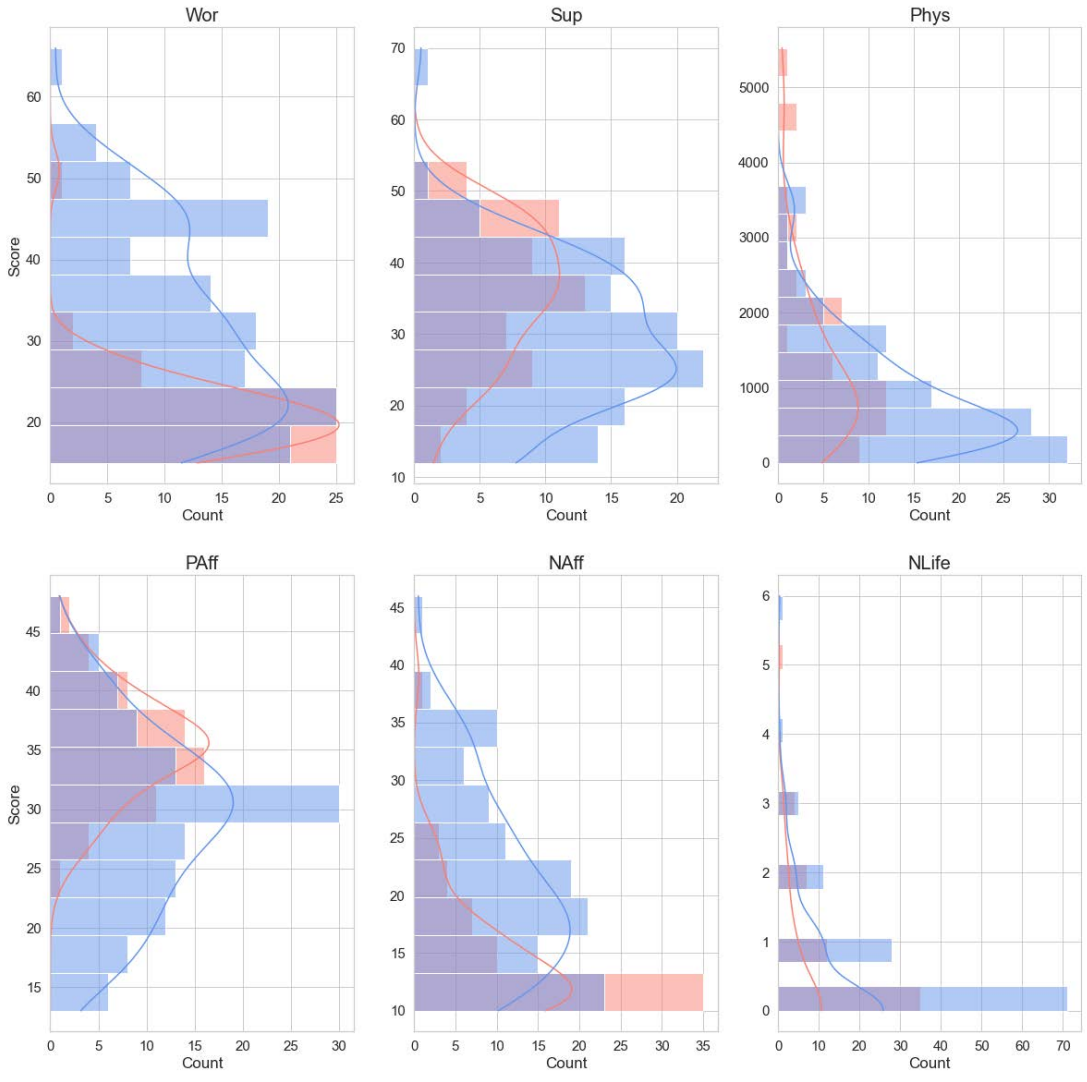


### S9.2.4 Distribution of scores on cluster variables across diagnostic groups for replication data




*sFigure 9.2.1.* A. Distribution of scores on cluster variables across diagnostic groups (i.e., Autism and COMP) for replication data.

*Note.* COMP = comparison, Edu = education, Soc = social skills, AttS = attention switching, AttD = attention to detail, Com = communication, Imag = imagination, Sens = sensory sensitivity, Mas = mastery.



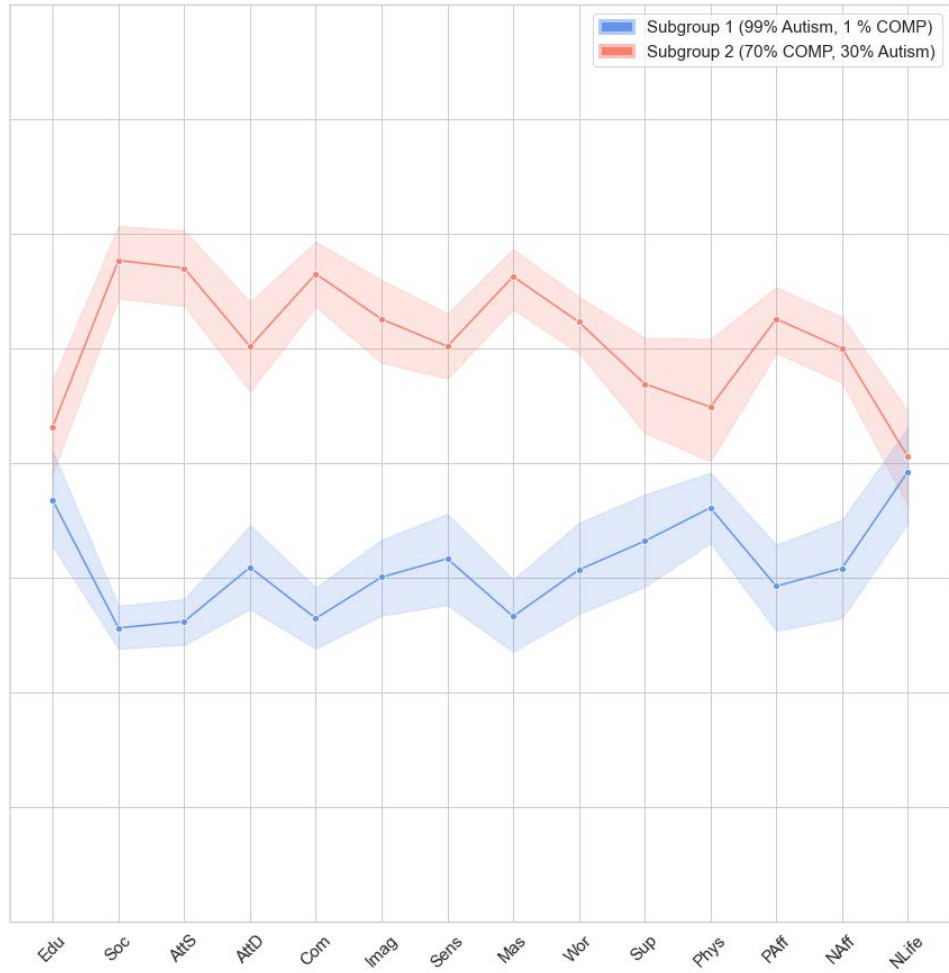

*sFigure 9.2.1.* B. Distribution of scores on cluster variables across diagnostic groups (i.e., Autism and COMP) for replication data.

*Note.* Wor = worry, Sup = emotional support, Phys = physical activity, PAff = positive affect, NAff = negative affect, NLife = negative life events





**S9.2.5 Profile plot for Autism and COMP subgroups formed on original data**




*sFigure 9.2.2.* Subgroup profiles based on data from the Autism and COMP groups for each of the two community detection-based subgroups formed on replication data.

*Note.* COMP = comparison, Edu = education, Soc = social skills, AttS = attention switching, AttD = attention to detail, Com = communication, Imag = imagination, Sens = sensory sensitivity, Mas = mastery, Wor = worry, Sup = emotional support, Phys = physical activity, PAff = positive affect, NAff = negative affect, NLife = negative life events. Higher z-scores represent higher scores on Edu, Soc, AttD, AttS, Com, Imag, Mas, Sup, Phys, PAff. Higher z-scores represent better scores on Sens, Wor, NAff, NLife (less sensitivity, less worrying, less negative affect, fewer negative life events). Shaded area represents 95%-confidence interval

## S9.2.6 Descriptive statistics for each of the autism subgroups formed on replication data

sTable 9.2.4
*Raw cluster variable scores and descriptive for each of the three autism subgroups formed on replication data (N=261).*

| Variable | Subgroup HighGr N = 124 | Subgroup LowGr N = 130 | Rest N = 7[d] | test statistic(*df*) | HighGr vs. LowGr (*Z*) | HighGr vs. Rest[d] (*Z*) | LowGr vs. Rest[d] (*Z*) |
|---|---|---|---|---|---|---|---|
| **Cluster variables** | | | | | | | |
| Education | 5.93 (0.91) | 6.00 (0.79) | 6.71 (0.49) | *F*(2, 255) = 2.87 | -0.39[a] | -2.47*[a] | -2.35*[a] |
| AQ social skill | 6.43 (2.45) | 8.61 (1.36) | 8.29 (1.38) | *F*(2, 258) = 39.77*** | -7.71***[a] | -1.88[a] | 0.62 |
| AQ attention switching | 6.92 (2.23) | 8.72 (1.34) | 8.57 (0.79) | *F*(2, 258) = 31.93*** | -6.99***[a] | -1.77[a] | 0.49 |
| AQ attention to detail | 6.40 (2.41) | 6.95 (2.04) | 6.29 (1.89) | *F*(2, 258) = 2.06 | -1.88[a] | 0.24 | 0.85 |
| AQ communication | 5.91 (2.27) | 7.55 (1.93) | 8.00 (1.41) | *F*(2, 258) = 20.69*** | -5.76***[a] | -2.42*[a] | -0.56[a] |
| AQ imagination | 4.98 (2.02) | 6.84 (1.97) | 7.57 (1.27) | *F*(2, 258) = 30.24*** | -6.86***[a] | -3.16*[a] | -0.94[a] |
| Sensory sensitivity | 6.53 (2.76) | 7.79 (2.27) | 6.00 (2.08) | *F*(2, 253) = 8.62*** | -3.79*[a] | 0.70 | 1.94 |
| Mastery | 23.21 (4.30) | 16.50 (3.82) | 22.71 (5.06) | *F*(2, 257) = 86.96*** | 10.30***[a] | 0.33 | -3.01* |
| Worry | 28.99 (9.63) | 38.39 (11.33) | 36.57 (12.16) | *F*(2, 258) = 25.31*** | -6.67***[a] | -1.74[a] | 0.41 |
| Emotional support | 33.13 (10.72) | 24.75 (10.10) | 28.14 (8.97) | *F*(2, 251) = 20.13*** | 5.71***[a] | 0.91 | -0.96[a] |
| Physical activity | 1314.80 (2028.13) | 908.81 (1022.04) | 635.33 (661.15) | *F*(2, 252) = 2.30 | 2.19*[a] | 1.37 | 0.71 |
| Positive affect | 32.46 (6.43) | 25.04 (6.15) | 27.86 (6.39) | *F*(2, 258) = 44.26*** | 8.27***[a] | 1.66 | -1.01 |
| Negative affect | 18.44 (6.65) | 25.45 (8.36) | 15.00 (5.54) | *F*(2, 258) = 30.46*** | -6.74***[a] | 1.22 | 3.40*** |
| Negative life events | 0.81 (1.07) | 0.73 (0.98) | 0.57 (0.53) | *F*(2, 255) = 0.36 | 0.49 | 0.16 | 0.01 |
| **Descriptive variables** | | | | | | | |
| Age *M*(*SD*), range | 50.61 (13.76), 30-81 | 51.34 (11.58), 30-84 | 60.43 (10.01), 47-72 | *F*(2, 258) = 2.01 | -0.51[a] | -2.04[a] | -1.88[a] |
| Biological sex[b] | | | | $\chi^2(4) = 0.51$ | | | |
| % male | 53 | 44 | 57 | | | | |
| % female | 47 | 55 | 43 | | | | |
| IQ score[c] | 116.70 (17.15) | 113.44 (15.25) | 120.50 (7.78) | *F*(2,93)=0.60 | 1.41 | -0.19 | -0.60 |

*Note.* HighGr = Feelings of high grip. LowGr = Feelings of low grip. Rest = Rest-subgroup. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. [a] Negative *z* test statistics indicate that the first mentioned group scores lower than the second group in the comparison. [b] The remaining percentage was classified as "other". [c] Sample size is lower for this variable because data are only available for participants who completed the interview. [d] Please note that the group sizes were severely unbalanced in the comparisons that involved the Rest-subgroup (Stevens, 1996). Therefore, these results should not be used to draw conclusions regarding the Rest-subgroup. The results were included because all group comparisons were preregistered.





## S9.2.7 Scores on external validation measures for the two replicated autism subgroups formed on original data

sTable 9.2.5
*Scores for external validation measures for the two replicated autism subgroups formed on original data (N=97).*

| | Subgroup HighGr N=49 (51%) | Subgroup LowGr N=48 (49%) | | |
|---|---|---|---|---|
| **Variable** | ***M (SD);* range** | ***M (SD);* range** | **Test statistic** | **Effect size (d)** |
| Cognitive difficulties | 42.9(11.5); 21-65 | 52.4(15.1); 18-86 | *t*(95)=3.5* | -0.71 |
| SCL-90 total score | 135.9(26.7); 97-211 | 204.7(45.9); 124-303 | | -1.83 |
| SCL-90 anxiety | 14.1(4.05); 10-15 | 22.0(7.9); 11-43 | *t*(69.7)=-6.2* | -1.27 |
| SCL-90 agoraphobia | 9.4(3.6); 7-25 | 13.3(3.9); 7-24 | *t*(95)=-5.1* | -1.04 |
| SCL-90 depression | 25.0(7.8); 16-56 | 40.8(11.5); 18-63 | *t*(82.6)=-7.9* | -1.61 |
| SCL-90 somatization | 17.7(4.5); 12-28 | 23.2(7.2); 12-40 | *t*(78.3)=-4.5* | -0.92 |
| SCL-90 cognitive performance deficits | 17.0(4.3); 9-30 | 24.4(5.9); 13-38 | *t*(86.0)=-7.1 | -1.46 |
| SCL-90 interpersonal sensitivity | 26.4(6.0); 18-43 | 42.9(11.5); 24-73 | *t*(70.6)=-8.8* | -1.81 |
| SCL-90 hostility | 8.1(2.3); 6-16 | 10.8(4.2); 6-22 | *t*(73.0)=-3.9* | -0.80 |
| SCL-90 sleep difficulties | 5.6(2.1); 3-11 | 8.1(3.3); 3-15 | *t*(80.1)=-4.4* | -0.89 |
| SCL-90 rest | 12.7(3.6); 9-24 | 19.0(5.9); 9-31 | *t*(77.1)=-6.5* | -1.75 |
| QoL Physical health | 14.8(2.5); 7-19 | 12.3(2.3); 7-19 | *t*(95)=4.9* | 0.99 |
| QoL Psychological | 14.1(2.3); 9-19 | 10.2(2.2); 6-17 | *t*(95)=8.6* | 1.74 |
| QoL Social relationships | 13.4(2.9); 7-19 | 10.6(3.2); 4-16 | *t*(95)=4.6* | 0.93 |
| QoL Environment | 16.3(2.2); 11-20 | 13.8(2.4); 10-19 | *t*(95)=5.5* | 1.12 |
| **Multivariate analyses** | | | | |
| SCL-90 | | | *F*(9,87)=10.1* | |
| QoL | | | *F*(4,92)=19.1* | |

