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Screening for autism in adulthood – Exploratory data analysis for psychopathological self-assessment of 1382 individuals of a clinical population

Screening bei Autismus im Erwachsenenalter – Eine explorative Datenanalyse zur psychopathologischen Selbstbeurteilung von 1382 Individuen der Inanspruchnahme-Population einer Spezialambulanz für Autismus im Erwachsenenalter

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Abbreviations

ADHD = Attention deficit/ hyperactivity disorder

ADI-R = Autism Diagnostic Instrument-Revised

ADOS = Autism Diagnostic Observation Schedule

AS = Asperger-syndrome

ASD = Autism spectrum disorders

ASD+ = Patients in this study with an autism spectrum disorder.

ASD- = Patients in this study, where a diagnosis of an autism spectrum disorder was ruled out, representing the clinical control-group.

ANOVA = Analysis of variance

APA = American Psychiatric Association

AQ = Autism-Spectrum Quotient, all versions

AQ-10 = Autism-Spectrum Quotient, short version self-assessment questionnaire by Allison et al. (2012) consisting of 10 items (2 most discriminating items of each subscale) of the AQ-50 by Baron-Cohen et al. (2001).

AQ-50 = Autism-Spectrum Quotient, full length self-assessment questionnaire by Baron-Cohen et al. (2001) consisting of 50 items.

AUC = Area under the curve

BDI = Beck depression inventory

CBT = Cognitive behavioural therapy

DI = Discrimination index

DGfS = Deutsche Gesellschaft für Sexualforschung

DGPPN = Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde

DSM = Diagnostic and Statistical Manual of Mental Disorders

DSM-IV = The 4th version of the Diagnostic and Statistical Manual of Mental Disorders

DSM-5 = The 5th version of the Diagnostic and Statistical Manual of Mental Disorder

FSIQ = Full-scale intelligence quotient

GDG = Guideline development group

ICD = International Statistical Classification of Diseases and Related Health Problems

ICD-10 = The 10th version of the International Statistical Classification of Diseases and Related Health Problems

ICD-11 = The 11th version of the International Statistical Classification of Diseases and Related Health Problems

IDAS = Inventory of Depression and Anxiety Symptoms

IQ = Intelligence quotient

IMSB = Institut für Medizinische Statistik und Bioinformatik der Universität zu Köln

HFA = High-functioning autism

MBT = Mentalization-based treatment

n/ N = Size of a group (*n*) or the sample (*N)*

NICE = National Institute for Health and Care Excellence

NPT = Neuropsychological-testing

OCD = Obsessive-compulsive disorder

p = *p*-value

PD = Personality disorder

PDD-NOS = Pervasive developmental disorders, not otherwise specified

PHQ-9 = Patient Health Questionnaire

PIQ = Performance intelligence quotient

r = correlation coefficient

R^2 = coefficient of determination

ROC = Receiver operating characteristic

S.D. = Standard deviation

Sig. = Significance

SP = Social phobia

SPCD = Social (pragmatic) communication disorder (DSM-5: 315.39)

SPSS = Statistical Product and Service Solution

SSRI = Serotonin reuptake inhibitor

t = Test statistic for Student's *t*-test

UK = United Kingdom

US = United Sates

VIQ = Verbal intelligence quotient

Vs. = Versus

WAIS-III = Wechsler-Adult-Intelligence-Scale-III

WIE = Wechsler Intelligenztest für Erwachsene

1. Summary

1.1 English Summary

The aim of this study is to gain new insights into psychopathological self-assessment and hypotheses for improving the screening of autism based on the largest clinical sample of an outpatient clinic for adults with late diagnosed autism spectrum disorder (ASD) to date. This retrospective and exploratory data analysis focuses on the two most widespread self-assessment questionnaires for screening ASD in adulthood, the Autism-Spectrum Quotient (AQ-50) and its short version the AQ-10.[1] Although these screening instruments are widely used, they have hardly been examined for „clinically relevant questions of validity in relation to a clinical population", as stated in the S-3 guideline on the diagnostics of ASD of the German Association for Psychiatry and Psychotherapy ("Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde", DGPPN).[2] To date, both versions have been validated mainly on the basis of a control group with healthy individuals from the general population, which probably led to an overestimation of the specificity of these questionnaires for clinical screening.[2] Specificities in previous studies varied significantly from the selection of the control group, since individuals in a clinical control group presumably show more often symptoms similar to an ASD than those from a healthy control group.[3] In studies with healthy adults in the control group, specificity of the AQ-50 ranged from 0.80 - 0.92, whereas specificity in studies with clinical control groups ranged from 0.20 - 0.52.[2,3,4] Since sensitivity is constant and sufficiently high (0.88 - 0.95) at the cut-off of 26, independent of the population used, the AQ-50 is still in use for screening.[3,5,6,7] Thus, the authors of the above-mentioned S-3 guideline evaluate the informative value of the AQ-50 (and AQ-10) as being limited if the score is above the cut-off of 26.[2] In order to objectify this evaluation and subsequently generate hypotheses for an improvement of clinical screening, 1382 individuals of a clinical population of the Autism Outpatient Clinic for Adults of the University Hospital in Cologne were included in the present study. Only adults suspected of having an ASD (for example, suggested by a resident psychiatrist) and with a score above the cut-off of ≥26 in the AQ-50 were invited to the diagnostic process at the Autism Outpatient Clinic.[2,7] Furthermore, only individuals who completed the AQ-50 without any missing items were included in this study, due to item analysis that was conducted subsequently. After a complex diagnostic process, the diagnosis ASD could be confirmed in 528 adults (group ASD+) and ruled out in 854 adults (group ASD-). The variables 'diagnosis', 'age' and 'gender', as well as responses to the AQ-50 at item level were collected from all individuals. Based on the responses to each item, scores were calculated for the AQ-50, its five subscales ('social skills'; 'attention switching'; 'attention to detail'; 'communication'; 'imagination') and the AQ-10.

In addition, neuropsychological-testing (NPT) was performed on 315 patients in order to assess the intelligence quotient (IQ) via the “Wechsler Intelligenztest für Erwachsene” (WIE) and depressive symptoms by means of the “Beck Depression Inventory” (BDI). Since the assumption of normality for the AQ-50 including its subscales and the AQ-10, as well as the IQ and the variable ‘age’ was considered as not fulfilled, only non-parametric tests were performed regarding these variables.

Based on Mann-Whitney *U* tests and receiver operating characteristic (ROC) analyses, it could be demonstrated that both the AQ-50 and the AQ-10 separates poorly between adults with an ASD (ASD+) and patients where an ASD could be ruled out (ASD-). This supports the above-mentioned evaluation that no further conclusion can be made on whether an ASD is likely to be present or not, once the cut-off of ≥26 has been exceeded. In order to generate hypotheses for improving clinical screening, influences of ‘gender’ and ‘age’ on the AQ-50, its subscales, and the AQ-10 were examined. Results of Mann-Whitney *U* tests concerning the influence of gender on the AQ suggest that females score significantly higher on the self-assessment of autistic traits than their male counterparts, independent of the diagnosis ASD. Findings from Spearman’s correlations between age and AQ indicate that older individuals tend to score higher on the AQ-50, however, this influence appears to be greater in ASD+. Neither Full-Scale-IQ (FSIQ) nor severity of depressive symptoms seemed to differ significantly between ASD+ and ASD-. By means of Spearman’s correlations, a positive relationship between IQ and self-assessment of autistic traits could only be observed in adults with an ASD. The BDI did not correlate with the AQ-50, only subscale ‘attention switching’ appeared to overlap with the depressive psychopathology in both ASD+ and ASD-.