*Note.* HighGr = Feelings of high grip. LowGr = Feelings of low grip. SCL-90 = Symptom Checklist. QoL = World Health Organization Quality of Life Questionnaire-BREF.
* $p < 0.005$.

sTable 9.2.6
*Scores for external validation measures for each of the three autism subgroups formed on replication data (N=261).*

| | Subgroup | | | | | | |
|---|---|---|---|---|---|---|---|
| | HighGr | LowGr | Rest[c] | | High-Gr vs. LowGr | High-Gr vs. Rest[c] | LowGr vs. Rest[c] |
| Variable | *M*(*SD*) | *M*(*SD*) | *M*(*SD*) | *F*(*df*) | | | |
| Cognitive failures | 43.087 (14.84) | 51. 81 (13.83) | 50.57 (13.49) | $F(2, 258) = 9.88$* | -4.24*[b] | -1.16[b] | 0.21 |
| SCL-90 total score | 149.37 (40.97) | 199.31 (52.45) | 153.29 (33.86) | $F(2, 255) = 36.28$* | -8.05*[b] | -0.29[b] | 2.33 |
| SCL-90 anxiety | 15.93 (5.78) | 21.58 (7.74) | 15.86 (6.33) | $F(2, 257) = 22.14$* | -6.54*[b] | 0.11 | 2.24 |
| SCL-90 agoraphobia | 9.29 (3.10) | 12.85 (5.05) | 11.29 (4.79) | $F(2, 257) = 22.38$* | -6.83*[b] | -1.16[b] | 1.05 |
| SCL-90 depression | 27.98 (9.06) | 40.56 (13.08) | 27.29 (7.20) | $F(2, 257) = 41.08$* | -7.93*[b] | -0.03[b] | 2.54 |
| SCL-90 somatization | 19.21 (6.62) | 22.52 (7.69) | 16.57 (3.87) | $F(2, 255) = 7.99$* | -3.99*[b] | 1.05 | 2.35 |
| SCL-90 cognitive performance deficits | 18.00 (6.21) | 23.55 (6.78) | 19.00 (5.47) | $F(2, 257) = 23.35$* | -6.76*[b] | -0.32[b] | 1.86 |
| SCL-90 interpersonal sensitivity | 29.96 (10.00) | 41.12 (12.97) | 32.57 (7.55) | $F(2, 256) = 29.74$* | -7.31*[b] | -0.80[b] | 1.56 |
| SCL-90 hostility | 8.67 (3.34) | 10.38 (4.00) | 10.00 (3.87) | $F(2, 257) = 6.81$* | -4.44*[b] | -1.08[b] | 0.36 |
| SCL-90 sleep difficulties | 6.55 (2.90) | 8.47 (3.54) | 6.57 (2.07) | $F(2, 257) = 11.58$* | -4.37*[b] | -0.27[b] | 1.14 |



**S9.2.8 Scores on external validation measures for each of the three autism subgroups formed on replication data**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| SCL-90 not included in any specific factor | 13.79 (4.67) | 17.70 (5.48) | 14.14 (3.98) | $F(2, 257) = 19.12$* | -6.37*[b] | -0.38[b] | 1.69 |
| QoL Physical health | 14.28 (2.62) | 12.09 (2.56) | 12.71 (2.36) | $F(2, 256) = 22.69$* | 6.26* | 1.39 | -0.61[b] |
| QoL Psychological | 13.43 (2.29) | 10.75 (2.43) | 12.00 (2.24) | $F(2, 257) = 40.60$* | 8.01* | 1.32 | -1.27[b] |
| QoL Social relationships | 12.88 (2.80) | 10.68 (3.15) | 10.00 (2.00) | $F(2, 258) = 18.62$* | 5.40* | 2.45 | 0.71 |
| QoL Environment | 15.83 (2.09) | 14.05 (2.42) | 13.86 (1.35) | $F(2, 257) = 20.50$ | 5.68* | 2.38 | 0.54 |
| **Multivariate analyses** | | | | | | | |
| QoL | | | | $F(8, 504) = 11.15$*[a] | | | |
| SCL-90 | | | | $F(18, 494) = 5.45$*[a] | | | |

*Note.* HighGr = Feelings of high grip. LowGr = Feelings of low grip. SCL-90 = Symptom Checklist. QoL = World Health Organization Quality of Life Questionnaire-BREF.
* $p < 0.005$. [a] not corrected for multiple testing (i.e., $p < 0.05$). [b] Negative *z* test statistics indicate that the first mentioned group scores lower than the second group in the comparison. [c] Please note that the group sizes were severely unbalanced in the comparisons that involved the Rest-subgroup (Stevens, 1996). Therefore, these results should not be used to draw conclusions regarding the Rest-subgroup. The results were included because all group comparisons were preregistered.

# Chapter 4

**Table of content**



## S9.3.1 Simulation studies

***Simulations 1 & 2: Required sample size to estimate one network***

For our network study, we aimed to include 16 preselected variables. We performed a simulation study to determine whether we could estimate the networks with sufficient sensitivity and specificity given a sample size varying between 80 and 160 adults. We also varied the percentage of missing data from 0 to 15% to see whether we could estimate the networks in spite of the missing data in our sample.

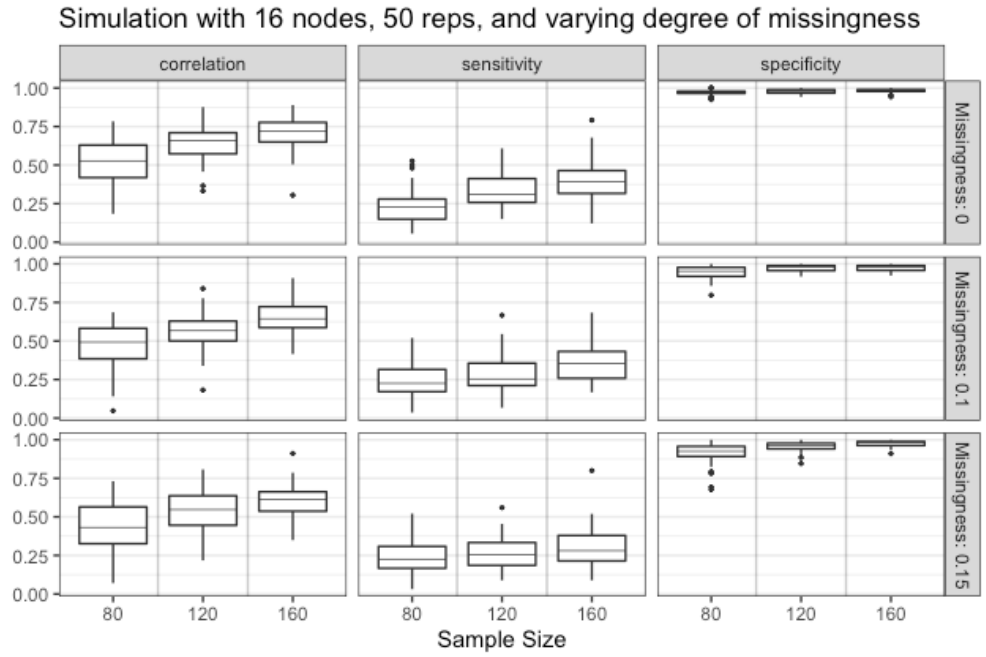
First, we generated a true network consisting of 16 nodes that we could use to simulate data under. We then simulated a corresponding data set and estimated a network based on this data. We used the “CompareNetworks” function of the “bootnet” package to determine at what sample size and which amount of missing data, we would end up with a good correspondence between the true network and our estimated network.

Please note that at the time of our preregistration and our simulation studies, we did not know how many subgroups we would identify in our subgrouping study we base these networks on (Chapter 3; Radhoe, Agelink van Rentergem, Torenvliet, et al., 2023). As we included approximately 400 autistic participants, and we expected to observe two to four subgroups based on the first analyses and literature overview, it was likely that we would have 100 to 200 participants per subgroup. Therefore, we varied the sample size in our simulation study by setting it to 80, 120 and 160 participants. Regarding the percentage of missing data, we simulated 0, 10 and 15% of missingness. We used 50 repetitions in this simulation.





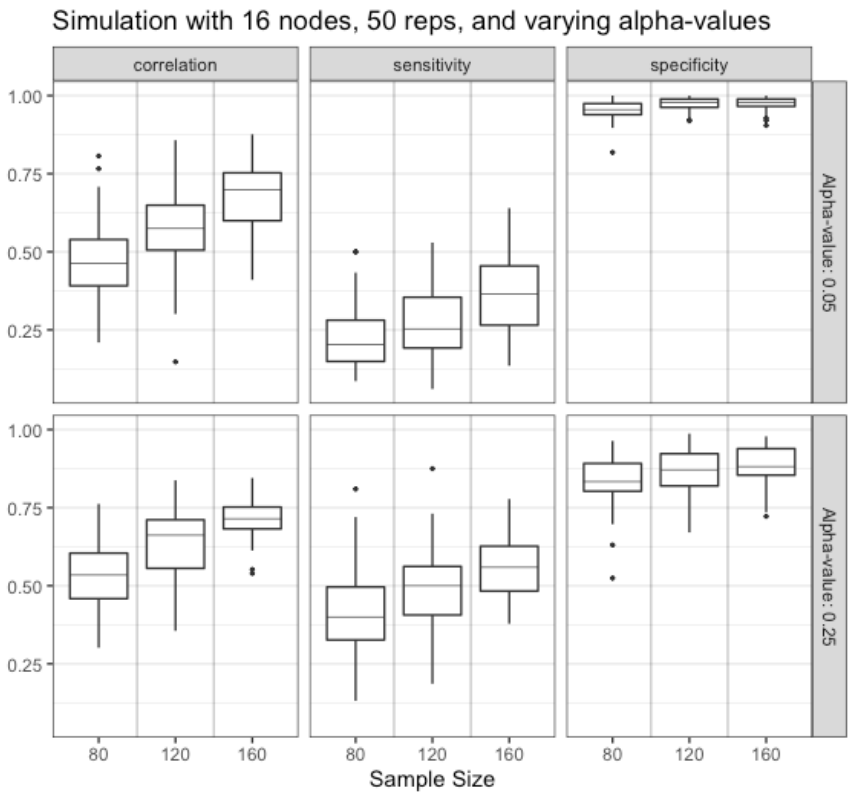
Results (see sFigure 9.3.1) show that sample sizes of 80, 120, and 160 resulted in a high specificity, but a relatively low sensitivity. Also, 0 to 15% of missing data was associated with similar results across the varying sample sizes.




*sFigure 9.3.1.* Results of simulations in which the sample size and percentage of missing data are varied to determine the correlation between edge weights, sensitivity and specificity.

Therefore, we performed a second simulation, in which we varied the value of alpha to see whether we could improve the sensitivity. We again simulated sample sizes of 80, 120 and 160. Regarding the percentage of missing data, we now chose to simulate 10% of missingness, since it does not greatly affect the results compared to 0% of missingness. Also, in our earlier study in which we identified the subgroups (Chapter 3; Radhoe, Agelink van Rentergem, Torenvliet, et al., 2023), we performed our community detection analyses with 10% of missing data. We set the alpha-value at 0.05 (which is the default) and 0.25 to see how this would affect the results.

The results are presented in sFigure 9.3.2. Results show that using α=0.25 results in a higher sensitivity while the specificity remains high. Thus, based on these simulations we decided to use a maximum of 10% of missing data and an alpha-value of 0.25.




*sFigure 9.3.2.* Results of simulations in which the sample size and alpha-value are varied to determine the correlation between edge weights, sensitivity and specificity.





***Simulation 3: Comparing two distinct networks to assess True Positives***

Besides estimating networks, we also aimed to compare the estimated networks in this study. Therefore, we also performed simulations to determine at which sample size we would be able to detect differences between the networks.

In the third simulation, we generated two distinct true networks and simulated two corresponding data sets. Next, we estimated two networks based on these data sets using EBICglasso. We performed a Network Comparison Test (NCT) to see at what sample size and at which gamma-value, we would detect a significant difference between these two distinct estimated networks. We again used 80, 120 and 160 as sample size. We varied the gamma-value from 0 to 0.5.

We looked at two p-values resulting from the NCT:

1. Global strength: the sum of the absolute values of all edges (i.e., the connectivity). This test explores whether the overall level of connectivity is equal across the two networks.
2. Maximum difference in edge weights: The p-value resulting from the test concerning the maximum difference in edge weights between the two networks.

Results are presented in sTable 9.3.1, and indicate that Gamma=0 can best be used to detect differences between networks belonging to two separate (sub)groups.
For global strength, a sample size of 80 would result in a True Positive rate of 58% (i.e., 29 out of 50 repetitions), which is slightly above chance level. A sample size of 160 would result in a True Positive rate of 64% (i.e., 32 out of 50 repetitions).
For the maximum difference in edge weights, with a sample size of 80, a significant difference (i.e., True Positive) would be detected in 70% of cases (i.e., 35 out of 50 repetitions). A sample size of 160 would result in a True Positive rate of 94% (i.e., 47 out of 50 cases).

sTable 9.3.1
*Number of True Positives and False Negatives resulting from 50 repetitions of the Network Comparison Test given varying gamma values.*

| Gamma | Outcome NCT | Sample size | | |
|---|---|---|---|---|
| | | 80 | 120 | 160 |
| 0 | Glstrinv.pval | | | |
| | False[1]: $p$ >.05 | 21 | 18 | 18 |
| | True[2]: $p$ <.05 | 29 | 32 | 32 |
| | Nwinv.pval | | | |
| | False[1]: $p$ >.05 | 15 | 6 | 3 |
| | True[2]: $p$ <.05 | 35 | 44 | 47 |
| 0.25 | Glstrinv.pval | | | |
| | False[1]: $p$ >.05 | 29 | 23 | 18 |
| | True[2]: $p$ <.05 | 21 | 27 | 32 |
| | Nwinv.pval, | | | |
| | False[1]: $p$ >.05 | 29 | 22 | 10 |
| | True[2]: $p$ <.05 | 21 | 28 | 40 |
| 0.50 | Glstrinv.pval | | | |
| | False[1]: $p$ >.05 | 40 | 32 | 25 |
| | True[2]: $p$ <.05 | 10 | 18 | 25 |
| | Nwinv.pval, | | | |
| | False[1]: $p$ >.05 | 40 | 30 | 20 |
| | True[2]: $p$ <.05 | 10 | 20 | 30 |

*Note.* Numbers indicate how frequent, out of 50 repetitions, a certain result was obtained.
Glstrinv.pval = difference in global strength. Nwinv.pval = maximum difference in edge weights.
[1] False indicates "No difference between networks" (i.e., False Negative).
[2] True indicates "Significant difference between networks" (i.e., True Positive).





***Simulation 4: Comparing two networks to assess False Positives***
In the fourth simulation, we aimed to determine the false positive rate when performing the NCT given various sample sizes. Thus, we first generated one true network with two corresponding data sets. Next, we estimated two networks based on these data sets using EBICglasso. Please note that there is only one underlying true network; therefore, there should not be a significant difference between the networks. We performed a NCT to assess the number of False Positives (i.e., we obtain a significant result even though the underlying network is similar). We again used 80, 120 and 160 as sample size. We varied the gamma-value from 0 to 0.5, and used 50 repetitions. The results are presented in sTable 9.3.2.

sTable 9.3.2
*Number of False Positives and True Negatives resulting from 50 repetitions of the Network Comparison Test given varying gamma values.*

| Gamma | Outcome NCT | Sample size | | |
|---|---|---|---|---|
| | | 80 | 120 | 160 |
| 0 | Glstrinv.pval: | | | |
| | False[1]: $p$ >.05 | 44 | 48 | 48 |
| | True[2]: $p$ <.05 | 6 | 2 | 2 |
| | Nwinv.pval | | | |
| | False: $p$ >.05 | 47 | 47 | 48 |
| | True: $p$ <.05 | 3 | 3 | 2 |
| 0.25 | Glstrinv.pval | | | |
| | False: $p$ >.05 | 42 | 45 | 48 |
| | True: $p$ <.05 | 8 | 5 | 2 |
| | Nwinv.pval | | | |
| | False: $p$ >.05 | 46 | 47 | 46 |
| | True: $p$ <.05 | 4 | 3 | 4 |
| 0.50 | Glstrinv.pval | | | |
| | False: $p$ >.05 | 48 | 49 | 47 |
| | True: $p$ <.05 | 2 | 1 | 3 |
| | Nwinv.pval | | | |
| | False: $p$ >.05 | 48 | 48 | 47 |
| | True: $p$ <.05 | 2 | 2 | 3 |

*Note.* Numbers indicate how frequent, out of 50 repetitions, a certain result was obtained.
Glstrinv.pval = difference in global strength. Nwinv.pval = maximum difference in edge
[1] False indicates "No difference between networks" (i.e., True Negative).
[2] True indicates "Significant difference between networks" (i.e., False Positive).

Results indicate that Gamma=0.50 provides the lowest False Positive rate when comparing two networks that do not differ. However, as the difference with Gamma=0 is relatively small, and Gamma=0 resulted in the highest True Positive rate, we proceed with Gamma=0.

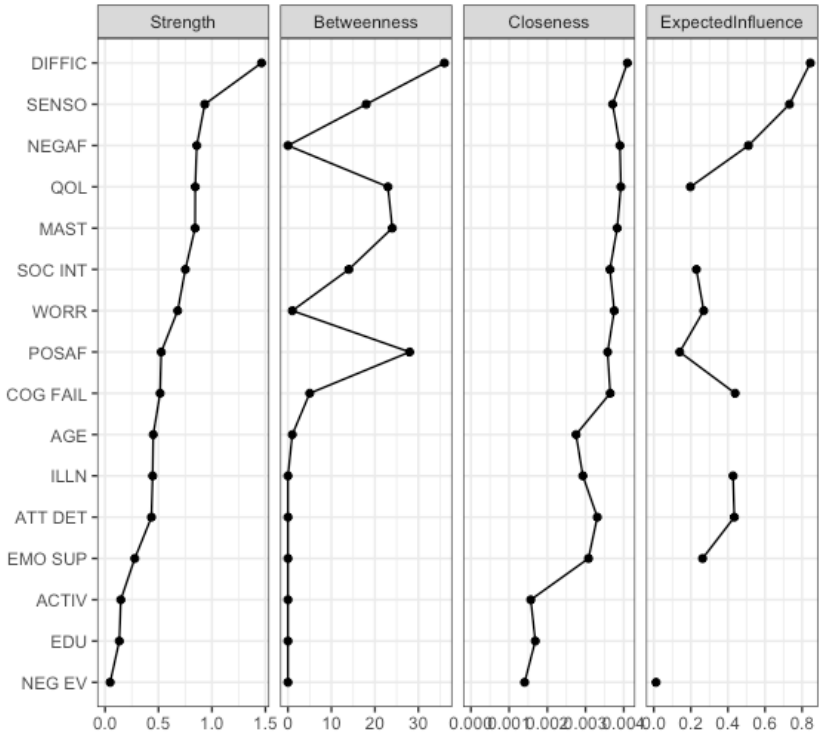
For global strength, a sample size of 80 would results in a False Positive rate of 12% (i.e., 6 out of 50 repetitions). A sample size of 160 would result in a False Positive rate of 4% (i.e., 2 out of 50 repetitions).
For the maximum difference in edge weights, a sample size of 80 would result in a False Positive rate of 6% (i.e., 3 out of 50 repetitions), and a sample size of 120 would result in a False Positive rate of 4% (i.e., 2 out of 50 repetitions).

Thus, with a maximum of 10% of missing data and α=0.25 or γ=0, we can compare networks with medium power and an acceptable false discovery rate with as few as 80 participants per subgroup. The R-code for the simulations can be found at https://osf.io/qbh29.





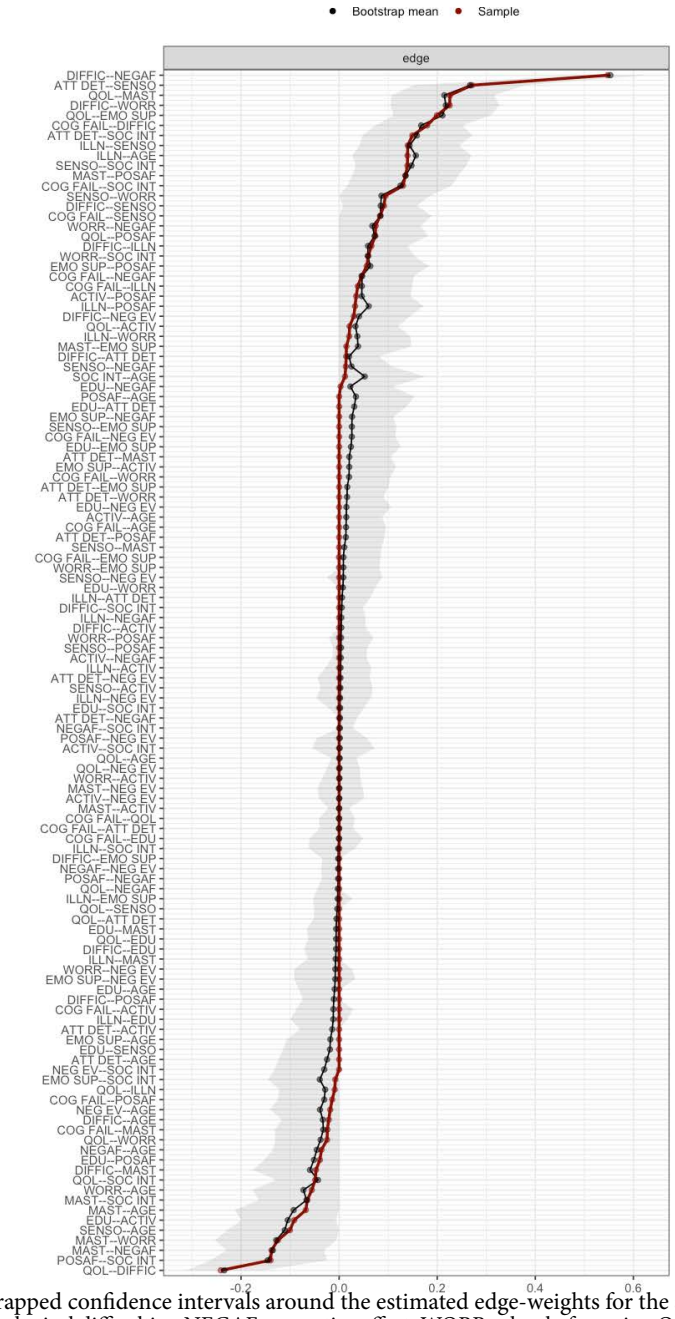
**S9.3.2 Plot of centrality indices for the autism group**




*sFigure 9.3.3.* Centrality indices for the estimated network of the autism group ordered by node strength.

Note. DIFFIC = psychological difficulties, NEGAF = negative affect, WORR = level of worries, QOL = quality of life, SENSO = sensory sensitivity, ATT DET = attention to detail, COG FAIL = cognitive difficulties, EMO SUP = emotional support, SOC INT = social interaction difficulties, ACTIV = physical activity, MAST = mastery, POSAF = positive affect, AGE = biological age, ILLN = physical illnesses, EDU = education, NEG EV = negative life events.

### S9.3.3 Plot of bootstrapped confidence intervals around the edge-weights for autism group

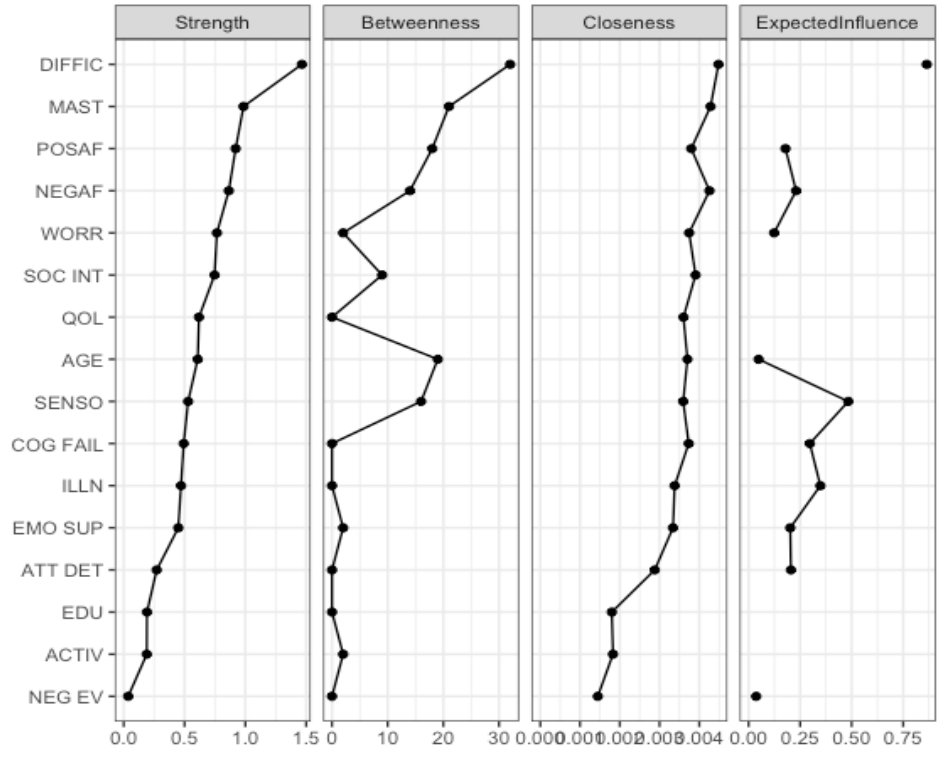



*sFigure 9.3.4.* Bootstrapped confidence intervals around the estimated edge-weights for the autism group.
Note. DIFFIC = psychological difficulties, NEGAF = negative affect, WORR = level of worries, QOL = quality of life, SENSO = sensory sensitivity, ATT DET = attention to detail, COG FAIL = cognitive difficulties, EMO SUP = emotional support, SOC INT = social interaction difficulties, ACTIV = physical activity, MAST = mastery, POSAF = positive affect, AGE = biological age, ILLN = physical illnesses, EDU = education, NEG EV = negative life events. The y-axis displays all edges in the network, ordered from the highest edge to the lowest edge weights. The x-axis displays the edge weights. The red dots indicate the value in the sample, the black dots indicate the mean in the bootstrapped samples, and the grey area represents the bootstrapped confidence intervals.





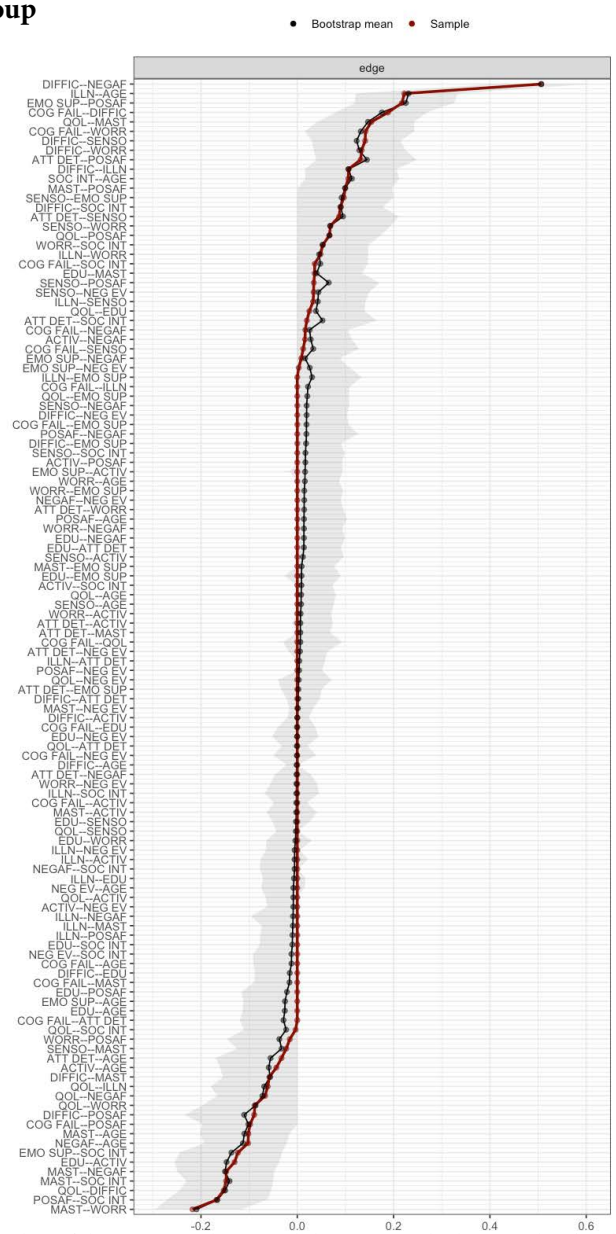
### S9.3.4 Plot of centrality indices for the Comparison group




*sFigure 9.3.5.* Centrality indices for the estimated network of the Comparison group ordered by node strength.

*Note.* DIFFIC = psychological difficulties, NEGAF = negative affect, WORR = level of worries, QOL = quality of life, SENSO = sensory sensitivity, ATT DET = attention to detail, COG FAIL = cognitive difficulties, EMO SUP = emotional support, SOC INT = social interaction difficulties, ACTIV = physical activity, MAST = mastery, POSAF = positive affect, AGE = biological age, ILLN = physical illnesses, EDU = education, NEG EV = negative life events.