Although previous research observed that autistic symptoms tended to be less severe in females, older individuals and individuals with higher IQ with autism, these groups of individuals assessed their autistic traits as significantly more severe than their counterparts in the present study (males; younger adults; individuals with a lower IQ in the normal range).[8,9,10] From these contradictory findings, it was hypothesized that the interpretation of screening ASD via self-assessment could be biased by a limited ability of self-perception. Based on the interpretation of effect sizes, it can be assumed that the influence of gender and IQ on the AQ is comparable to that of the diagnosis ASD. In ASD+, age even had a greater effect on the AQ-50 than the variable ‘diagnosis’. Therefore, the hypothesis seemed reasonable that screening could be improved by controlling the variables ‘age’ and ‘gender’. This hypothesis was supported by findings of ROC analyses, since a better discrimination could be achieved after splitting the sample into subgroups (gender and age). Only for 3 of the 5 subscales a significant difference in scores between ASD+ and ASD- could be found, excluding ‘attention switching’ and ‘attention to detail’. Subscale ‘imagination’ had an exceptional position in this study, which was implemented by the authors of the AQ-50 due to the limited ability of imagination observed

in individuals with an ASD.[5] Although this aspect is hardly represented in the common diagnostic systems (DSM-5[11] and ICD-10[12]), individuals with an ASD rated their limitations in the domain of imagination as significantly higher than individuals without an ASD. 'Imagination' also was the only subscale that was not influenced by variables 'gender' and 'IQ', independent of the diagnosis ASD. Finally, the AQ-50 was analysed at item level, also in order to compare the selection of items of the existing AQ-10 from Allison et al. (2012)[6] with an AQ-10-revised created in this study. Firstly, it was found that in 9 items of the AQ 50, which are supposed to be sensitive for autism, adults without an ASD (ASD-) scored more frequently than adults with an ASD (ASD+). Secondly, only 3 out of 10 items of the AQ-10 overlapped with the AQ-10-revised created here. The AQ-10-revised was created using the same method that Allison et al. (2012)[6] used to identify the two most selective items of each of the five subscales. However, the main difference was that the analysis in the present study was based on a clinical control group instead of a control group from the general population. The AQ-10-revised should be validated in further studies, as this selection of items may be more appropriate for clinical screening, which was also demonstrated by the results of the ROC analyses. The most accurate differentiation between ASD+ and ASD- was achieved with the 14 most discriminating items as a separate test (AQ-top-14). Due to the above-mentioned pre-selection (only adults with a cut-off of ≥26 were included), no 'actual' sensitivity and specificity could be determined here, but 'relative' probabilities.

The hypotheses generated in this project should be investigated in further studies. To determine whether the value of the AQ is limited by a reduced self-perception ability, it should be investigated how influences of 'gender', 'age' and 'IQ' on the self-assessment of autistic traits is related to the observed severity of these traits. Furthermore, clinical studies should investigate if screening could be improved by controlling variables 'gender' and 'age', or by the AQ-10-revised. This research is necessary to increase the probability that an ASD is present after a positive screening. In this way, the scarce and limited resources of the specialised outpatient clinics could be used more effectively and, as a result, the affected individuals suspected of having an ASD could be helped by shortening the waiting periods for the diagnostic procedures.

1.2 Deutsche Zusammenfassung

Das Ziel dieser Studie war anhand der bisher größten Stichprobe von Individuen einer Inanspruchnahme-Population einer Spezialambulanz für Autismus im Erwachsenenalter neue Erkenntnisse zur psychopathologischen Selbstbeurteilung und Hypothesen zur Verbesserung des Screenings von Autismus-Spektrum-Störungen (ASD) zu gewinnen. Im Zentrum dieser retrospektiven und explorativen Datenanalyse stehen die zwei meist genutzten Selbstbeurteilungsfragebögen zum Screening von ASD im Erwachsenenalter, der

Autismus-Spektrum Quotient (AQ-50), sowie die auf 10 Items gekürzte Version des AQ-50, der AQ-10.[1] Denn obwohl diese Screening-Instrumente eine breite Anwendung finden, wurden sie kaum auf „die klinisch relevante Fragestellung der Validität in Bezug einer klinischen Inanspruchnahme-Population“ untersucht, wie in der interdisziplinären S-3 Leitlinie zur Diagnostik von ASD[2] festgestellt wurde. Beide Versionen wurden bislang überwiegend anhand einer Kontrollgruppe mit gesunden Individuen der Allgemeinbevölkerung validiert.[2] Daher wurde vermutlich die Spezifität dieser Selbstbeurteilungsfragebögen für ein klinisches Screening überschätzt. Begründet wird diese Vermutung durch die Beobachtung, dass die Spezifitäten in den bisherigen Studien abhängig von der Auswahl der Kontrollgruppe deutlich variierten, da Individuen einer klinischen Kontrollgruppe häufig Symptome aufweisen, die einer ASD ähnlich sein können.[3] In Untersuchungen in denen die Kontrollgruppe aus gesunden Individuen bestand, lag die Spezifität des AQ-50 zwischen 0.80 – 0.92 und bei klinischen Kontrollgruppen nur zwischen 0.20 – 0.52.[2,3,4] Da die Sensitivität aber bei einem Cut-off von 26 unabhängig der zugrundeliegenden Population mit 0.88 – 0.95 relativ konstant und ausreichend hoch ist, wird der AQ-50 dennoch für das Screening genutzt.[3,5,6,7] So schätzen die Autoren der obengenannten S-3 Leitlinie die Aussagekraft des AQ-50 (und AQ-10) insgesamt aber als eingeschränkt ein, wenn der Score über dem Cut-off von ≥26 liegt.[2] Um diese Einschätzung objektivieren zu können und darauffolgend Hypothesen für eine Verbesserung des Screenings unter klinischen Bedingungen zu generieren, konnten in der vorliegenden Studie insgesamt 1382 Individuen einer klinischen Inanspruchnahme-Population der Spezialambulanz für Autismus in Köln eingeschlossen werden. Der Aufnahmemodus zur spezialisierten Diagnostik der Ambulanz sah vor, dass nur Erwachsene mit einem initialen Verdacht auf eine ASD (der z.B. durch einen niedergelassenen Kollegen geäußert wurde) und einem Punktewert über dem oben genannten Cut-off von 26 im AQ-50 eingeladen wurden.[2,7] Außerdem wurden aufgrund der später folgenden Item-Analyse in dieser Untersuchung nur Individuen einbezogen, die den AQ-50 ohne fehlende Items beantwortet haben. Nach einem aufwendigen diagnostischen Prozess konnte bei 528 Erwachsenen die Diagnose ASD bestätigt (Gruppe ASD+) und bei 854 eine ASD ausgeschlossen (Gruppe ASD-) werden. Von allen Individuen wurden neben den Variablen ‚Diagnose‘, ‚Alter‘ und ‚Geschlecht‘, die Antworten auf den AQ-50 auf Item-Ebene gesichert. Aus den einzelnen Werten der Items wurden dann die Punktwerte des AQ-50 und der fünf dazugehörigen Subskalen (‚Soziale Kompetenz‘; ‚Aufmerksamkeitswechsel‘; ‚Detailfokussiertheit‘; ‚Kommunikation‘; ‚Fantasie‘), sowie des AQ-10 errechnet. Für 315 Personen dieser Stichprobe wurden zusätzlich im Rahmen einer Neuropsychologische-Testung (NPT) der Intelligenzquotient (IQ) mittels des “Wechsler Intelligenztest für Erwachsene” (WIE) und eine depressive Psychopathologie über den „Beck Depression Inventar“ (BDI) bestimmt. Da sich der AQ-50 inklusive seiner Subskalen

und der AQ-10, sowie der BDI und die Variable ‚Alter' als nicht-normalverteilt präsentierten, wurden hier nicht-parametrische Tests durchgeführt.

Anhand von Mann-Whitney *U* Tests und ROC-Analysen (receiver operating characteristic) ließ sich demonstrieren, dass sowohl der AQ-50 als auch der AQ-10 insgesamt ungenügend zwischen den Gruppen ASD+ und ASD- trennt. Demnach bestätige sich die obengenannte Einschätzung, dass nach Überschreiten des Cut-offs von 26 Punkten keine weitere Aussage darüber getroffen werden kann, ob eine ASD wahrscheinlich vorliegt oder nicht. Um darauffolgend Hypothesen zur Verbesserung des Screenings zu generieren, wurden zunächst die Einflüsse des Geschlechts und des Alters auf den AQ-50, inklusive der Subskalen und den AQ-10 untersucht. Die hier durchgeführten Mann-Whitney *U* Tests bezüglich des Einflusses des Geschlechts weisen darauf hin, dass Frauen unabhängig von der Diagnose ASD signifikant höher in der Selbstbeurteilung der autistischen Züge scoren als Männer. Die Ergebnisse der Spearman Korrelationen zwischen dem Alter und dem AQ legen nahe, dass ältere Individuen tendenziell höher im AQ-50 scoren, wobei dieser Einfluss in der Gruppe ASD+ größer zu sein scheint. Anhand der im Rahmen der NPT erhobenen Daten konnten weder signifikante Unterschiede im Gesamt-IQ noch in der Ausprägung der depressiven Symptomatik zwischen Personen mit und ohne ASD beobachtet werden. Mittels weiterer Spearman Korrelationen konnte ein positiver Zusammenhang zwischen dem IQ und der Selbstbeurteilung autistischer Züge beobachtet werden, jedoch nur bei Erwachsenen mit einer ASD. Der BDI korrelierte nicht mit dem AQ-50, lediglich der Faktor ‚Aufmerksamkeitswechsel' schien sich unabhängig von der Diagnose ASD mit der depressiven Psychopathologie zu überschneiden. Obschon in der bisherigen Forschung bei Frauen, älteren Individuen und Personen mit höherem IQ mit einer ASD tendenziell geringere Ausprägung der autistischen Symptome beobachtet wurden, schätzten diese Personengruppen in der vorliegenden Untersuchung ihre autistischen Züge als signifikant schwerer ein als ihr jeweiliges Gegenüber (Männer; jüngere Erwachsene; Personen, bei welchen sich der IQ im unteren Normbereich befindet).[8,9,10] Aus diesen gewissermaßen widersprüchlichen Befunden entstand die Hypothese, dass die Interpretierbarkeit des Screenings mittels Selbstbeurteilung durch eine reduzierte Selbstwahrnehmungsfähigkeit maßgeblich verzerrt sein könnte.

Aufgrund der Interpretation der Effektstärken kann vermutet werden, dass der Einfluss des Geschlechts und des IQs auf die Beantwortung des Screening-Fragebogen vergleichbar mit dem der Diagnose ASD ist. Das Alter zeigte bei ASD+ sogar einen größeren Effekt auf den AQ-50 als die Variable ‚Diagnose'. Daher erschien die Hypothese naheliegend das Screening verbessern zu können, indem die Variablen ‚Alter' und ‚Geschlecht' zuvor kontrolliert werden. Die Ergebnisse der ROC Analysen konnten diese Hypothese zusätzlich unterstreichen, denn nach der Aufteilung in Subgruppen (nach Geschlecht und Alter) konnte eine sicherere Differenzierung zwischen ASD+ und ASD- erzielt werden.

Auf der Ebene der Subskalen konnte nur für 3 der insgesamt 5 Faktoren ein signifikanter Unterschied zwischen ASD+ und ASD- gefunden werden, davon ausgeschlossen waren ‚Aufmerksamkeitswechsel' und ‚Detailfokussiertheit'. Eine besondere Stellung nahm der Faktor ‚Fantasie' ein, welcher von den Autoren des AQ-50 aufgrund der beobachteten limitierte Imaginationsfähigkeit von Erwachsenen mit einer ASD eingeführt wurde.[5] Obwohl dieser Aspekt wenig in den gängigen Diagnosesystemen (DSM-5[11] und ICD-10[12]) berücksichtigt wird, schätzten Individuen der Gruppe ASD+ ihre Einschränkungen im Bereich der Imagination als signifikant höher ein als Personen ohne Autismus. Die ‚Fantasie' war auch der einzige Faktor, der in der Selbstbeurteilung nicht durch das Geschlecht und den IQ beeinflusst wurde, unabhängig der Gruppe ASD+ oder ASD-.

Schließlich wurde der AQ-50 auf der Ebene der einzelnen Items analysiert, auch um die Auswahl der Items für den bereits bestehenden AQ-10 von Allison et al. (2012)[6] anhand eines neu erstellten AQ-10-revised zu untersuchen. Zum einen zeigte sich, dass 9 Items des AQ-50, die als sensitiv für das Vorliegen von Autismus gelten sollten, im Schnitt häufiger von der Ausschlussgruppe als von Erwachsenen mit einer ASD bestätigt wurden. Zum anderen überschnitten sich nur 3 von 10 Items des AQ-10 mit dem hier erstellten AQ-10-revised. Zur Erstellung des AQ-10-revised wurde die gleiche Methode gewählt, mit der auch Allison et al. (2012)[6] die jeweils zwei trennschärfsten Items der fünf Subskalen aus dem AQ-50 selektierten. Der wesentliche Unterschied lag jedoch in der Stichprobe, da in der vorliegenden Studie eine klinische und keine Kontrollgruppe der Allgemeinbevölkerung genutzt wurde. Der AQ-10-revised sollte in weiteren Untersuchungen validiert werden, denn möglicherweise ist diese Selektion von Items besser für das Screening einer Inanspruchnahme-Population geeignet, wie auch die Ergebnisse der ROC Analysen näherlegten. Mit den 14 trennschärfsten Items als separater Test (AQ-top-14) konnte die genauste Differenzierung zwischen ASD+ und ASD- erzielt werden. Aufgrund der oben genannten Vorselektion (es wurden nur Personen mit einem Cut-off von ≥26 einbezogen), konnten in dieser Studie jedoch keine „echten" Werte der Testgütekriterien (Sensitivität, Spezifität, positiver und negativer prädiktiver Wert), sondern nur „relative" Werte bestimmt werden.

Die hier gewonnenen Hypothesen sollten nun in zukünftigen Studien gezielt weiterverfolgt werden. Um zu bestimmen ob die Aussagekraft des AQ durch eine reduzierte Selbstwahrnehmungsfähigkeit eingeschränkt ist, könnte untersucht werden, wie sich der Einfluss von ‚Geschlecht', ‚Alter' und ‚IQ' auf die Selbstbeurteilung der autistischen Symptomatik in Abhängigkeit von der beobachteten Ausprägung dieser Symptomatik verhält. Außerdem sollte durch klinische Studien untersucht werden, inwieweit sich das Screening durch die Kontrolle der Variablen ‚Geschlecht' und ‚Alter', oder durch den AQ-10-revised verbessern lässt. Diese Forschung ist notwendig, um die Wahrscheinlichkeit zu erhöhen, dass nach einem positiven Screening auch eine ASD vorliegt. Denn so könnten die knappen und

wertvollen Ressourcen der Spezialambulanzen effizienter genutzt und infolgedessen die betroffenen Personen mit Verdacht auf eine ASD durch eine Verkürzung der Wartezeiten zur Diagnostik und Diagnosestellung entlastet werden.

2. Introduction

Although Autism spectrum disorders (ASD) have an early onset and diagnosis is commonly been made in childhood, epidemiological findings in the last decades showed that a substantial proportion of autistic individuals reach adulthood undiagnosed.[13,14] Especially normal to highly intelligent individuals who are supposedly capable to camouflage their autistic symptoms remain unidentified until their compensational strategies no longer withstand the increasing social demands of adult life. Instances might be job-related and relationship difficulties. However, the diagnostic approach in adults is complex, due to the difficult distinction between symptoms of an ASD and other mental disorders, such as schizoid or schizotypal personality disorder, chronic depression or complex posttraumatic stress disorder after childhood traumata, as well as other differential diagnoses, which might mimic the autism-related social interactional difficulties.[15,16,17] This distinction is even more challenging since some differential diagnoses might even be present as "true" psychiatric comorbidities and therefore overlaying the autistic background, such as depressive and anxiety disorders, attention deficit/ hyperactivity disorder or obsessive-compulsive disorder.[3,18] Due to these differential diagnostic considerations and the fact that to date it is not yet possible to make a diagnosis using a technical method or a biomarker, it is necessary to obtain information on the current and past symptoms during childhood.[19] For this purpose several interviews with patients and relatives, especially on symptoms during childhood as well as neuropsychological assessments are needed.[17] Therefore, this diagnostic process is highly time- and cost-intensive. This and further reasons such as an increased media attention and the lack of clinical experts offering diagnostic services for adults lead to overcrowded specialized clinics and thus to waiting periods up to one year.[20] From the patient perspective this prolonged time interval from a suspected diagnosis up to the confirmation or rejection of an ASD might be painful. In addition to the feeling of uncertainty, there are also work- and relationship-related difficulties which, if the diagnosis is confirmed, require more adequate help in the form of ASD-oriented psychotherapy or special support on the labour market.[21,22]

In order to save the scarce resources and provide more diagnostic capabilities, a more precise pre-selection of patients should be provided. For this purpose, the UK National Institute for Health and Care Excellence (NICE)[23] and the German Association for Psychiatry and Psychotherapy ("Deutsche Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde", DGPPN)[2] suggested self-assessment questionnaires like the Autism-Spectrum Quotient (AQ-50)[5] and its short version the AQ-10[6] as a screening tool. However, Ashwood et al. (2016)[3] just recently demonstrated that especially the specificity of the AQ-50 and AQ-10 were roughly overestimated in the original studies from Baron-Cohen et al. (2001)[5] and Allison et al. (2012)[6] (AQ-50 with the cut-off ≥26, Baron-Cohen et al. (2001) vs. Ashwood et al. (2016): sensitivity 0.95 vs. 0.88; specificity 0.92 vs. 0.20) and (AQ-10 with the

cut-off ≥6, Allison et al. (2012)[6] vs. Ashwood et al. (2016)[3]: sensitivity 0.88 vs. 0.77; specificity 0.91 vs. 0.29). The main difference between the studies was, that Ashwood et al. (2016)[3] examined the screening tests on the basis of a clinical population (patients suspected of having an ASD), rather than trying to separate mentally healthy people from people with ASD, as researchers did in the original studies.[5,6] Due to the fact that hitherto the questionnaires have been hardly investigated on the basis of clinical populations, the DGPPN[2] called for more research on more practice-oriented conditions, which was a key motivation for this study.