### S9.3.5 Plot of bootstrapped confidence intervals around the edge-weights for the Comparison group

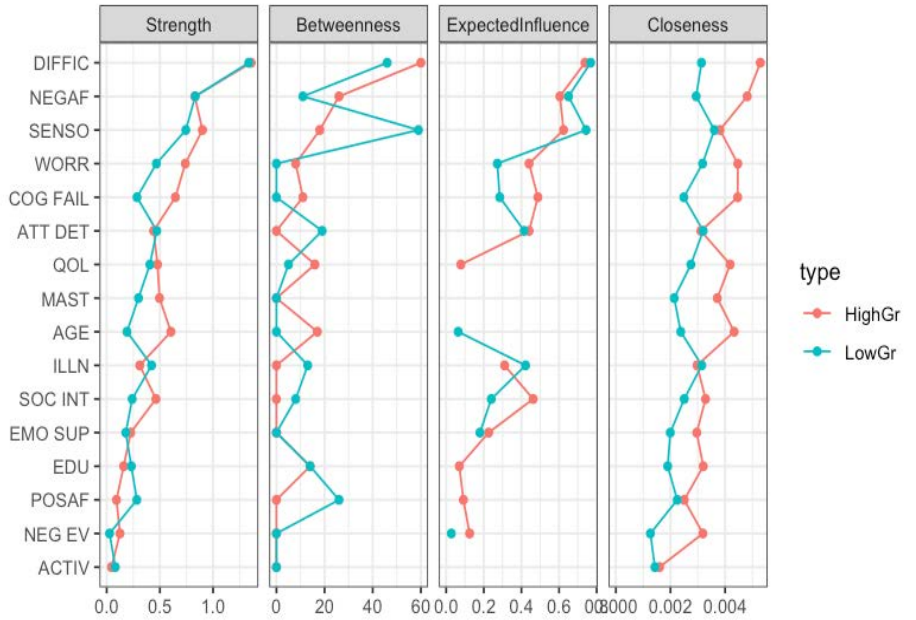



*sFigure 9.3.6.* Bootstrapped confidence intervals around the estimated edge-weights for the Comparison group.
*Note.* DIFFIC = psychological difficulties, NEGAF = negative affect, WORR = level of worries, QOL = quality of life, SENSO = sensory sensitivity, ATT DET = attention to detail, COG FAIL = cognitive difficulties, EMO SUP = emotional support, SOC INT = social interaction difficulties, ACTIV = physical activity, MAST = mastery, POSAF = positive affect, AGE = biological age, ILLN = physical illnesses, EDU = education, NEG EV = negative life events. The y-axis displays all edges in the network, ordered from the highest edge to the lowest edge weights. The x-axis displays the edge weights. The red dots indicate the value in the sample, the black dots indicate the mean in the bootstrapped samples, and the grey area represents the bootstrapped confidence intervals.





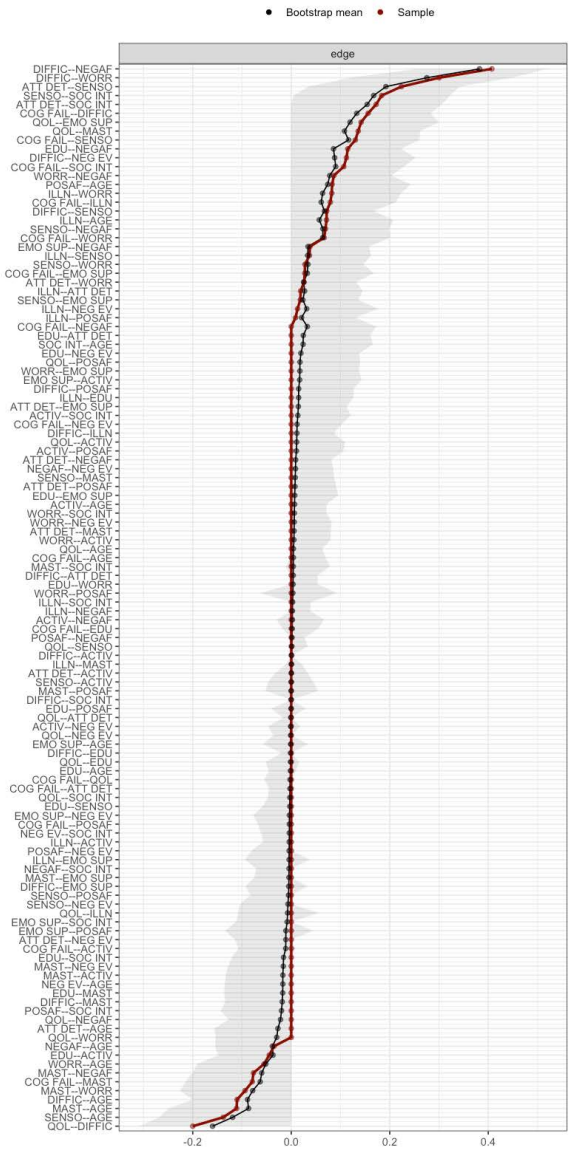
### S9.3.6 Plot of centrality indices for the two autism subgroups: "Feelings of High Grip" and "Feelings of Low Grip"




*sFigure 9.3.7.* Centrality indices for the estimated networks of the "Feelings of High Grip" and "Feelings of Low Grip" subgroups ordered by node strength.

Note. HighGr = Feelings of High Grip, LowGr = Feelings of Low Grip, DIFFIC = psychological difficulties, NEGAF = negative affect, WORR = level of worries, QOL = quality of life, SENSO = sensory sensitivity, ATT DET = attention to detail, COG FAIL = cognitive difficulties, EMO SUP = emotional support, SOC INT = social interaction difficulties, ACTIV = physical activity, MAST = mastery, POSAF = positive affect, AGE = biological age, ILLN = physical illnesses, EDU = education, NEG EV = negative life events.

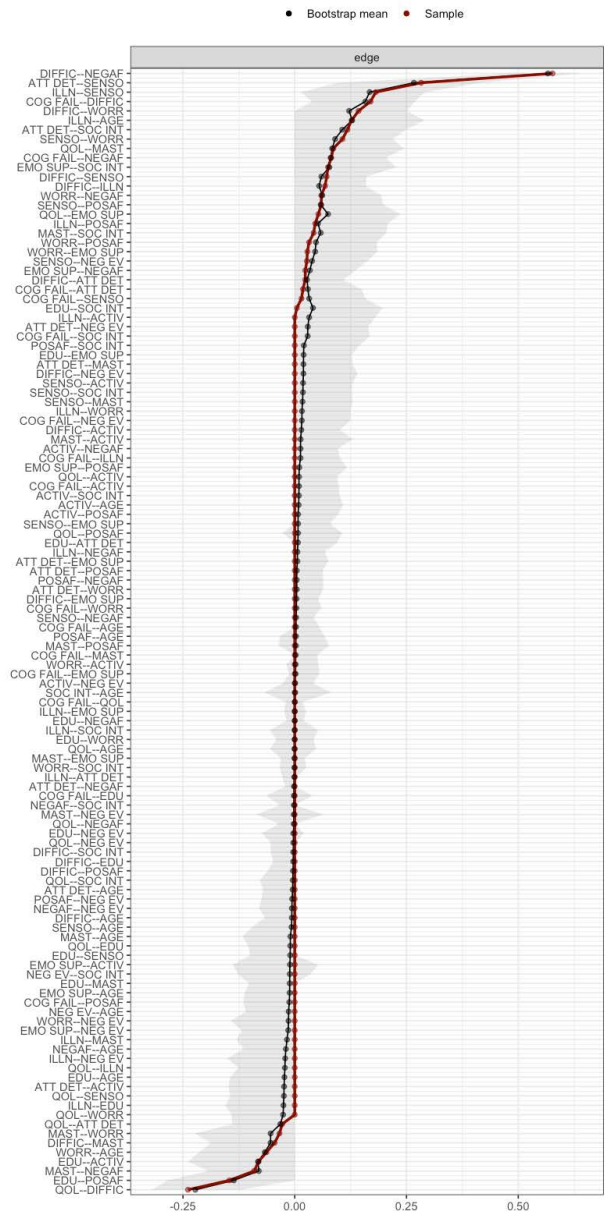
### S9.3.7 Plot of bootstrapped confidence intervals around the edge-weights for the autism subgroups: "Feelings of High Grip" and "Feelings of Low Grip"




*sFigure 9.3.8.* Bootstrapped confidence intervals around the estimated edge-weights for the "Feelings of High Grip" subgroup.
*Note.* DIFFIC = psychological difficulties, NEGAF = negative affect, WORR = level of worries, QOL = quality of life, SENSO = sensory sensitivity, ATT DET = attention to detail, COG FAIL = cognitive difficulties, EMO SUP = emotional support, SOC INT = social interaction difficulties, ACTIV = physical activity, MAST = mastery, POSAF = positive affect, AGE = biological age, ILLN = physical illnesses, EDU = education, NEG EV = negative life events. The y-axis displays all edges in the network, ordered from the highest edge to the lowest edge weights. The x-axis displays the edge weights. The red dots indicate the value in the sample, the black dots indicate the mean in the bootstrapped samples, and the grey area represents the bootstrapped confidence intervals.








*sFigure 9.3.9.* Bootstrapped confidence intervals around the estimated edge-weights for the "Feelings of Low Grip" subgroup.
*Note.* The y-axis displays all edges in the network, ordered from the highest edge to the lowest edge weights. The x-axis displays the edge weights. The red dots indicate the value in the sample, the black dots indicate the mean in the bootstrapped samples, and the grey area represents the bootstrapped confidence intervals.

### S9.3.8 Results of Network Comparison Tests (NCT)

sTable 9.3.3
*P-values per edge from the permutation test concerning differences in edge weights based on comparing the autism group vs. comparison group.*

| Variable 1 | Variable 2 | P-value |
|---|---|---|
| ATT DET | SENSO | 0.01 |
| QOL | EMO SUP | 0.02 |
| DIFFIC | POSAF | 0.04 |
| ATT DET | POSAF | 0.01 |
| SENSO | POSAF | <0.01 |
| EMO SUP | POSAF | <0.01 |
| QOL | NEGAF | 0.05 |
| DIFFIC | SOC INT | <0.01 |
| ATT DET | SOC INT | 0.03 |
| EMO SUP | SOC INT | 0.05 |
| SOC INT | AGE | 0.02 |

*Note.* DIFFIC = psychological difficulties, NEGAF = negative affect, QOL = quality of life, SENSO = sensory sensitivity, ATT DET = attention to detail, EMO SUP = emotional support, SOC INT = social interaction difficulties, POSAF = positive affect, AGE = biological age.

sTable 9.3.4
*P-values per edge from the permutation test concerning differences in edge weights based on comparing the autism subgroups ("Feelings of High Grip" vs. "Feelings of Low Grip").*

| Variable 1 | Variable 2 | P-value |
|---|---|---|
| DIFFIC | WORR | 0.02 |
| EDU | POSAF | 0.04 |
| SENSO | POSAF | 0.02 |
| DIFFIC | NEGAF | 0.01 |

*Note.* DIFFIC = psychological difficulties, WORR = worries/fears, EDU = education, NEGAF = negative affect, POSAF = positive affect, SENSO = sensory sensitivity.





# Chapter 5

**Table of content**



### S9.4.1 Attrition analysis results

Groups were compared on sex, age, estimated IQ score, and total AQ score.
Sample 1: At five-year follow-up, 34 autistic adults dropped out. Reasons for dropout were (1) withdrawn consent to participate at follow-up (N=8), (2) death (N=1), (3) exclusion at follow-up (N=1), and (4) could not be contacted or other reasons (N=10). In the autism group, there were no differences between the group that dropped out and those included at follow-up in sex, age, estimated IQ, and autism characteristics. Between the autism subgroups, there was a difference in total AQ score: Adults who dropped out in the "Feelings of High Grip" subgroup (HighGr) had a lower total AQ score compared to those who dropped out from the "Feelings of Low Grip" (LowGr) subgroup.
Sample 2: At two-year follow-up, 96 participants dropped out (Nautism=20). Reasons for dropout were (1) withdrawn consent to participate at follow-up ($N_{total}$=22, $N_{autism}$=5), (2) illness ($N_{Autism}$=2), (3) exclusion at follow-up ($N_{total}$=16, $N_{autism}$=0), (4) could not be contacted or other reasons ($N_{total}$=56, $N_{autism}$=13). In the autism group, the dropout group included relatively more men compared to the group that was included. In the comparison group, the dropout group was younger and had a lower IQ compared to those included at follow-up. In the comparison group, there was more dropout than in the autism group. There were no differences in dropout between the autism subgroups (i.e., HighGr and LowGr) aside from total AQ score: higher scores for those who dropped out in the HighGr subgroup.

sTable 9.4.1
*Attrition analysis results for Sample 1 (N=80): total autism group and autism subgroups.*

| | **Total autism group** | | | **Autism subgroups** | | |
|---|---|---|---|---|---|---|
| | Dropout (N=34) | Included at five-year FU (N=80) | Test statistic | HighGr (N=12) | LowGr (N=20) | Test statistic |
| Dropout % | 30 | 70 | | 25[a] | 42[a] | $\chi^2(1) = 2.51$ |
| Sex ($N_{female}$ (%)) | 8 (24) | 34 (43) | $\chi^2(1) = 2.92$ | 3 (25) | 5 (20) | $\chi^2(1) = 0.00$ |
| Age (M; SD) | 55.5; 14.7 | 53.6; 10.8 | $F(1,112) = 0.57$ | 51.8; 12.4 | 55.9; 15.6 | $F(1,30) = 0.58$ |
| AQ (M; SD) | 34.3; 7.0 | 34.7; 6.8 | $F(1,111) = 0.08$ | 28.7; 5.3 | 37.8; 5.8 | $F(1,29) = 18.27$*** |

*Note.* FU = follow-up, HighGr = "Feelings of High Grip", LowGr = "Feelings or Low Grip". *** $p < 0.001$. ** $p < 0.01$. * $p < 0.05$.
[a] represents the percentage of people who dropped out within a specific subgroup (i.e., within HighGr or LowGr).

sTable 9.4.2
*Attrition analysis results for Sample 2: total sample, autism sample, and comparison sample.*

| | | **Dropout** | **Inclusion two-year FU** | **Test statistic** |
|---|---|---|---|---|
| **Total sample** | N | 96 | 452 | |
| | Sex ($N_{female}$ (%)) | 43 (45) | 220 (49) | $\chi^2(2) = 5.08$ |
| | Age (M; SD) | 53.4; 14.5 | 53.6; 13.3 | $F(1,546) = 0.01$ |
| | IQ ( M; SD) | 105.4; 15.6 | 113.9; 16.8 | $F(1,214) = 6.71$* |
| | AQ | 17.4; 9.6 | 25.0; 12.8 | $F(1,546) = 30.83$ |
| **AUT sample** | N | 20 | 241 | |
| | Sex ($N_{female}$ (%)) | 8 (40) | 125 (52) | $\chi^2(2) = 12.74$* |
| | Age (M; SD) | 55.5; 14.9 | 50.9; 12.5 | $F(1,259)=2.46$ |
| | IQ (M; SD) | 113.6; 13.6 | 115.2; 16.3 | $F(1,94) = 0.06$ |
| | AQ | 31.8; 6.6 | 35.1; 7.7 | $F(1,259) = 3.60$ |
| **COMP sample** | N | 76 | 211 | |
| | Sex $N_{female}$ (%)) | 35 (46) | 95 (45) | $\chi^2(1) = <0.01$ |
| | Age (M; SD) | 52.9; 14.5 | 56.7; 13.5 | $F(1,285) = 4.16$* |
| | IQ (M; SD) | 102.9; 15.5 | 112.7; 17.2 | $F(1,118) = 6.16$* |
| | AQ (M; SD) | 13.6; 15.5 | 13.6; 17.2 | $F(1,285) = <0.01$ |

*Note.* AUT = autism, COMP = comparison, FU = follow-up.
*** $p < 0.001$. ** $p < 0.01$. * $p < 0.05$.