Although there are indications for different cognitive profiles and clinical phenotypes for females and males in high-functioning autism and that the severity and prevalence of the autistic symptoms can change over time, the AQ has not yet been investigated on the basis of a larger clinical population, focusing on these aspects.[24,9] Therefore, this explorative and retrospective study will first elaborate whether variables such as age and gender have an influence on the response to the self-evaluation questionnaire with or without the diagnoses of being autistic. Since Bishop et al. (2012)[25] indicated in their research with a small group of 65 individuals with ASD, that intelligence affects self-report of people with an ASD, this study will also investigate how general intelligence as evaluated by the "Wechsler Intelligenztest für Erwachsene" (WIE) influences AQ values in people with and without an ASD. In addition, it will also be examined whether depressive symptoms might have influence on the self-assessment of autistic traits by means of the Beck Depression Inventory (BDI), because depression is the most common comorbidity in adults with ASD and there are overlapping symptoms between both disorders.[26] And finally, this study includes a single item analysis, which will be conducted to determine whether the same 10 most discriminating items for the separation between adults with an ASD and without an ASD detected within a clinical population corresponds to results of Allison et al. in their AQ-10 study (2012)[6], which included affected cases and healthy controls. In this investigation, only adults were included who were suspected of having autism and scored higher or equal to the threshold of 26 out of 50 possible points in the AQ-50. This cut-off (≥26) was recommended by Woodbury-Smith et al. (2005)[7] after achieving a higher percentage of correctly classified individuals in a clinical population than the originally threshold of 32 recommended by Baron-Cohen et al. (2001) in their study with healthy controls[5] (Woodbury-Smith et al. (2005) cut-off 32 vs. 26: 76% vs. 83% correctly classified)[7].

In the following chapter 'Theoretical Background' the characteristic ASD symptoms, diagnostic criteria as well as the findings of the undiagnosed adult phenotype regarding differential diagnoses and comorbidities will be introduced. In the third chapter 'Methods', the sample of this study, the various questionnaires and instruments, as well as the statistical tests will be presented. This is followed by the 'Results' of the respective questions with the corresponding calculations. At the end, these results will be discussed in the context of previous research and limitations of this study will be outlined (chapter 'Discussion').

To the best of my knowledge this is the largest study on the AQ based on a large clinical sample of 1382 individuals, 38% of which with confirmed autism, which is supposed to help to explore all these open questions and generate further hypotheses for a facilitated screening and improved diagnostics of suspected ASD late in lifetime.

2.1 Theoretical Background

Autism spectrum disorders (ASD) are described as a group of neurodevelopmental and lifelong conditions with an onset typically in early childhood, associated with limitations in social interaction and communication as well as restricted and repetitive patterns of behaviour and interests.[11] As this study is about screening of autism in adulthood, the following will primarily refer to facts and data of individuals with an ASD diagnosis late in lifetime, unless otherwise stated.

With a prevalence rate of about 1-2%, autism is not a rare syndrome and is accompanied with substantial costs for the healthcare system (1-2 million $ in the lifespan of an individual with an ASD in the US or UK).[27,28,29] ASD is understood as a disorder of multifactorial aetiology resulting from both genetic and non-genetic risk factors, which also interact with each other, whereby environmental factors such as the following are discussed: prenatal, perinatal, birth and neonatal complications, viral infection, autoimmune diseases and the influences of teratogenic substances and drugs.[30,31,32] Altogether, the pathophysiological mechanisms of autism are not fully understood, and thus various models are used in the different disciplines like genetics, neuroanatomy, neuroendocrinology and neuropsychology, in order to draw a more precise and holistic picture of this complex disorder.[33] According to the current state of the art there is no biomarker or other technical method, e.g. structural or functional cerebral imaging, available in clinical practice that can predict or confirm the diagnosis of an ASD.[19] Therefore, the disorder must be diagnosed on the basis of a present symptom assessment and a detailed history of symptoms during childhood and adulthood, which will be described in detail in the following chapter ‘Classification, Symptoms and Diagnostic criteria’.[2]

2.1.1 Therapy options

The course of ASD is characterized by the fact that there is no remission and still no available therapy to treat this disorder causatively.[22] Likewise, core symptoms of the disorder remain unaffected by psychopharmacological treatment, which is rather effective against comorbidities or accompanying symptoms. For instance antipsychotics like risperidone and aripiprazole were found to be effective against strong irritability and aggression, while positive effects against comorbid anxiety or depressive symptoms were reported for serotonin reuptake inhibitors (SSRIs).[34] Furthermore, the influence of the neuropeptide oxytocin on social impairment in children and adults with ASD is discussed.[35] Various studies in which young individuals with ASD were treated with oxytocin nasal spray showed significant improvements

in “retention of affective speech comprehension”[35,36], “mind-reading performance” [35,37], “more frequent engagement in positive social interactions, and enhanced feelings of trust and preference towards partners within positive interactions”[35,38]. However, the clinical effectiveness of oxytocin in ASD individuals could not be confirmed unequivocally in a more recent systematic review by Ooi et al. (2017)[39]. Especially with methods of “cognitive behavioural therapy (CBT)”, attempts are made to improve the quality of life of individuals with ASD, by enhancing social skills and learning coping strategies for situations experienced by the patients as stressful. Furthermore, there is also ongoing research regarding the effectiveness of psychodynamic therapies such as “mentalization-based treatment (MBT)” in ASD, where clinical evidence of a positive influence of these therapies has already been observed.[40,41] Also in psychotherapy, the treatment of comorbidities such as depression and anxiety disorders is crucial.[42]

2.1.2 Classification, Symptoms and Diagnostic criteria

Autism spectrum disorders are diagnosed according to the systems of ICD (International Statistical Classification of Diseases and Related Health Problems) and DSM (Diagnostic and Statistical Manual of Mental Disorders). In their versions ICD-10 (World Health Organization 1992)[12] and DSM-IV (American Psychiatric Association 2000)[43], which were applied in this study, autistic disorders are categorized in “childhood autism” (ICD-10: F84.0; DSM-IV: 299.00), “atypical autism” (ICD-10: F84.1), “Asperger syndrome” (ICD-10: F84.5; DSM-IV: 299.80), “other pervasive developmental disorders” (ICD-10: F84.8) and “pervasive developmental disorder, unspecified” (ICD-10: F84.9) or “pervasive developmental disorders, not otherwise specified (PDD-NOS)” (DSM-IV: 299.80), which are then summarized under “pervasive developmental disorders” (ICD-10: F84; DSM-IV: 299).[2] In these systems the following core symptoms are distinguished for the diagnosis of the disorder: impaired social interaction (I), impaired social communication (II) and restricted, stereotyped, repetitive behaviour (III). (I) in particular refers to difficulties in initiating, maintaining and shaping interpersonal relationships in the context of family, friendship and partnership at the different stages of life.[2] With (II), problems in verbal and non-verbal communication such as atypical eye contact, difficulties in understanding others people’s facial expressions, vocal intonation, making small talk or reading between the lines are understood in adults.[23] In the last category (III), symptoms/ characteristics like “attention to small details”, “narrow deep interests, rather than broad superficial interests” or “anxiety in face of change” are subsumed (see Table 2.1). Further necessary criteria are the manifestation in childhood (until the age of 3) (IV), clinically significant impairment of the affected person (V) and the symptoms cannot be explained by any another disorder (VI) (see Table 2.2). According to the ICD-10, the diagnoses differ mainly in the presence or absence of criteria (I-III) and in the delay of cognitive or language development. In “childhood autism” all core symptoms (I-III) and difficulties in language and

development before the age of 2 must be present. In the case of “Asperger syndrome” mainly I-III exist without impairments in cognitive or language development. An “atypical autism” is coded if only one or two of the core criteria are present and a developmental delay is found before the age of 2 or the core symptoms were only detected after the first 2 years of life. If there are signs suggesting a disorder with autistic symptoms, but the diagnosis cannot be clearly assigned to one of the aforementioned disorders, “pervasive developmental disorder, unspecified” (ICD-10: F84.9) or “pervasive developmental disorders, not otherwise specified (PDD-NOS)” (DSM-IV: 299.80) can be coded (diagnostic criteria ICD-10: F84.0 - F84.9 compare).[2,12,44] However, these diagnoses (often summarised as PDD-NOS) are frequently given without careful consideration, which can lead to false positive ASD diagnoses, as subclinical autistic traits are also taken into account in some cases.[45]

Nevertheless, research in the disciplines of neuropsychology and neurobiology has shown that all of these mentioned sub-diagnoses, as described in the ICD-10 and DSM-IV, are not clearly distinguishable.[45,46,47] Thus, the path of “categorial” differentiation has been left and it is assumed that the disorders lie “dimensionally” in a spectrum. Similar to the latest version of the DSM (DSM-5 published in 2013), the guideline of the German Association for Psychiatry and Psychotherapy (DGPPN) on the diagnosis of autism (2016) recommends that all autistic disorders should be summarized under the term “Autism spectrum disorder” (ASD).[2] There has also been a broad discussion about whether it is reasonable to distinguish dimensionally between autistic and non-autistic disorders. Here, the guideline suggests that a categorical distinction should be made between ASD and non-ASD.[2] Altogether, a hybrid model (Frazier et al. 2012)[48] was chosen, which integrates both approaches, the categorial and the dimensional. So a categorial distinction is made between individuals with ASD and without ASD, however the symptoms are represented dimensionally.[48]

Considering that much has changed in the understanding of the disorder (see above) as well as the announced changes in the diagnostic criteria (ICD-11 in 2021) and since the screening instrument “Autism-Spectrum Quotient” (AQ) examined in this study was developed at the time of the ICD-10 (1994) and DSM-IV (2001), the innovations in the latest versions of the two systems will be described.

Since the ICD-11 will probably be used in Germany, which is intended to “harmonize”[2] with the DSM-5 at least in terms of the ASD, the most important changes of the fifth edition of the DSM (compared to the ICD-10), which has been extensively investigated so far, will be presented in the following.[49] (1) The first significant modification concerns, as mentioned above, the merging of all autistic disorders into a single diagnostic group of ASD. (2) There should be a change in the diagnostic criteria in which the symptom groups social interactions and communication are combined into one criterion (see Table 2.2). (3) A classification into three different clinical

degrees of severity of the symptom domains A (social interaction and communication) and B (restrictive, repetitive patterns of behaviour, interest or activities) should be defined. (4) A description of ASD over the different stages of life with the possibility of delayed onset of the first symptoms (after the age of three) should be established. (5) With the DSM-5 it is possible to code other disorders simultaneously besides the ASD, which had been formerly interpreted as exclusive, such as hyperkinetic disorders (F90).[50] (6) The above-described PDD-NOS is no longer intended to be assigned in the DSM-5, but is redefined as a "social (pragmatic) communication disorder (SPCD)" (DSM-5: 315.39) if an individual present only "deficits in social interaction and communication" (Criterion A) and not "restrictive, repetitive patterns of behaviour, interest or activities" (Criterion B).[51] According to the DSM-5, the SPCD is located outside of the actual ASD and was also created to avoid false positive diagnoses.[45,51] In a more recent study, Mandy et al. (2017)[52] described that this diagnosis is rather assumed to lie "on the border between ASD and non-ASD".

So far known and published innovations in the latest version of the ICD-11 concern the classification of "Childhood autism" and "Asperger syndrome" into ASD, the examination of symptoms over the lifespan, and the inclusion of quantitative differentiation between intellectual functioning and language abilities (e.g. "6A02.0 Autism spectrum disorder without disorder of intellectual development and with mild or no impairment of functional language" or "6A02.1 Autism spectrum disorder with disorder of intellectual development and with mild or no impairment of functional language").[49,53]

The following study is oriented on the hybrid model described above (dimensional construct of symptoms in ASD but categorial distinction between ASD and non-ASD)[48] and PDD-NOS are excluded from the autistic spectrum, as they cannot be clearly assigned to ASD or non-ASD ("it (*SPCD*) exist on the border between ASD and non-ASD" Mandy et al. 2017)[52].

Table 2.1 *List of symptoms sorted according to the two main domains A and B – Extract from "The NICE guidelines on recognition, referral, diagnosis and management of adults on the autism spectrum" p18-19*[23]

A) Difficulties in Social Interaction and Communication	B) Repetitive behaviour, problems adapting to sudden and unforeseen change and special interests
- "atypical eye contact (staring at people for too long or not maintaining eye contact)"	- "avoiding crowded places"
- "intrusion into others' personal space (standing too close to someone else, talking too loud or touching people inappropriately)"	- "difficulties multi-tasking"
- "reduced interest in socialising"	- "doing one thing at a time"
- "difficulties understanding others' behaviour, motives and intentions"	- "narrow deep interests, rather than broad superficial interests"
- "difficulties reading other people's facial expressions or vocal intonation"	- "preference for repetition and routine"
- "difficulties taking turns in conversation or tendency towards monologue"	- "narrow deep interests, rather than broad superficial interests"
- "difficulties making small talk or maintaining a conversation"	- "anxiety in face of change"
- "bluntness or lack of diplomacy"	- "need for strict order and precision."
- "social naïveté and vulnerability to exploitation"	- "being extremely passive if an activity of interest is not available or initiated by someone else"
- "difficulties anticipating what might offend others (faux pas)"	- "need for sameness (eating the same foods, wearing the same clothes, taking the same routes, going to the same places) and avoidance of novelty"
- "lack of social awareness"	- "preference for predictability and predictable events (watching washing machines spinning or trains going down tracks)"
- "difficulties reading between the lines or picking up hints"	- "development of 'fixated interests'"
- "difficulties seeing things from another person's perspective"	- "need for clarity and expressing a pedantic request for precision and avoiding ambiguity"
- "difficulties resolving conflict"	- "attention to small details"
- "difficulties keeping track of what the listener or reader needs to know"	
- "difficulties making or keeping friends"	
- "difficulties understanding other people's expectations"	
- "difficulties conforming"	
- "difficulties judging what might be relevant or irrelevant to others"	
- "difficulties coping with or interacting in social groups"	
- "unable to tell white lies"	
- "difficulties coping with ambiguity in language"	
- "becoming obsessed with a person to an intrusive extent"	
- "social anxiety"	
- "loneliness (and risk of depression)"	
- "reduced empathy"	

Table 2.2 *Comparison of the diagnostic criteria of ICD-10*[12] *and DSM-5*[11] *(compare*[20,44,50,54,55]*).*

ICD-10	**DSM-5**
Pervasive developmental disorders	**ASD diagnostic criteria A-E**
I. "Qualitative impairment in social interaction are manifest" in at least 2 (F84.0, F84.5) or ≥1 (F84.1) a. "Failure adequately to use eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction." b. "Failure to develop (in a manner appropriate to mental age, and despite ample opportunities) peer relationships that involve a mutual sharing of interests, activities and emotions." c. "Lack of socio-emotional reciprocity as shown by an impaired or deviant response to other people's emotions; or lack of modulation of behaviour according to social context; or a weak integration of social, emotional, and communicative behaviours." d. "Lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g. a lack of showing, bringing, or pointing out to other people objects of interest to the individual)."	A. "Persistent deficits in social communication **and** social interaction across various contexts, **must be manifested in the following 3 areas"** 1. "Deficits in social-emotional reciprocity." 2. "Deficits in nonverbal communicative behaviours used for social interaction." 3. "Deficits in developing, maintaining, and understanding relationships."
II. "Qualitative abnormalities in communication as manifest in at least one of the following areas." (F84.0) or ≤1 (F84.1): a. "Delay in or total lack of development of spoken language that is not accompanied by an attempt to compensate through the use of gestures or mime as an alternative mode of communication (often preceded by a lack of communicative babbling)." b. "Relative failure to initiate or sustain conversational interchange (at whatever level of language skill is present), in which there is reciprocal responsiveness to the communications of the other person." c. "Stereotyped and repetitive use of language or idiosyncratic use of words or phrases." d. "Lack of varied spontaneous make-believe play or (when young) social imitative play."	
III. "Restricted, repetitive, and stereotyped patterns of behaviour, interests, and activities are manifested" in at least one (F84.0, F84.5) or ≤1 (F84.1): a. "An encompassing preoccupation with one or more stereotyped and restricted patterns of interest that are abnormal in content or focus; or one or more interests that are abnormal in their intensity and circumscribed nature though not in their content or focus." b. "Apparently compulsive adherence to specific, non-functional routines or rituals."	B. "Restrictive, repetitive patterns of behaviour, interest or activities that are manifested in at least 2 of the following domains" 1. "Stereotyped or repetitive speech, motor movements, or use of objects." 2. "Excessive adherence to routines, ritualized patterns of verbal or nonverbal behaviour, or excessive resistance to change." 3. "Highly restricted, fixated interests that is abnormal in intensity or focus."