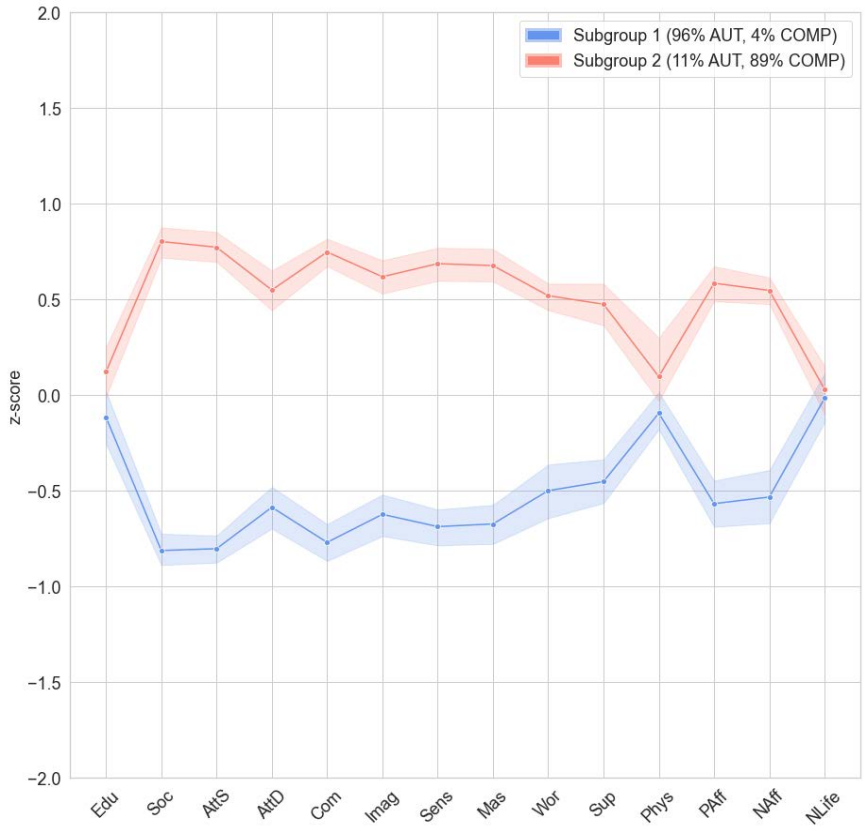


sTable 9.4.3
*Attrition analysis results for Sample 2: diagnostic groups (comparison vs. autism), and autism subgroups.*

| | **Group** | | | **Subgroups** | | |
|---|---|---|---|---|---|---|
| | COMP (N=76) | AUT (N=20) | COMP vs. AUT | HighGr (N=10) | LowGr (N=9) | HighGr vs. LowGr |
| Dropout %[a] | 27 | 8 | $\chi^2(1) = 32.21$*** | 8 | 7 | $\chi^2(1) = 0.01$ |
| Sex ($N_{female}$ (%)) | 35 (46) | 8 (40) | $\chi^2(2) = 3.93$ | 3 (30) | 4 (44) | $\chi^2(2) = 1.91$ |
| Age (M; SD) | 52.9; 14.5 | 55.5; 14.9 | $F(1,94) = 0.50$ | 57.8; 17.3 | 52.1; 12.8 | $F(1,17) = 0.66$ |
| IQ (M; SD) | 102.9; 15.5 | 113.6; 13.6 | $F(1,28) = 2.66$ | 106; 8.7 | 117; 17.3 | $F(1,4) = 0.97$ |
| AQ (M; SD) | 13.6; 6.0 | 31.8; 6.6 | $F(1,94) = 138.7$*** | 28.3; 7.7 | 35.3; 2.6 | $F(1,17) = 6.77$* |

*Note.* COMP = comparison, AUT = autism, HighGr = "Feelings of High Grip", LowGr = "Feelings of Low Grip". *** $p < 0.001$. ** $p < 0.01$. * $p < 0.05$.
[a] represents the percentage of people who dropped out within a specific group (i.e., within COMP, AUT, HighGr or LowGr).

### S9.4.2 Profiles of autism and comparison subgroups at two-year follow-up




*sFigure 9.4.1.* Subgroup profiles based on data from the autism and comparison groups for each of the two community detection-based subgroups formed on Sample 1.

*Note.* AUT = autism, COMP = comparison, Edu = education, Soc = social skills, AttS = attention switching, AttD = attention to detail, Com = communication, Imag = imagination, Sens = sensory sensitivity, Mas = mastery, Wor = worry, Sup = emotional support, Phys = physical activity, PAff = positive affect, NAff = negative affect, NLife = negative life events. Higher z-scores represent higher scores on Edu, Soc, AttD, AttS, Com, Imag, Mas, Sup, Phys, PAff. Higher z-scores represent better scores on Sens, Wor, NAff, NLife (less sensitivity, less worrying, less negative affect, fewer negative life events). Shaded area represents 95%-confidence interval.

sTable 9.4.4

*Raw cluster variable scores and descriptives for the Feelings of High Grip and Feelings of Low Grip subgroups formed on Sample 1 (N=65) and Sample 2 (N=231).*

| | Sample 1 (N=65) | | | | Sample 2 (N=231) | | | |
|---|---|---|---|---|---|---|---|---|
| | HighGr (N=30) | LowGr (N=35) | | | HighGr (N=109) | LowGr (N=122) | | |
| | **M (SD); range** | **M (SD); range** | **Test statistic** | **ES ($\eta^2$)** | **M (SD); range** | **M (SD); range** | **Test statistic** | **ES ($\eta^2$)** |
| **Cluster variables** | | | | | | | | |
| Education | 6.0 (0.8); 5-7 | 5.9 (0.7); 5-7 | $F(1,61) = 0.95$ | 0.02 | 6.0 (0.8); 2-7 | 6.0 (0.9); 4-7 | $F(1,229) = <0.1$ | <0.01 |
| Social skills | 5.2 (1.7); 1-9 | 8.5 (1.1); 6-10 | $F(1,63) = 85.6^{***}$ | 0.58 | 5.8 (2.5); 0-10 | 8.6 (1.4); 3-10 | $F(1,229) = 111.8^{***}$ | 0.33 |
| Attention switching | 5.8 (2.2); 2-9 | 8.2 (1.5); 4-10 | $F(1,63) = 26.1^{***}$ | 0.29 | 7.0 (2.0); 1-10 | 8.4 (1.6); 3-10 | $F(1,229) = 35.6^{***}$ | 0.14 |
| Attention to detail | 5.6 (2.5); 2-10 | 5.1 (2.1); 2-10 | $F(1,63) = 1.0$ | 0.02 | 6.4 (2.3); 1-10 | 7.2 (2.1); 2-10 | $F(1,229) = 6.1^{*}$ | 0.03 |
| Communication | 4.6 (2.5); 0-10 | 6.9 (1.9); 3-10 | $F(1,63) = 18.3^{***}$ | 0.22 | 5.4 (2.3); 0-10 | 7.3 (1.9); 2-10 | $F(1,229) = 44.1^{***}$ | 0.16 |
| Imagination | 5.0 (2.0); 1-10 | 6.7 (1.9); 2-9 | $F(1,63) = 12.2^{***}$ | 0.16 | 4.9 (2.0); 0-10 | 6.9 (2.0); 0-10 | $F(1,229) = 57.9^{***}$ | 0.20 |
| Sensory sensitivity | 5.4 (2.9); 0-12 | 5.8 (2.7); 1-10 | $F(1,63) = 3.4$ | 0.01 | 6.7 (2.7); 1-12 | 7.9 (2.3); 1-12 | $F(1,228) = 12.4^{***}$ | 0.05 |
| Mastery | 24.7 (3.6); 19-34 | 19.3 (4.7); 7-31 | $F(1,63) = 26.1^{***}$ | 0.29 | 23.1 (4.1); 11-35 | 17.1 (3.9); 9-28 | $F(1,229) = 133.2^{***}$ | 0.37 |
| Worry | 24.1 (7.8); 15-46 | 29.4 (8.3); 18-53 | $F(1,63) = 7.0^{**}$ | 0.10 | 26.8 (8.6); 15-59 | 38.3 (12.9); 15-72 | $F(1,229) = 61.3^{***}$ | 0.21 |
| Emotional support | 33.8 (9.6); 12-50 | 23.6 (8.7); 12-41 | $F(1, 62) = 20.1^{***}$ | 0.25 | 31.9 (11.6); 12-59 | 24.7 (9.5); 12-48 | $F(1,229) = 26.8^{***}$ | 0.11 |
| Physical activity | 1394.6 (1234.5); 150-5460 | 723.3 (539.0); 0-2390 | $F(1,60) = 8.0^{**}$ | 0.12 | 1167.9 (1700); 0-14680 | 788.5 (833.6); 0-5220 | $F(1,220) = 4.6^{*}$ | 0.02 |



**S9.4.3 Raw cluster variable scores and descriptives for the autism subgroups at follow-up**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Positive affect | 33.7 (7.1); 13-47 | 24.7 (6.5); 14-37 | $F(1,63) = 28.7^{***}$ | 0.31 | 32.4 (6.7); 13-49 | 23.3 (5.9); 12-38 | $F(1,228) = 119.4^{***}$ | 0.34 |
| Negative affect | 17.3 (6.9); 10-39 | 20.7 (7.8); 11-43 | $F(1,63) = 3.3$ | 0.05 | 17.6 (6.4); 10-37 | 25.2 (8.9); 10-49 | $F(1,229) = 53.2^{***}$ | 0.19 |
| Negative life events | 0.6 (0.8); 0-2 | 0.3 (0.4); 0-1 | $F(1,63) = 5.0^{*}$ | 0.07 | 0.7 (1.1); 0-5 | 0.7 (0.9); 0-4 | $F(1,227) = 0.3$ | <0.01 |
| **Descriptive variables** | | | | | | | | |
| Age | 58.5 (11.3); 38-83 | 58.3 (10.3); 37-78 | $F(1,63) = <0.01$ | 0.00 | 52.8 (13.7); 32-80 | 52.4 (11.6); 32-86 | $F(1,228) = <0.1$ | 0.00 |
| Biological sex (% female) | 37% | 46% | $c^2(1) = 0.5$ | | 50% | 55% | $c^2(2) = 1.5$ | |
| IQ score[a] | 120.4 (10.5); 100-133 | 122.9 (12.4); 100-141 | $F(1,24) = 0.29$[a] | 0.01 | 113.3 (15.8); 81-137 | 116.0 (15.0); 79-144 | $F(1,53) = 0.4$[b] | 0.01 |

*Note.* HighGr = Feelings of High Grip, LowGr = Feelings of Low Grip, ES = effect size. *** $p < 0.001$. ** $p < 0.01$. * $p < 0.05$.

[a] Sample size (N=25) is lower for this variable because data are only available for participants who completed the interview.

[b] Sample size (N=54) is lower for this variable because data are only available for participants who completed the interview.

sTable 9.4.5

*Bayes factors per cluster variable that indicate similarity between baseline and follow-up for the total autism group based on Sample 1 (N=80) and Sample 2 (N=241).*

| | **Sample 1 (N=80)** | | | **Sample 2 (N=241)** | | |
|---|---|---|---|---|---|---|
| | Baseline | 5-Year FU | | Baseline | 2-Year FU | |
| **Cluster variables** | **M (SD)** | **M (SD)** | **$BF_{01}$** | **M (SD)** | **M (SD)** | **$BF_{01}$** |
| Education | 5.7 (0.9) | 5.8 (0.9) | 5.0 | 6.0 (0.8) | 6.0 (0.8) | 8.7 |
| Social skills | 7.1 (2.1) | 7.1 (2.1) | 0.1 | 7.6 (2.3) | 7.3 (2.4) | 0.3 |
| Attention switching | 7.9 (1.8) | 7.2 (2.1) | <0.1 | 7.9 (2.0) | 7.8 (1.9) | 4.6 |
| Attention to detail | 6.3 (2.3) | 5.8 (2.4) | 0.4 | 6.8 (2.1) | 6.7 (2.3) | 10.5 |
| Communication | 6.6 (2.3) | 6.1 (2.4) | 0.8 | 6.8 (2.3) | 6.5 (2.3) | 0.3 |
| Imagination | 6.2 (2.2) | 5.8 (2.0) | 0.6 | 6.0 (2.2) | 6.0 (2.3) | 13.6 |
| Sensory sensitivity | 6.2 (2.8) | 6.1 (2.8) | 7.0 | 7.2 (2.6) | 7.3 (2.6) | 9.1 |
| Mastery | 20.4 (4.9) | 21.5 (4.9) | 1.2 | 19.9 (5.3) | 20.0 (5.0) | 13.4 |
| Worry | 30.0 (10.9) | 27.2 (8.6) | 0.1 | 34.2 (11.5) | 32.6 (12.4) | 0.6 |
| Emotional support | 29.9 (10.7) | 29.3 (10.1) | 6.7 | 28.9 (11.1) | 27.9 (11.0) | 2.0 |
| Physical activity | 955.1 (798.1) | 1024.1 (992.2) | 7.2 | 1047.4 (1219.9) | 981.3 (1327.8) | 9.7 |
| Positive affect | 29.1 (7.1) | 29.1 (8.1) | 8.1 | 28.7 (7.2) | 27.7 (7.6) | 1.0 |
| Negative affect | 21.0 (7.7) | 18.9 (7.2) | 0.1 | 22.0 (8.3) | 21.6 (8.5) | 8.9 |
| Negative life events | 0.6 (0.9) | 0.6 (0.8) | 8.1 | 0.7 (1.0) | 0.7 (1.0) | 11.6 |

*Note.* FU = follow-up. $BF_{01}$ = Bayes factor in favor of null hypothesis (i.e., cluster variable scores are similar from baseline to follow-up).



### S9.4.4 Bayesian analysis results for the overall autism group from baseline to follow-up

At two-year follow-up, most cluster variable scores (i.e., 9 out of 14, +/- 64%) were similar ($BFs_{01}$ > 3). Moreover, there was moderate evidence in favor of the alternative hypothesis (i.e., cluster variable scores decreased over time) for social skills, and communication.

At five-year follow-up, scores on half of the cluster variables were similar with $BF_{01}$>3. There was moderate evidence in favor of the alternative hypothesis (i.e., decrease in cluster variable scores at follow-up) for social skills, worries, and negative affect, and strong evidence in favor of H1 for attention switching (i.e., decrease at follow-up).

## S9.4.5 Bayesian analysis results for Sample 2 subgroups: two-year follow-up

sTable 9.4.6
*Bayes factors per cluster variable that indicate similarity between baseline and two-year follow-up for each of the two subgroups identified in Sample 2.*

| | Subgroup | | | |
|---|---|---|---|---|
| | HighGr | | LowGr | |
| **Cluster variable** | **$BF_{01}$** | **Evidence** | **$BF_{01}$** | **Evidence** |
| Education | 5.3 | Moderate H0 | 7.2 | Moderate H0 |
| Social skills | 1.1 | Anecdotal H0 | 7.0 | Moderate H0 |
| Attention switching | 6.6 | Moderate H0 | 2.1 | Anecdotal H0 |
| Attention to detail | 6.6 | Moderate H0 | 2.1 | Anecdotal H0 |
| Communication | 2.1 | Anecdotal H0 | 4.5 | Moderate H0 |
| Imagination | 6.6 | Moderate H0 | 6.7 | Moderate H0 |
| Sensory sensitivity | 6.0 | Moderate H0 | 6.7 | Moderate H0 |
| Mastery | 6.9 | Moderate H0 | 3.8 | Moderate H0 |
| Worry | 1.5 | Anecdotal H0 | 7.2 | Moderate H0 |
| Emotional support | 4.9 | Moderate H0 | 7.2 | Moderate H0 |
| Physical activity | 5.9 | Moderate H0 | 4.4 | Moderate H0 |
| Positive affect | 6.9 | Moderate H0 | 0.7 | Anecdotal H1 |
| Negative affect | 4.6 | Moderate H0 | 7.0 | Moderate H0 |
| Negative life events | 6.1 | Moderate H0 | 6.3 | Moderate H0 |

*Note.* HighGr = Feelings of High Grip, LowGr = Feelings of Low Grip, $BF_{01}$ = Bayes factor in favor of null hypothesis (i.e., cluster variable scores are similar from baseline to follow-up).