c. "Stereotyped and repetitive motor mannerisms that involve either hand or finger flapping or twisting or complex whole-body movements." d. "Preoccupations with part-objects of non-functional elements of play materials (such as their odour, the feel of their surface, or the noise or vibration they generate)."	**4. "Hyper- or hypo- reactivity to sensory input or unusual interest in sensory aspects of environment."**
IV. **"**Abnormal or impaired development is evident before the age of 3 years" **(**F84.0, F84.11) or after (F84.10, F84.12) **"**in at least one of the following areas:**"** 1. "receptive or expressive language as used in social communication;" 2. "the development of selective social attachments or of reciprocal social interaction;" 3. "functional or symbolic play."	C. "Symptoms must be present in the early developmental period (**but may not become fully manifest until social demands exceed limited capacities or may be masked by learned strategies in later life**)."
	D. "Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning." And **classification according to degree of severity.**
V. "The clinical picture is not attributable to the other varieties of pervasive developmental disorders; specific development disorder of receptive language (F80.2) with secondary socio-emotional problems, reactive attachment disorder (F94.1) or disinhibited attachment disorder (F94.2); mental retardation (F70-F72) with some associated emotional or behavioural disorders; schizophrenia (F20.-) of unusually early onset; and Rett's Syndrome (F84.12)."	E. "These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level."

Bold: New Feature in DSM-5

2.1.3 Undiagnosed adults with an ASD

Although, typically the diagnosis of an ASD is made in childhood, up to 40% of individuals with autism remain undiagnosed and reach adulthood without being identified as being autistic.[14] In the group of undiagnosed adults with ASD, a distinction is made between individuals with an intellectual disability and normal to highly intelligent individuals. The latter was again divided into two sub-diagnoses: Asperger-syndrome (AS) and high-functioning autism (HFA) (childhood autism associated with normal to high intelligence).[20] Since these two autistic subgroups could not be clearly distinguished neither by neurobiology, nor clinical criteria or outcome (see above, recommendation of the DGPPN guideline[2]), they are merged into one group of normal to highly intelligent individuals with an ASD. Both groups, adults with an intellectual disability and without, differ strongly from each other in their phenotype as well as in their approach in diagnostics.[33] The following study will focus on the normal to highly intelligent individuals with ASD, for whom the AQ was originally designed. Several hypotheses try to explain this phenomenon of the diagnosis late in lifetime. The first three of the following hypotheses were suggested by Geurts et al. (2011)[56] and are particularly connected with developments in the understanding of ASD (diagnostic criteria, familiarity, phenotypes) since

the 1980s. The fourth hypothesis describes a more general phenomenon and refers to all age groups of normal to highly intelligent individuals with a diagnosis late in life:

1) When the affected individuals were children, the diseases were not as well-known as they are now. This refers especially to individuals born before 1990.
2) Later it was discovered that the spectrum of intelligence in ASD is very broad.
3) Back then, the diagnosis criteria were more "stringent", and therefore those individuals were misdiagnosed or not diagnosed at all.[56,57,58] However, this also refers mainly to the generation of individuals born before the 1990s, since the Asperger syndrome was included in 1992 in the ICD-10[12] and in 1994 in the DSM-IV.[21,43,59]
4) Another approach to understanding this issue is that some individuals within the normal to high intelligent range are learning to compensate their autistic deficits. This involves training rigid rules of social communication and interaction using different methods including "social learning".[21] Some of these describe how they learned gestures and facial expressions like vocabulary or intentionally try to keep eye contact with great effort.[60] These cognitive compensation mechanisms which aim to conceal the autistic core symptoms are summarized under the term "camouflaging".[61] Typically, a "unsuspicious level of psychosocial functioning" [61] can then be reached for the observer with additional high linguistic skills and a certain degree of self-reflection.[21,62] However, these efforts only work to a limited extent, since it is trained behaviour that must be actively retrieved and controlled repeatedly, it never has the same intuitive and spontaneous character as it is with unaffected individuals.[60] Then, especially in "threshold" situations, that result in more complex social demands on their camouflaging skills, such as moving out from home, starting at university or working life or getting involved in the first partnership these coping mechanisms may collapse.[33,63] As a result, these individuals are known to seek professional help for the first time. This is especially the case when these psychosocial stressors give rise to psychiatric comorbidities (see next subchapter 'Comorbidity or differential diagnosis'), which leads them to an outpatient psychiatric clinic primarily with suspected depression or anxiety disorders.

2.1.4 Comorbidity or differential diagnosis?

Besides the additional distress caused by a manifest comorbidity, these also lead to further difficulties in identifying the primary disorder ASD. Nylander and Gillberg (2001)[64] state that the symptoms of the secondarily developed disorders "overshadow" the impairments and behaviour of the autistic phenotype. This is further complicated by the fact, that the symptoms of the most common psychiatric comorbidity depression and anxiety disorder overlap with core symptoms of ASD and therefore often cannot be unequivocally attributed.[26] For instance, both depression and ASD can cause "social withdrawal, difficulties with sleep, flat affect and

reduced eye contact"[26] and can aggravate symptoms in both directions, which needs to be differentiated thoroughly in terms of the clinical course of symptoms.[65] Moreover, it is important to point out that depression is not only the most common comorbidity, but that the risk of depression for adults with ASD is considerably higher than in the normal population. In the study by Joshi et al. (2013)[66] 77% of persons with ASD had at least one depressive episode compared to the control group without ASD where 46% suffered from at least one episode, this difference was statistically significant. Furthermore, the other important comorbidities anxiety disorders and obsessive-compulsive disorder (OCD) were also significantly more prevalent in the group of adults with ASD than in the control group. Also common comorbidities are eating disorders, somatoform disorders, attention deficit/ hyperactivity disorder (ADHD), psychotic disorders and substance-related disorders.[67] It is also important to emphasise, that the majority of these psychiatric disorders must also be included in differential diagnostic considerations (see Figure 2.1).[61] This circumstance, on the one hand implies the next difficulty in the diagnostic process and on the other hand hints at one of the central questions in this study: 'the discrimination between ASD and differential diagnoses or mental states that mimics autistic symptoms or complete phenotypes'. In other words, 'the discrimination between an ASD and the exclusion of an ASD'. Psychiatric disorders, which also cause impairments in the field of social interaction and communication or in restrictive, repetitive patterns of behaviour are particularly of great relevance as differential diagnoses.[33] For adults with an ASD in the normal to highly intelligent range, these diagnoses mainly include affective disorders (mainly depression), anxiety disorders, OCD, personality disorders and psychotic disorders.[16,68] Due to the fact, that the control group in this study consists of individuals where the diagnosis ASD was ruled out in the diagnostic process, it is very likely that most of those differential diagnoses occur in this heterogeneous group, even though they were not determined here. Therefore, it seems reasonable in the following to look at the differences and similarities between the various disorders and ASD (compare Table 2.1).

In depression, as already mentioned, some of the symptoms overlap with those of ASD. Thereby this concerns the two core symptom domains (according to DSM-5): (1) "reduced eye to eye contact", "social withdrawal" (social interaction and communication – Criterion A)[26]; (2) "lack of interest in age-appropriate activities" (Restrictive, repetitive patterns of behaviour, interest or activities – Criterion B). However, the major difference between both disorders is that depression has an episodic course and does not necessarily manifest itself in early childhood.[2]

Also, in anxiety disorders some of the symptoms coincide with those associated with ASD and can be a serious challenge in the diagnostic process. On the one hand, this includes general

fears such as “anxiety in the face of change” (Criterion B), on the other hand more specific fears familiar to us from social phobias (SP) (ICD-10: F40.1) or “anxious (avoidant) personality disorder” (ICD-10: F60.6) (Criterion A). An essential part of social anxieties is the fear of being in the spotlight and being judged by others, which results primarily in the avoidance of such situations and can be quite similar to the behaviour of individuals with an ASD (Criterion A and B).[69] Moreover, already in childhood there can be reduced eye contact and disturbances in the non-verbal communication of individuals with SP, similar to children with ASD.[70] The identification of emotions (Criterion A) can also be impaired in people with a social phobia, but these tend not to appear outside of social demanding situations. Thus, for example, an adequate emotional perspective can be acquired in a family setting. This is explained by a “selective perception of social stimuli” that suggest a negative evaluation, “e.g. rejection or disregard”.[2] However, these impairments are more likely to be stable in any situation for adults with an ASD.

Concerning OCD (F42), substantial overlaps of symptoms in the area of Criterion B exist, since especially in “Predominantly compulsive acts (obsessional rituals)” (ICD-10: F42.1) and “Mixed obsessional thoughts and acts” (ICD-10: F42.2) stereotypical, constantly repetitive behaviour (rituals or collecting habits) typically occur.[12] However, this behaviour can also result in difficulties in “social interaction”, “reduced interest” in “socialising and loneliness” (Criterion A).[2] The fundamental difference, is that the behaviour of people with OCD functions as a prevention against an “objectively unlikely event” but is experienced as “pointless or ineffectual” and “repeated attempts are made to resist” them.[12] This does not apply to individuals with ASD, here the repetitive behaviour is not perceived as unpleasant (only in case of disturbance) and accordingly there is no attempt to avoid it.[71]

In the case of personality disorders (PDs), several different disorders must be included in the differential diagnostic considerations. To begin with, a common characteristic of all PDs must be mentioned, which clearly distinguishes them from an ASD: they are typically diagnosed not before early adulthood and do not already manifest in early childhood.[72] Nevertheless, there are certain similarities which complicate the distinction in the diagnostic, particularly in case of an incomplete anamnesis of the patient’s childhood through a third party.[2] The guideline of the DGPPN[2] includes the following PDs, in which various aspects overlap with the symptoms of ASD:

1) “Schizotypal disorder” (ICD-10: F21): is among other symptoms (“paranoid or bizarre ideas”, “quasi-psychotic episodes” and “magic thinking”) characterized by “eccentric behaviour” and “social withdrawal” (Criterion A).

2) “Schizoid personality disorder” (ICD-10: F60.1): is among other symptoms (“excessive preoccupation with fantasy”) characterized by “social withdrawal”, “marked insensitivity to prevailing social norms and convention is unintentional”, “limited capacity to express either warm, tender feelings or anger towards others” (Criterion A) and “few, if any, activities provide pleasure” (Criterion B).
3) “Narcissistic personality disorder” (ICD-10: F60.8 “other specific personality disorders”): is among other symptoms (feelings of “grandiosity” in relation to their own performance, “need for excessive admiration”, “frequent envy”) characterized by “lack of empathy” (Criterion A).
4) “Anankastic personality disorder” (ICD-10: F60.5): is among other symptoms (“feelings of doubt”, “perfectionism”, “There may be insistent and unwelcome thoughts or impulses that do not attain the severity of an obsessive-compulsive disorder”) characterized by “checking and preoccupation with details” (Criterion B).
5) “Anxious (avoidant) personality disorder” (ICD-10: F60.6): see above.
6) “Dissocial personality disorder” (ICD-10: F60.2): is among other symptoms (“Behaviour is not readily modifiable by adverse experience, including punishment”, “there is a tendency to blame others”) characterized by “reduced empathy” [72] (Criterion A).
7) “Emotionally unstable personality disorder – Borderline-Type” (ICD-10: F60.31): is among other symptoms (“tendency to act impulsively and without consideration of the consequences”) characterized by “major difficulties in interpersonal relationships” (Criterion A), “identity problems”, “difficulties in affect regulation”.[72,73]

(The content in quotation marks above was quoted directly from the ICD-10[12], if not marked otherwise with [72] and [73]).

In addition, there are also some similarities between psychotic disorders and ASD, which complicates the discrimination between these disorders. On the one hand, negative symptoms of schizophrenia can be mistaken for symptoms of ASD, as social withdrawal and other restrictions in social communication and interaction can also occur in schizophrenia (especially in the “Simple schizophrenia” ICD-10: F20.6). On the other hand, the behaviour of people with ASD can also be misinterpreted with positive symptoms of schizophrenia. Fitzgerald et al. (2001) describe several examples such as that the answer of individuals with autism to the question whether “they hear voices when people aren’t there”, might be positive and actually referring to the “voices of people in an adjacent room”.[16] However, the two disorders differ especially with regard to their age of onset and development history.[16] Psychoses usually do not manifest in early childhood and have an episodic course with usually varying symptoms.

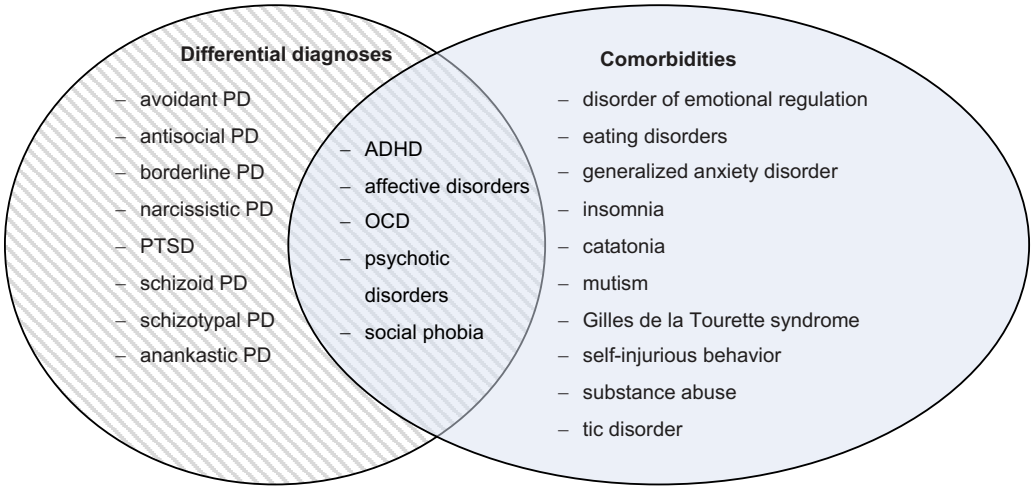
The “attention deficit/ hyperactivity disorder” (ADHD; ICD-10: F90) is also one of the most relevant differential diagnoses, but can also manifest as a comorbidity in individuals with an

ASD.[2] Among children with an ASD, the prevalence of a co-morbid ADHD is estimated to range from 37% to 78%.[74] This disorder is characterized by “inattention” (G1), “hyperactivity” (G2) and “impulsivity” (G3), however, difficulties in correctly recognizing and interpreting emotions as well as deficits in the area of social skills (Criterion A) can also be observed (G1 - G3 criteria of ICD-10[12]).[2,75] Nevertheless, here, restrictive or repetitive patterns of behaviour as known from ASD (Criterion B) is rather untypical.[2]

In this context it must be emphasized that not only manifest disorders must be distinguished in differential diagnostic considerations, but also subclinical “autistic like traits”.[2,76] Thus, the DGPPN guideline[2] mentions that healthy persons or persons with other disorders may also pursue unusual special or “circumscribed interests” (in terms of Criterion B DSM-5).[77] Possibly these individuals are also rather on the borderline between ASD and non-ASD, like SPCD, for whom Criterion A in particular must be fulfilled (see Classification, Symptoms and Diagnostic criteria). If these autistic traits (Criterion A or B) are considered as clinically relevant, it is not uncommon that these individuals are also diagnosed with an “atypical autism” (ICD-10: F84.1).[2] In literature, the term “broader autistic phenotype” is also used for transitional forms, which originally described family members of individuals with autism who showed “subsyndromal” expressions of autistic symptoms (Criterion A and/or B).[61,78]

The difficulties mentioned in distinguishing between differential diagnoses, comorbidities and ASD underlines the importance that diagnostics are done by specialists (see chapter ‘Methods’), especially considering that a wrong diagnosis can have major influences on the course and prognosis of the affected persons.[2] The diagnostic process is followed by therapy, and if this is not adequate, it can further worsen the condition of the patient.