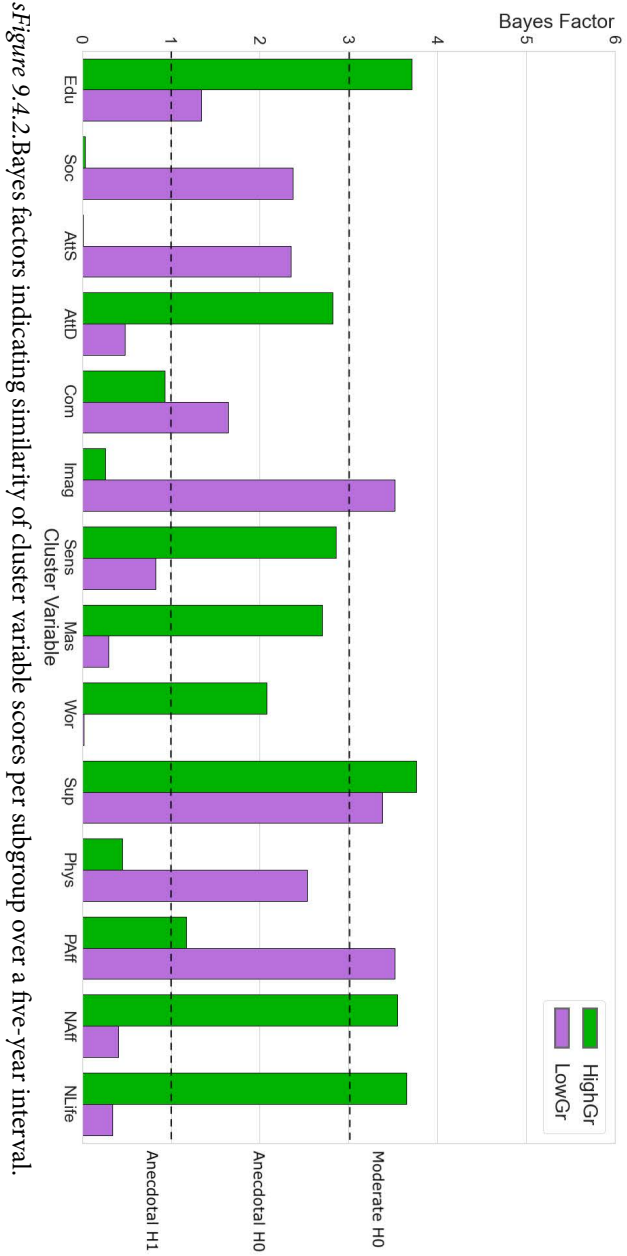


## S9.4.6 Bayesian analysis results for Sample 1 subgroups: five-year follow-up

sTable 9.4.7
*Bayes factors per cluster variable that indicate similarity between baseline and five-year follow-up for each of the two subgroups identified in Sample 1.*

| | Subgroup | | | |
|---|---|---|---|---|
| | HighGr | | LowGr | |
| **Cluster variable** | **$BF_{01}$** | **Evidence** | **$BF_{01}$** | **Evidence** |
| Education | 3.7 | Moderate H0 | 1.3 | Anecdotal H0 |
| Social skills | <0.1 | Moderate H1 | 2.4 | Anecdotal H0 |
| Attention switching | 0.1 | Moderate H1 | 2.3 | Anecdotal H0 |
| Attention to detail | 2.8 | Anecdotal H0 | 0.5 | Anecdotal H1 |
| Communication | 0.9 | Anecdotal H1 | 1.6 | Anecdotal H0 |
| Imagination | 0.3 | Moderate H1 | 3.5 | Moderate H0 |
| Sensory sensitivity | 2.9 | Anecdotal H0 | 0.8 | Anecdotal H1 |
| Mastery | 2.7 | Anecdotal H0 | 0.3 | Moderate H1 |
| Worry | 2.1 | Anecdotal H0 | <0.1 | Moderate H1 |
| Emotional support | 3.8 | Moderate H0 | 3.4 | Moderate H0 |
| Physical activity | 0.5 | Anecdotal H1 | 2.5 | Anecdotal H0 |
| Positive affect | 1.2 | Anecdotal H0 | 3.5 | Moderate H0 |
| Negative affect | 3.5 | Moderate H0 | 0.4 | Anecdotal H0 |
| Negative life events | 3.6 | Moderate H0 | 0.3 | Moderate H1 |

*Note.* HighGr = Feelings of High Grip, LowGr = Feelings of Low Grip, $BF_{01}$ = Bayes factor in favor of null hypothesis (i.e., cluster variable scores are similar from baseline to follow-up).




*sFigure 9.4.2.* Bayes factors indicating similarity of cluster variable scores per subgroup over a five-year interval.

*Note.* Bayes factors under 1 indicate evidence for a difference over time, a value of 1 represents no evidence, and values above 1 indicate evidence for similarity of cluster variable scores over time. HighGr = Feelings of High Grip, LowGr = Feelings of Low Grip, Edu = education, Soc = aocial skills, AttS = attention switching, AttD = attention to detail, Com = communication, Imag = imagination, Sens = sensory sensitivity, Mas = mastery, Wor = worries/fears, Sup = emotional support, Phys = physical activity, PAff = positive affect, NAff= negative affect, NLife = negative life events.





## S9.4.7 Predictive validation results for Sample 1: five-year follow-up

sTable 9.4.8

*Scores for predictive validation (at five-year follow-up) for the HighGr and LowGr subgroups formed at baseline with data from Sample 1.*

| | Subgroup | | | |
|---|---|---|---|---|
| | HighGr | LowGr | | |
| | **M(SD); range** | **M(SD); range** | **Test statistic** | **ES ($\eta^2$)** |
| **Cognitive failures** | | | | |
| Total score | 39.8 (11.9); 12-67 | 50.0 (12.2); 28-69 | $F(1,53) = 9.6^{**}$ | 0.15 |
| **Psychological difficulties** | | | | |
| Total score | 127.1 (30.2); 98-215 | 193.5 (58.); 97-333 | $F(1,53) = 30.2^{***}$ | 0.36 |
| Anxiety | 13.7 (4.5); 10-30 | 20.7 (8.7); 11-42 | $F(1,53) = 15.6^{***}$ | 0.23 |
| Agoraphobia | 8.2 (2.3); 7-15 | 12.0 (5.3); 7-27 | $F(1,53) = 12.9^{***}$ | 0.20 |
| Depression | 24.7 (10.7); 16-66 | 38.0 (14.1); 17-76 | $F(1,53) = 15.9^{***}$ | 0.23 |
| Somatization | 16.0 (3.8); 12-26 | 23.4 (8.5); 12-44 | $F(1,53) = 19.3^{***}$ | 0.27 |
| Cognitive performance deficits | 14.7 (4.0); 9-26 | 22.4 (6.1); 11-37 | $F(1,53) = 31.8^{***}$ | 0.38 |
| Interpersonal sensitivity | 24.7 (7.2); 18-44 | 40.5 (15.7); 18-81 | $F(1,53) = 25.9^{***}$ | 0.33 |
| Hostility | 7.2 (1.2); 6-10 | 10.4 (3.5); 7-20 | $F(1,53) = 23.0^{***}$ | 0.30 |
| Sleep difficulties | 5.7 (2.3); 3-12 | 8.3 (3.4); 4-15 | $F(1,53) = 11.9^{**}$ | 0.18 |
| Rest | 12.2 (3.5); 9-24 | 17.7 (6.9); 9-32 | $F(1,53) = 15.0^{***}$ | 0.22 |
| **Quality of life** | | | | |
| Physical health | 15.2 (2.4); 10-19 | 12.4 (3.0); 6-18 | $F(1,53) = 16.0^{***}$ | 0.23 |
| Psychological | 13.9 (2.2); 9-17 | 10.7 (1.9); 7-14 | $F(1,53) = 31.8^{***}$ | 0.38 |
| Social relationships | 13.6 (3.0); 7-20 | 10.7 (2.8); 7-16 | $F(1,52) = 12.4^{***}$ | 0.19 |
| Environment | 16.4 (1.8); 13-20 | 14.4 (2.3); 10-18 | $F(1,52) = 12.6^{***}$ | 0.20 |

*Note.* HighGr = Feelings of High Grip, LowGr = Feelings of Low Grip, ES = effect size. *** $p < 0.001$. ** $p < 0.01$.

# Chapter 6

**Table of content**



## S9.5.1 Exclusion criteria

The following exclusion criteria were applied to the autism subgroups and non-autistic comparison group: (1) history of neurological disorders (e.g., epilepsy, stroke), (2) an IQ-score below 70 according to the Wechsler Adult Intelligence Scale-III or IV (Wechsler, 1997a, 2003) or Mini Mental State Examination (MMSE; Folstein et al., 1975; R. M. Kok & Verhey, 2002) below 18, (3) current alcohol or drug dependency according to the MINI International Neuropsychiatric Interview (Sheehan et al., 1997). For the autism subgroups, the following additional exclusion criteria were applied: (1) no registered autism diagnosis according to the DSM (American Psychiatric Association, 2013), (2) a score below the cut-off on both the Autism Diagnostic Observation Schedule (-2) (ADOS(-2); Bastiaansen et al., 2011; Bildt et al., 2013; Lord et al., 2012), and the Autism Spectrum Quotient (AQ; Baron-Cohen et al., 2001) < 26.
Four additional exclusion criteria were applied to the non-autistic comparison group: (1) a history of autism or Attention Deficit/Hyperactivity Disorder (AD[H]D); (2) close family members with autism or AD(H)D (i.e., sibling(s), parent(s), child(ren)), (3) AQ-score above 32, (4) ADHD Rating Scale (Kooij et al., 2005) score ≥ 7 for childhood symptoms and/or ≥ 6 for symptoms in adulthood.





## S9.5.2 Overview of included cognitive measures

sTable 9.5.1
*Overview of included cognitive measures*

| Domain | Test | Outcome | Included score (range) | H1 | H2 |
|---|---|---|---|---|---|
| Visual memory | WMS-III[a] | Visual recall I | Immediate recall (0-104) | X | X |
| | | Visual recall II | Delayed recall (0-104) | X | |
| | | Visual recognition | Total correct (0-48) | X | |
| Verbal memory | RAVLT[b] | Verbal recall I | Immediate recall trial 1-5 (0-75) | X | X |
| | | Verbal recall II | Delayed recall (0-15) | X | |
| | | Verbal recognition | Total correct (0-30) | X | |
| Verbal fluency | COWAT[c] | Letter Fluency | Number of correct words | X | X |
| | GIT[d] | Category Fluency | Number of correct words | X | X |
| Processing speed | CRT[e] | Psychomotor speed | Mean response time correct trials | X | X |
| Theory of Mind | Faux-Pas[f] | Theory of Mind | Total score (0-38) | X | |
| Visual working memory | N-back[g] | Working memory | Accuracy ratio (-1.0-1.0) | X | |

*Note.* H1: included to test Hypothesis 1A + 1B. H2: included to test Hypothesis 2A+2B.
[a] Wechsler memory scale III (Wechsler, 1997b).
[b] Rey Auditory Verbal Learning Test (Rey, 1964; Saan & Deelman, 1986)
[c] Controlled oral word association task (Mulder et al., 2006).
[d] Groninger Intelligentie Test-2, subtask naming (Luteijn & Barelds, 2004).
[e] Choice response task, in house development (Lever et al., 2015).
[f] Baron-Cohen et al., 1999; Spek et al., 2010
[g] In house development (Lever et al., 2015).

## S9.5.3 Descriptive statistics and cognitive outcomes of the comparison group

sTable 9.5.2
*Descriptive characteristics and cognitive outcomes in the comparison group and differences with the HighGr and LowGr subgroups*

| | Comparisons (n=254) | HighGr vs. Comparisons | | | LowGr vs. Comparisons | | |
|---|---|---|---|---|---|---|---|
| Sex (M/F, M%) | 148/106 (58.3%) | $\chi^2$=1.34 | | | $\chi^2$=.26 | | |
| Education[a] | 5/161/88 | $\chi^2$=3.42 | | | $\chi^2$=.13 | | |
| | Mean, SD (min-max) | *t*-value | Cohen's *d* | $BF_{10}$ | *t*-value | Cohen's *d* | $BF_{10}$ |
| Age (yrs.) | 50.4,16.7 (21-85) | 0.86 | 0.11 | 0.21 | 0.61 | 0.07 | 0.17 |
| Estimated IQ[b] | 113.0,16.8 (73-155) | **3.14**** | **0.42** | **14.68** | 0.54 | 0.07 | 0.16 |
| | | | | | | | |
| Visual recall I | 87.21,11.6 (54-104) | 1.74 | 0.23 | 0.62 | -0.22 | -0.03 | 0.15 |
| Visual recall II | 74.6, 21.7 (2-103) | -0.04 | -0.01 | 0.15 | -0.24 | -0.03 | 0.15 |
| Visual recognition | 45.0, 2.7 (28-48) | 0.31 | 0.04 | 0.16 | -0.91 | -0.11 | 0.21 |
| Verbal recall I | 48.9, 9.7 (20-71) | -1.80 | -0.28 | 0.69 | -1.94 | -0.26 | 0.86 |
| Verbal recall II | 10.4, 3.0 (2-15) | -0.97 | -0.14 | 0.24 | -1.92 | -0.26 | 0.80 |
| Verbal recognition | 29.1,1.4 (22-30) | -1.03 | -0.21 | 0.25 | -1.81 | -0.30 | 0.67 |
| Theory of Mind | 29.28,5.6 (6-38) | **-2.39*** | **-0.32** | 2.15 | **-3.46**** | **-0.49** | **38.53** |
| Letter Fluency | 41.81,10.7 (19-70) | -0.94 | -0.15 | 0.23 | **-2.72**** | **-0.34** | **4.51** |
| Category Fluency | 45.7, 9.6 (26-76) | -0.78 | -0.12 | 0.20 | **-2.93**** | **-0.38** | **7.91** |
| Working memory | 0.9, 0.1 (0.7-1.1) | 0.62 | 0.09 | 0.18 | -1.94 | -0.26 | 0.83 |
| Processing speed | 398.4,61.5 (274-651) | **2.21*** | **0.32** | 1.48 | **2.02*** | **0.27** | 0.97 |

*Note.* M, male; F, female; yrs., years; $BF_{10}$, Bayes Factor evidence for H1 (group difference); **=*p*<.01; *=*p*<.05.
[a] Level of education was determined by the Verhage coding system (Verhage, 1964), between slashes: junior secondary or practical education / senior secondary education or vocational college / university degree.
[b] IQ was estimated at baseline by using two subtests (matrix reasoning and vocabulary) of the Wechsler Intelligence Scale-III or IV (WAIS-III, WAIS-IV; Wechsler, 1997a, 2003).





## S9.5.4 Detailed statistics of regression models containing age, subgroup and their interaction

sTable 9.5.3
*Statistical details of the regression models containing age, subgroup, and their interaction.*

| | | **VisI** | **VerbI** | **LeFl** | **CaFl** | **ProSp** |
|---|---|---|---|---|---|---|
| | Adj. $R^2$ | .07 | .13 | .03 | .04 | .22 |
| | AIC | 1133 | 1081 | 1105 | 1059 | 1541 |
| | BIC | 1148 | 1096 | 1119 | 1074 | 1556 |
| Age | *t* | **-2.80** | **-4.46** | -0.66 | -1.72 | **6.13** |
| | *Beta* | **-0.21** | **-0.28** | -0.05 | -0.10 | **2.14** |
| | *p* | **.01** | **<.01** | .51 | .09 | **<.01** |
| Subgroup | *t* | -0.48 | -0.13 | -2.02 | -1.09 | 0.36 |
| | *Beta* | -3.78 | -0.89 | -14.97 | -7.08 | 13.51 |
| | *p* | .64 | .89 | .05 | .28 | .72 |
| Age x subgroup | *t* | 0.08 | 0.13 | 1.81 | 0.71 | -0.44 |
| | *Beta* | 0.01 | 0.02 | 0.25 | 0.09 | -0.31 |
| | *p* | .94 | .89 | .07 | .48 | .66 |

*Note.* Adj., adjusted; VisI, visual recall I; VerbI, verbal recall I; LeFl, letter fluency; CaFl, category fluency; ProSp, processing speed/ Values in **bold** are significant (uncorrected *p*-value <.05).

### S9.5.5 Detailed statistics of the longitudinal sample, and multilevel regression models containing interval, subgroup, and their interaction

sTable 9.5.4

*Descriptive characteristics of the longitudinal sample in Cohort 1 and Cohort 2.*

| **Cohort 1 (n=40)** | HighGr (n=25) | LowGr (n=15) | | | |
|---|---|---|---|---|---|
| Sex (M/F, M%) | 18/7, 72% | 11/4 (73.3%) | $\chi^2$<.01 | | |
| Education[a] | 2/15/8 | 0/12/3 | $\chi^2$=2.25 | | |
| | Mean, SD (min-max) | Mean, SD (min-max) | *t*-value | Cohen's *d* | $BF_{10}$ |
| Age (yrs.) | 49.7,14.2(24-70) | 46.9,13.1(30-71) | -0.63 | -0.20 | 0.37 |
| Time T1-T2 (yrs.) | 5.9, 0.7 (5-7) | 6.2,0.6 (5-7) | 1.60 | 0.51 | 0.85 |
| Estimated IQ[b] | 119.7, 18.7 (90-153) | 110, 12.6 (90-139) | -1.95 | -0.58 | 1.37 |
| **Cohort 2 (n=63)** | HighGr (n=23) | LowGr (n=40) | | | |
| Sex (M/F, M%) | 15/8, 65% | 24/16, 60% | $\chi^2$=0.02 | | |
| Education[a] | 1/13/9 | 1/22/17 | $\chi^2$=0.20 | | |
| | Mean, SD (min-max) | Mean, SD (min-max) | *t*-value | Cohen's *d* | $BF_{10}$ |
| Age (yrs.) | 57.3,15.1 (32-79) | 52.99,13.7 (31-79) | -1.13 | -0.30 | 0.5 |
| Time T1-T2 (yrs.) | 2.0, 0.2 (1.6-2.5) | 1.9,0.2 (1.6-2.7) | -0.45 | -0.12 | 0.3 |
| Estimated IQ[b] | 121.1, 11.9 (85-137) | 113.2, 15.6 (85-147) | **-2.26*** | **-0.55** | 2.2 |

*Note.* M, male; F, female; yrs., years; $BF_{10}$, Bayes Factor evidence for H1 (group difference); **=*p*<.01; *=*p*<.05.

[a] Level of education was determined by the Verhage coding system, between slashes: junior secondary or practical education / senior secondary education or vocational college / university degree.

[b] IQ was estimated at baseline by using two subtests (matrix reasoning and vocabulary) of the Wechsler Intelligence Scale-III or IV (WAIS-III, WAIS-IV).

sTable 9.5.5

*Statistical details of the multilevel regression models containing interval, subgroup, and their interaction by cohort.*

| | | **Cohort 1** | | | | | **Cohort 2** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | **VisI** | **VerbI** | **LeFl** | **CaFl** | **ProSp** | **VisI** | **VerbI** | **LeFl** | **CaFl** | **ProSp** |
| | Adj. $R^2$ | .01 | .01 | <.01 | .03 | .04 | <.01 | .03 | <.01 | .01 | .08 |
| | AIC | 619 | 574 | 580 | 600 | 834 | 955 | 925 | 914 | 854 | 1362 |
| | BIC | 636 | 591 | 597 | 617 | 850 | 975 | 945 | 934 | 873 | 1382 |
| Interval | *t* | -1.09 | -1.35 | -0.95 | -1.78 | **3.27** | -0.03 | **2.88** | 1.01 | 1.86 | **4.73** |
| | *Beta* | -0.41 | -0.25 | -0.16 | -0.45 | **4.38** | -0.02 | **1.71** | 0.52 | 0.77 | **18.75** |
| | *p* | .28 | .19 | .35 | .08 | **<.01** | .98 | **.01** | .32 | .07 | **<.01** |
| Subgroup | *t* | -0.12 | -0.16 | 0.36 | -1.05 | -0.33 | -0.66 | 1.35 | -0.09 | -0.02 | -0.45 |
| | *Beta* | -0.39 | -0.55 | 1.51 | -3.91 | -6.77 | -2.17 | 3.68 | -0.26 | -0.04 | -7.58 |
| | *p* | .91 | .88 | .72 | .30 | .74 | .51 | .18 | .93 | .98 | .65 |
| Interval x subgroup | *t* | 0.12 | 0.83 | -1.58 | 0.89 | -0.27 | 0.97 | -1.34 | 0.76 | -0.23 | -0.85 |
| | *Beta* | 0.09 | 0.30 | -0.52 | 0.45 | -0.73 | 1.27 | -1.59 | 0.78 | -0.20 | -6.78 |
| | *p* | .91 | .41 | .12 | .38 | .79 | .34 | .19 | .45 | .82 | .40 |

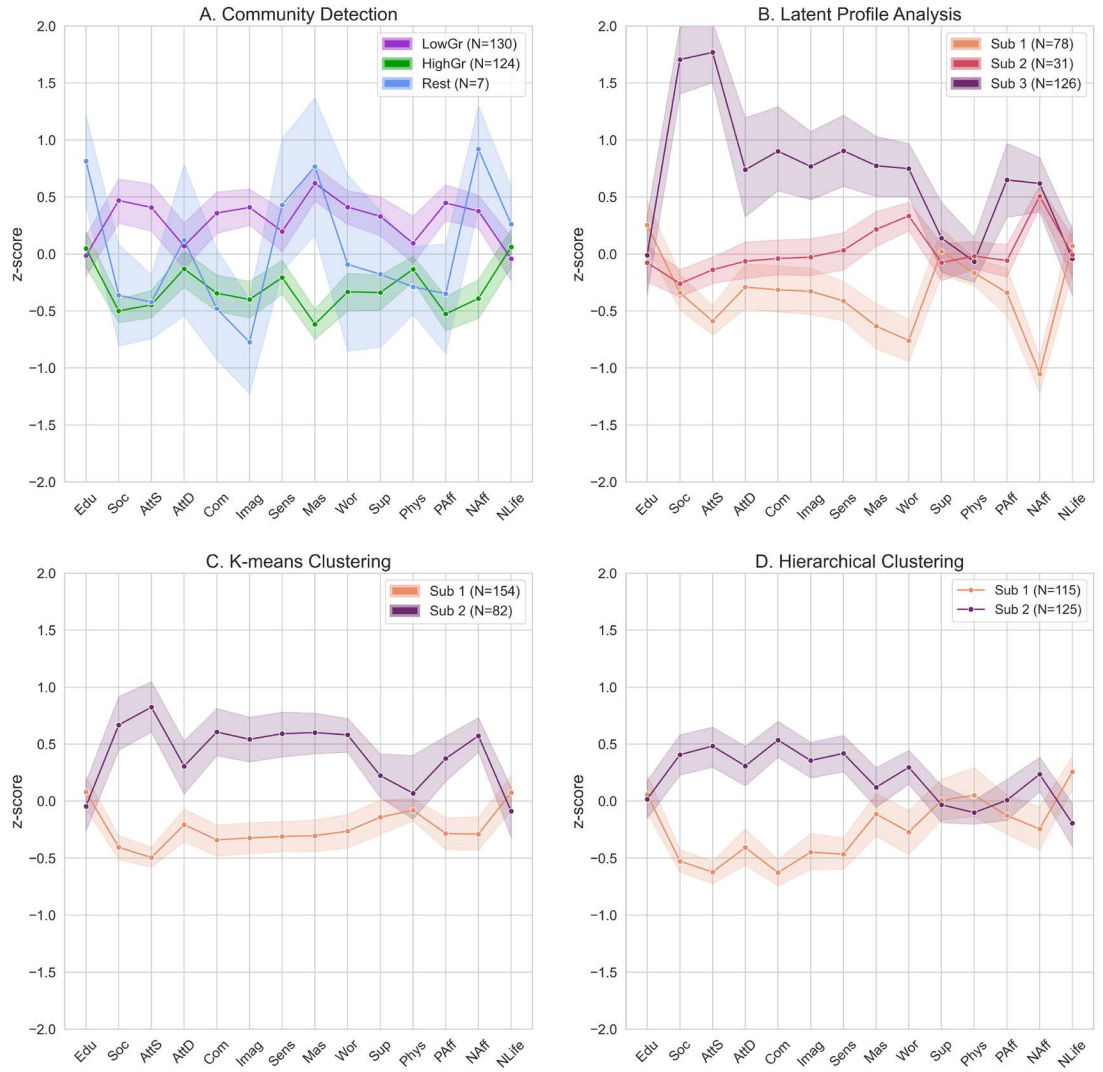
*Note.* Adj., adjusted; VisI, visual recall I; VerbI, verbal recall I; LeFl, letter fluency; CaFl, category fluency; ProSp, processing speed. Values in **bold** are significant (uncorrected *p*-value <.05).





# Additional supplementary materials

### S9.6.1 Cross-method replication results




*sFigure 9.6.1.* A. Subgroup profiles identified using community detection analysis. B. Subgroup profiles identified using Latent Profile Analysis. C. Subgroup profiles identified using K-means clustering. D. Subgroup profiles identified using Hierarchical Clustering.

*Note.* LowGr = Feelings of Low Grip, HighGr = Feelings of High Grip, Sub = subgroup, Edu = education, Soc = aocial skills, AttS = attention switching, AttD = attention to detail, Com = communication, Imag = imagination, Sens = sensory sensitivity, Mas = mastery, Wor = worries/fears, Sup = emotional support, Phys = physical activity, PAff = positive affect, NAff= negative affect, NLife = negative life events.



# Chapter 10

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# Chapter 11

## Article information and short CV

### Chapter 2

Radhoe, T. A., Agelink van Rentergem, J. A., Kok, A. L., Huisman, M., & Geurts, H. M. (2021). Subgroups in late adulthood are associated with cognition and wellbeing later in life. *Frontiers in Psychology*, 12, 780575. doi:10.3389/fpsyg.2021.780575

Author contributions

| | TAR | JAAR | AALK | MH | HMG |
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| Funding current study | | | | | |
| Study design LASA | | | | | |
| Statistical analysis plan | | | | | |
| Feedback on analysis plan | | | | | |
| First draft of the manuscript | | | | | |
| Feedback on subsequent versions of manuscript | | | | | |
| Final approval of the manuscript | | | | | |





### Chapter 3

Radhoe, T.A., Agelink van Rentergem, J.A., Torenvliet, C., Groenman, A.P., van der Putten, W.J., & Geurts, H.M. (2023). Finding similarities in differences between autistic adults: Two replicated subgroups. Journal of Autism and Developmental Disorders. doi: 10.1007/s10803-023-06042-2

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| | TAR | JAAR | CT | APG | WvdP | HMG |
|---|---|---|---|---|---|---|
| Funding current study | | | | | | |
| Study design | | | | | | |
| Pre-registration of analyses | | | | | | |
| Data collection | | | | | | |
| Statistical analyses | | | | | | |
| First drafts of the manuscript | | | | | | |
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|---|---|
| OSF project: | https://osf.io/5uyzd/ |
| R-code: | https://osf.io/bp2ak |
| Anonymized data: | https://uvaauas.figshare.com/articles/dataset/A_community_detection_study_Two_replicated_distinct_subgroups_in_autistic_adults/21333633 |

**Chapter 4**

Radhoe, T.A., Agelink van Rentergem, J.A., Torenvliet, C., Groenman, A.P., van der Putten, W.J., & Geurts, H.M. (2022). *Network structure differences between subgroups of autistic adults* [Manuscript accepted for publication at Autism]. Preprint doi: 10.31234/osf.io/zdg56

Author contributions

| | TAR | JAAR | CT | APG | WvdP | HMG |
|---|---|---|---|---|---|---|
| Funding current study | | | | | | |
| Study design | | | | | | |
| Pre-registration of analyses | | | | | | |
| Data collection | | | | | | |
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| OSF project: | https://osf.io/m9gjp/ |
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**Chapter 5**

Radhoe, T.A., Agelink van Rentergem, J.A., Torenvliet, C., Groenman, A.P., van der Putten, W.J., & Geurts, H.M. (2022). *The clinical relevance of subgroups of autistic adults: Stability and predictive value* [Manuscript under review at Autism Research]. Preprint doi: 10.31234/osf.io/ycp6q

Author contributions

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|---|---|---|---|---|---|---|
| Funding current study | | | | | | |
| Study design | | | | | | |
| Pre-registration of analyses | | | | | | |
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| First drafts of the manuscript | | | | | | |
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|---|---|
| OSF project: | https://osf.io/rba2e/ |

**Chapter 6**

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Author contributions

| | TAR | CT | JAAR | APG | HMG |
|---|---|---|---|---|---|
| Funding current study | | | | | |
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| Pre-registration of analyses | | | | | |
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# Chapter 13
## Nederlandse samenvatting

Autisme is een conditie waarbij de neurobiologische ontwikkeling anders verloopt. Ongeveer 1% van de wereldbevolking is autistisch. De diagnose “autismespectrumstoornis” wordt gesteld op basis van verschillende gedragskenmerken, volgens de Diagnostic and Statistical Manual of Mental Disorders (DSM, 5e editie), het handboek voor classificatie van psychische stoornissen. Volgens de DSM-5 hebben autistische mensen bepaalde overeenkomsten. Ze hebben vaak moeite met sociale communicatie of interactie, zoals het lastig vinden om een gesprek met iemand gaande te houden. Volgens de DSM-5 wordt autisme daarnaast gekenmerkt door herhalende gedragspatronen en beperkte interesses of activiteiten. Voorbeelden hiervan zijn extreme spanning ervaren bij veranderingen in gemaakte afspraken, of moeite hebben met overgangssituaties (zoals bij het wisselen van baan).

Naast deze overeenkomsten zijn er veel verschillen tussen autistische mensen in hun autismekenmerken, maar ook in hun sterke punten en ervaren moeilijkheden in het leven. Zo kan het zijn dat één autistisch persoon een sterke voorkeur heeft om informatie te verzamelen over een specifiek onderwerp en hier veel tijd aan kan besteden. Een ander autistisch persoon herkent dit mogelijk helemaal niet, maar vindt het juist lastig om over-en-weer gesprekken met iemand anders aan te gaan. Deze individuele verschillen binnen het autismespectrum worden ook wel aangeduid met de term heterogeniteit. Heterogeniteit betekent het samengesteld zijn uit ongelijksoortige onderdelen. Binnen de psychologie wordt hiermee bedoeld dat verschillende mechanismen onderliggend kunnen zijn aan eenzelfde classificatie (zoals autisme) bij verschillende subgroepen van mensen. Deze heterogeniteit binnen het autismespectrum zorgt ervoor dat het moeilijk is om te bepalen bij wat voor soort hulp of ondersteuning één autistisch persoon baat zou kunnen hebben.

Ondanks dat mensen het grootste deel van hun leven doorbrengen als volwassene, is onze kennis over autisme vooral beperkt tot de kindertijd. Dit is problematisch, omdat autisme een levenslange conditie is. Daarnaast heeft onderzoek aangetoond dat autistische mensen een lagere kwaliteit van leven en meer psychiatrische problemen hebben (zoals depressie, angsten en suïcidepogingen) dan de algemene bevolking. Naast de beperkte kennis over autisme in de volwassenheid is er nog minder bekend over het verouderingsproces van autistische volwassenen. Het onderzoek tot nu toe dat autistische mensen gevolgd heeft gedurende hun levensloop laat zien dat er veel verschillen zijn in uitkomsten wat betreft leefomstandigheden, werk, en medische en psychische

problematiek. Deze grote individuele verschillen zorgen ervoor dat het lastig is om prognoses te formuleren. Hierdoor leven veel autistische volwassenen in onzekerheid over wat ze kunnen verwachten naarmate ze ouder worden.

Een oplossing om meer inzicht te krijgen in deze heterogeniteit is het zoeken naar subgroepen binnen het autismespectrum. Een subgroep is een kleinere groep —in dit geval bestaande uit mensen— binnen een grotere groep, waarvan de leden een bepaalde specifieke overeenkomst hebben. Mensen binnen één subgroep hebben dus meer met elkaar gemeen dan met mensen buiten deze subgroep. Er zijn al veel studies geweest naar subgroepen binnen autisme. Veel van deze studies hebben zich gericht op biologische informatie van autistische kinderen en hadden een relatief kleine groep deelnemers. Deze eerdere studies kunnen op de lange termijn informatief zijn voor de klinische praktijk, omdat ze mogelijk informatie kunnen bieden over de oorzaken van autisme. Helaas is er nog geen onderzoek gedaan naar klinische voorspellingen in de volwassenheid. De studies tot nu toe onderzochten mensen maar één keer in hun leven. Om ervoor te zorgen dat onderzoek relevant is voor de klinische praktijk op de korte termijn, is het belangrijk om ook te kijken naar eigen ervaringen van autistische mensen, en om het verouderingsproces in kaart te brengen door meerdere metingen bij dezelfde mensen. Er is dus een duidelijke behoefte aan beter inzicht in de heterogeniteit binnen het autismespectrum, om daarmee meer informatie te bieden over de ontwikkeling binnen de volwassenheid. Zowel heterogeniteit als veroudering zijn de centrale thema's van dit proefschrift.

**Subgroepen bij reguliere veroudering**

In **Hoofdstuk 2** hebben we eerst onderzocht of we subgroepen konden onderscheiden bij de algemene bevolking. We onderzochten of de analysetechniek (genaamd community detection) die we wilden gebruiken voor de heterogeniteit binnen autisme, geschikt was voor subgroepenonderzoek door deze eerst te testen bij de algemene bevolking. Deze community detection analyse is uitgevoerd op een grote groep deelnemers van 61 tot 101 jaar oud. De data voor dit onderzoek was afkomstig van de Longitudinal Aging study Amsterdam (LASA). Data van twee meetmomenten is geanalyseerd (NT1=1478 en NT2=1186), waarbij er drie jaar tussen de twee metingen zat. Om de subgroepen te onderzoeken is er gekeken naar zeven bronnen van informatie, ook wel inputvariabelen genoemd: beschermende en kwetsbare factoren voor veroudering, zoals alcoholgebruik en fysieke activiteit. Uit de community detection analyse kwamen drie subgroepen naar voren die van elkaar verschilden op de inputvariabelen. Ook verschilden zij van elkaar op externe variabelen die relevant zijn bij het ouder worden, namelijk welzijn en subjectieve cognitieve achteruitgang. Met de data van drie jaar later, hebben we opnieuw dezelfde subgroepen gevonden. Minstens 47% van de volwassenen bleef in dezelfde subgroep na drie jaar. Deze studie laat zien dat we subgroepen





kunnen onderscheiden binnen de algemene bevolking die van elkaar verschillen op verschillende factoren die belangrijk zijn bij het ouder worden.

**Subgroepen bij autistische en niet-autistische volwassenen**

In **Hoofdstuk 3** is aangetoond dat dezelfde analysetechniek ook nuttig is om de heterogeniteit bij autisme in kaart te brengen. Voor deze studie is een nieuwe dataset verzameld van autistische volwassenen (N=375), niet-autistische volwassenen (N=345) en volwassenen met ADHD (N=123) met een leeftijd van 30 tot 89 jaar. We hebben deze dataset in twee aparte delen verdeeld (originele data en replicatiedata), zodat onderzocht kon worden of beide kleinere datasets tot dezelfde resultaten zouden leiden. Voor de community detection analyse zijn 14 inputvariabelen gebruikt afkomstig uit demografische, psychologische en levensstijlvragenlijsten. De resultaten toonden aan dat autistische en non-autistische volwassenen aparte subgroepen vormden. Wanneer volwassenen met ADHD werden toegevoegd aan de analyse, zagen we dat de ADHD-groep bijna gelijk was verdeeld over de twee eerder gevonden subgroepen. Enkel binnen de autismegroep waren drie autismesubgroepen gevonden, waarvan er twee ook werden gevonden in de replicatiedataset. Deze twee subgroepen zijn "Gevoelens van meer grip op het leven" (MeerGr) en "Gevoelens van minder grip op het leven" (MinderGr) genoemd. Autistische volwassenen in de MinderGr subgroep rapporteerden meer moeilijkheden in het dagelijkse leven vergeleken met de MeerGr subgroep. Deze verschillen werden ook teruggevonden op externe klinische maten. De MinderGr subgroep had namelijk een lagere kwaliteit van leven, maar ook meer psychische en cognitieve problemen dan de MeerGr subgroep. Deze studie laat zien dat we ook subgroepen kunnen onderscheiden binnen de groep mensen met een autismediagnose die van elkaar verschillen op verschillende factoren die belangrijk zijn bij het ouder worden.

**Verschillen in netwerkstructuur**

In Hoofdstuk 3 was aangetoond dat er grote verschillen zijn tussen autistische en niet-autistische volwassenen, maar ook tussen autistische volwassenen onderling, in hun score op demografische, psychologische en levensstijlvariabelen. Het doel van **Hoofdstuk 4** was om te onderzoeken of deze verschillen ook teruggezien werden in de onderliggende relatie tussen deze variabelen, ook wel de netwerkstructuur genoemd. Op deze manier werd geprobeerd inzicht te krijgen in welke variabelen (en relaties tussen de variabelen) belangrijk zijn voor autistische en niet-autistische volwassenen door middel van netwerkanalyses. Verschillen in netwerkstructuur zijn onderzocht tussen (a) autistische en niet-autistische volwassenen, en (b) de twee autismesubgroepen uit Hoofdstuk 3. De resultaten toonden aan dat er verschillen waren in de netwerken tussen autistische en niet-autistische volwassenen op basis van visuele inspectie en

vergelijking van individuele relaties tussen variabelen. De netwerken van de autisme-subgroepen vertoonden geen verschillen op basis van visuele inspectie en statistische vergelijkingen. Deze studie laat zien dat de netwerken van de autisme subgroepen meer overeenkomsten hebben dan verschillen, hoewel er enkele verschillen in individuele relaties tussen de variabelen zijn gevonden die mogelijk informatief kunnen zijn voor het bieden van gerichte ondersteuning aan autistische volwassenen. Op basis van deze studie concludeerden wij dat de verschillen in scores op de demografische, psychologische en levensstijl variabelen gevonden in Hoofdstuk 3, niet overeenkomen met verschillen in de onderliggende netwerkstructuur tussen deze variabelen. Om te bepalen welke variabelen (en relaties tussen variabelen) het meest belangrijk zijn voor autistische volwassenen, is het dus niet voldoende om enkel naar de scores op de vragenlijsten te kijken.

**Stabiliteit van subgroepen over de tijd**

**Hoofdstuk 5** was een longitudinaal vervolg —oftewel, met meerdere metingen van dezelfde personen over de tijd— van het onderzoek beschreven in Hoofdstuk 3. Het doel was om te onderzoeken of de eerder gevonden autisme subgroepen (MeerGr en MinderGr) stabiel zijn naarmate mensen ouder worden, en of ze voorspellende waarde hebben voor klinische uitkomsten in de toekomst, namelijk kwaliteit van leven, en psychische en cognitieve problemen. Hiervoor was de community detection analyse herhaald in twee aparte datasets: Dataset 1 (N=80 autistische volwassenen) was vijf jaar na de eerste meting opnieuw gemeten, en Dataset 2 (N=241 autistisch en N=211 niet-autistisch) was twee jaar na de eerste meting opnieuw gemeten. Als inputvariabelen waren dezelfde demografische, psychologische en levensstijlvariabelen meegenomen als in Hoofdstuk 3. De stabiliteit van de subgroepen was op drie manieren onderzocht: (1) het aantal subgroepen bij de eerste meting en de vervolgmeting, (b) de profielen van de subgroepen op de inputvariabelen, en (c) in hoeverre mensen in dezelfde subgroep bleven naarmate zij ouder werden. Voor de klinische voorspelling was onderzocht of de subgroepen van de eerste meting voorspellende waarde hadden voor de scores op de vervolgmeting wat betreft kwaliteit van leven, psychische en cognitieve problemen. De resultaten toonden aan dat autistische en niet-autistische volwassenen opnieuw aparte subgroepen vormden. Binnen beide autisme groepen (uit Dataset 1 en 2) werden de MeerGr en MinderGr subgroepen na twee jaar en na vijf jaar opnieuw gevonden. De profielen van de subgroepen op de input variabelen waren gelijk gebleven voor minstens 50% van de inputvariabelen na twee jaar, en voor 21% na vijf jaar. Twee jaar na de eerste meting zat 80% van de autistische volwassen nog in dezelfde autismesubgroep, en na vijf jaar was dit 64%. De subgroepen bleken voorspellende waarde hebben voor klinische uitkomsten na zowel twee als na vijf jaar: door te weten in welke subgroep iemand bij de eerste meting zat, waren diens scores op kwaliteit van leven, psychische en cognitieve problemen te voorspellen tot vijf jaar in de toekomst. Deze





studie laat zien dat de autisme subgroepen stabiel zijn naarmate men ouder wordt, en dat ze informatief zijn voor de klinische praktijk omdat ze nuttig blijken voor klinische voorspellingen tot vijf jaar in de toekomst. Hoewel de meerderheid van de autistische volwassenen in dezelfde subgroep zat bij de vervolgmetingen, bleek het ook mogelijk om te wisselen van subgroep. Het wisselen naar een andere subgroep —met een meer positieve uitkomst— is dus mogelijk en dat is goed nieuws, omdat dit mogelijkheden biedt voor verandering.

**Verschillen tussen subgroepen op cognitieve tests**

In de eerdere hoofdstukken (Hoofdstuk 3 en 5) was aangetoond dat de autisme subgroepen verschilden op allerlei variabelen, waaronder zelfgerapporteerde (of ervaren) cognitieve problemen. In **Hoofstuk 6** is onderzocht of deze ervaren verschillen ook gevonden zouden worden in daadwerkelijke cognitieve problemen, gemeten met psychologische tests. Er is op drie manieren naar deze verschillen tussen de MeerGr (N=65) en MinderGr (N=78) subgroepen gekeken, namelijk: (1) cognitieve tests, (2) cognitieve profielen (een afwijkend of niet-afwijkend cognitief profiel), en (3) leeftijdsgerelateerde cognitieve effecten. Daarnaast is gekeken of de subgroepen verschilden van een groep niet-autistische volwassenen (N=254). Voor deze studie zijn 11 cognitieve tests gebruikt die de volgende domeinen omvatten: visueel en verbaal geheugen, fluency, verwerkingssnelheid, Theory of Mind, en visueel werkgeheugen. Resultaten toonden aan dat de subgroepen niet verschilden op individuele cognitieve tests, cognitieve profielen en leeftijdsgerelateerde cognitieve effecten. De subgroepen scoorden ook niet verschillend van elkaar wanneer ze werden vergeleken met een groep niet-autistische volwassenen. Uit deze studie blijkt dat de zelfgerapporteerde verschillen in cognitieve problemen, niet terug werden gevonden op daadwerkelijke cognitieve tests. Dit betekent ook dat de MinderGr subgroep —die meer kwetsbaar lijkt te zijn voor zelfgerapporteerde problemen in het dagelijks leven— niet extra vatbaar lijkt voor objectieve cognitieve problemen en versnelde cognitieve veroudering.

**Conclusie**

Dit proefschrift verbreedt onze kennis over heterogeniteit en autisme op verschillende manieren. Voor reguliere veroudering blijken subgroepen een effectieve manier te zijn om de individuele verschillen tussen mensen beter te omschrijven. Bovendien is er meer inzicht verkregen in de heterogeniteit bij autisme in de volwassenheid door de identificatie van twee subgroepen: “Meer grip op het leven” en “Minder grip op het leven”. Deze subgroepen verschilden van elkaar in moeilijkheden in het dagelijks leven, maar ook op externe klinische uitkomsten (kwaliteit van leven, psychische en cognitieve klachten). Gedurende het ouder worden blijven deze subgroepen stabiel. Daarnaast zijn ze voorspellend voor klinische uitkomsten tot vijf jaar in de toekomst.

Ondanks dat de meeste autistische volwassenen in dezelfde subgroep blijven naarmate ze ouder worden, is het ook mogelijk om te wisselen van subgroep, bijvoorbeeld naar een subgroep met een meer positieve uitkomst. Hierdoor sluiten de resultaten uit dit proefschrift op belangrijke wijze aan op de klinische praktijk. De resultaten impliceren namelijk dat het verstandig is om verschillende factoren in acht te nemen wanneer we het klinische profiel van een autistische volwassene willen begrijpen, in plaats van enkel te focussen op autismekenmerken. Dit is ook in overeenstemming met de klinische richtlijnen voor autistische volwassenen. Daarnaast laat dit proefschrift zien welke variabelen, naast autismekenmerken, belangrijk kunnen zijn bij het onderscheiden van de subgroepen, waaronder zelfregie, zorgen, emotionele steun en affect. Deze factoren kunnen in verschillende mate beïnvloed worden d.m.v. interventie, en zijn hierom mogelijk belangrijke targets voor interventie in de klinische praktijk. Tot slot worden er verschillende suggesties gedaan voor verder onderzoek met als doel om gezamenlijk met autistische volwassenen te werken aan het verminderen van hun moeilijkheden en het verbeteren van hun levens.





# Chapter 14

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