Figure 2.1 *The differential diagnoses and comorbidities of ASD, modified from Lehnhardt et al.(2013)*[17]



PD = personality disorder; ADHD = attention deficit-hyperactivity disorder; PTSD = post-traumatic stress disorder; OCD = obsessive-compulsive disorder

2.2 Intension of this study

2.2.1 On the need for a screening tool and an adequate item analysis of the AQ

As shown in the previous chapter, the identification of autism in adulthood is challenging. The diagnostic process typically involves several sessions with well-trained professionals (for the process in this study see chapter 'Methods') who use clinical tools like the Autism Diagnostic Instrument-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS) to diagnose an ASD.[23] The ADI-R is the revision of a "semi structured, investigator-based interview for caregivers of children and adults" with a suspected ASD by Lord et al. (1994)[79]. ADOS is semi structured, standardised, consists of 4 modules and focuses on the observation of social interaction and communication, whereby the 4th of these modules was designed and is used for adolescents and adults.[80] However, both require frequent, extensive and expensive training and lead to substantial costs for the health care system due to their long execution duration (about 2-3 hours for the ADI-R and 40 minutes for the ADOS module 4 for adults).[2,23] Murphy et al. (2011)[81] estimated the average cost of an ASD-diagnostic for one adult in England at £2305 and in Germany waiting periods for diagnostics are up to one year, which can be very stressful for the affected patients.[20,21] Therefore, before the challenging diagnostic process should be initiated, a screening should be implemented according to the 3-step system of the DGPPN diagnostic guideline for ASD from 2016 (1. Symptoms/ 2. Screening/ 3. Diagnostics)[2]. In the case of adults with suspected ASD, screening is intended to make a preselection and is reasonable due to the already mentioned aspects, such as saving time, money and resources. Several screening tools were developed for this purpose, including the self-assessment questionnaire "Autism-Spectrum Quotient" by Baron-Cohen et al. (2001)[5], which was specifically designed for the target group of normal to highly intelligent adults with suspected autism (see chapter 'Methods'). The AQ is available in several versions and languages, the most relevant being the original full version with 50 items (AQ-50) by Baron-Cohen et al. (2001)[5] and the 10 item (AQ-10) version by Allison et al. (2012)[6], in which 10 items of the AQ-50 were merged into a shorter version. These 10 items were identified in a case-control study, distinguishing best between a group of individuals with an ASD and a healthy control group. The AQ (in all versions) is the only instrument, which is recommended by the NICE guideline development group (GDG) for screening of adults suspected of having an ASD and without an intellectual impairment. It is further recommended that the most time-efficient version AQ-10 should be submitted to this group and if they score above the threshold of ≥6, further special diagnostic assessment is advised.[23]

Problematic, however, is the fact that the AQ-10 was not validated in any other study than the original publication of Allison et al. (2012)[6] until these guidelines were published.[23] Furthermore, this publication was, as already mentioned, a case-control study with a healthy control group, which could have led to several biases. Most important, sensitivity (0.88) and

specificity (0.91) of the AQ-10 were overestimated, as Ashwood et al. (2016)[3] found out in their study with a clinical sample (sensitivity 0.77; specificity 0.29; 476 adults, 346 with ASD). Secondly, this short version was created using items that best separated healthy from autistic individuals. This does not ensure whether these items also distinguish best between a clinical control group and patients with an ASD. A clinical control group in this context are individuals suspected of having autism, but for which a diagnosis could be ruled in a specialized outpatient clinic. With this population the conditions are therefore closer to the reality of an outpatient clinic, because there only individuals suspected of having an ASD are tested and not mentally healthy individuals. Patients in this clinical control group also have difficulties in social interaction, communication or repetitive patterns of behaviour, which make them seek for diagnostic clarification. Therefore, it is unclear if the same 10 items can be detected within this population or whether there are other items of the AQ-50 that would be better suited for this purpose. Therefore, one of the goals of this study is to analyse the items of the AQ-50 to determine whether the same or different 10 best discriminative items apply to a clinical population. To date, there are still only two investigations with a reasonably large clinical samples for the AQ-50, namely the studies of Woodbury-Smith et al. (2005)[7] and Ashwood et al. (2016)[3] besides many studies with general populations (controls were mentally healthy).[2,5,82,83] In these two investigations from Woodbury-Smith et al. (2015)[7] and Ashwood et al. (2016)[3], an adequate sensitivity with a range from 0.88 to 0.95 could be shown, whereas low specificities of 0.20 and 0.52 were achieved (for further information see also chapter 'Sensitivity and Specificity' and 'Table 5.1'). So, the DGPPN[2] recommends that the AQ-50 is probably suitable as a screening instrument, but if the total score of a patient is above the cut-off of ≥26, no further conclusion can be drawn whether a diagnosis is likely or not.

In the following study, the clinical control group only consists of adults suspected of having an ASD, who are considering their own behaviour to be as autistic that they even score above the cut-off and qualify them for the further diagnostic process. Furthermore, the question is addressed whether there are possibly characteristics that influence self-assessment and potentially complicate the separation between individuals with a confirmed ASD from this control group using the AQ. This may relate to gender, age, intelligence or a comorbid depression. And if there are such characteristics, is it possible to achieve better screening results by controlling them statistically?

2.2.2 Influence of gender and age on the self-assessment of autistic traits

Due to the low specificity and thus close resemblance in assessing their autistic traits, along with a sufficient inter-rater- and test-retest-reliability, it seems reasonable to conclude, on the one hand, that there are undeniable commonalities between the group of affected individuals and the clinical control group.[23] On the other hand, it could be assumed that the validity of the questionnaire is limited.[23] Reliability as well as validity are psychometric quality criteria for a

test. Reliability describes how much of the variance of the results is due to actual differences or errors in measurement.[84] The inter-rater-reliability describes the correlation between the results of two different observers (raters) examining the same subject with the same test and the test-retest-reliability is a method to estimate the reliability by performing the same test twice on the same subjects, at a different time.[23] The NICE guideline on "recognition, referral, diagnosis and management of adults in the autism spectrum"[23] recommends a $r \geq 0.70$ as "relatively reliable". The validity of a measurement is the degree to which a test actually measures what it is intended to measure. The criterion validity refers to the correlation between the test result and an already existing method on the same subject. This can be separated again into predictive validity, where the new test should predict the result of the established test and the concurrent validity, where the two measurements are performed simultaneously and the results will be correlated. [23,85] In the already mentioned NICE guideline on adults in the autism spectrum, construct validity is also mentioned, which is further categorized into discriminant validity and convergent validity. [23,86] With the construct validity the extent to which the test measures the theoretical construct should be estimated.[87] With the convergent method tests are correlated that are supposed to measure the same construct. For discriminant validity, tests that are designed for different constructs should not correlate.[23]

Regarding the first conclusion, that there are undeniable similarities between the group of affected individuals and the clinical control group, it has already been discussed on the level of the various diagnoses in the previous chapter 'Comorbidity or differential diagnosis?'. However, these commonalities can only be determined for the individual after a completed and extensive diagnostic process.

This study addresses the question whether common characteristics could exist beyond the level of diagnosis, which could already be determined before diagnostics and could have an influence on the results of this self-assessment questionnaire. The patient characteristics gender and age are relatively simple to determine, even before diagnostics.

2.2.2.1 *Gender*

There is existing evidence that gender has an influence on the self-assessment of autistic traits in individuals with an ASD. In the study by Lai et al. (2011)[8], women with an ASD had significantly higher AQ scores than their male counterparts with an ASD matched in age and IQ. Lai et al. (2011)[8] see this result in the context of different gender "phenotypes" (male and female phenotype), which have already been discussed in the literature. Several epidemiological studies support the hypothesis of these phenotypes, since it could be shown that women with an ASD and without intellectual disability are diagnosed significantly later in life and that the identification of females with an ASD is more difficult than in their male counterparts, which could even lead to underrepresentation in their identification.[88,89,90,91,92,93] Lehnhardt et al. (2016)[24] and Lai et al. (2017)[93] discuss in this context, that women with an

ASD are probably more likely to camouflage their difficulties in social interaction, due to different "sex-related cognitive profile(s)"[24]. Lehnhardt et al. (2016)[24] could show that men who were diagnosed with ASD in adulthood had higher verbal abilities than their female counterparts, but females had higher processing speed and better executive functions. This, combined with the fact that both sexes were not diagnosed until adulthood, led them to the hypothesis that there must be different "sex-distinctive cognitive strategies".[24]

Furthermore, assuming that there are different phenotypes, a certain "gender bias" should be considered as well, since the diagnostic instruments were mainly standardized on male individuals.[61] Already Asperger (1944)[94] described the "autistic psychopathy" in his same titled report on the basis of 4 boys and no girls.[8]

Now the question arises whether the results on the different AQ scores between the genders described by Lai et al. (2011)[8] can be replicated in a large clinical population? And how do women and men in a clinical control group assess their autistic traits? Are there also clear tendencies or is this phenomenon limited to females with ASD?

2.2.2.2 *Age*

To date, there are hardly any studies that investigated age as a possible influence on the AQ, and in general little is known about the extent to which autistic symptoms develop over the years in adults.[95] One of the few studies dealing with this topic is the one by Siebes et al. (2018)[95] with 654 adults with an ASD of an outpatient clinic (Radboud University Hospital). In their investigation on the basis of 5 age groups (18-30, 30-40, 40-50, 50-60, >60) no significant influence of age on the AQ in individuals with ASD could be determined. However, Woodman et al. (2015)[9] demonstrated in their study that the severity of symptoms observed through the mothers (determined by means of the ADI-R) decreases with age in people with ASD. So, on the one hand there are results that age has no influence on the self-evaluation of autistic traits, on the other hand we have indications that the observable symptoms decrease with age in individuals with autism. The question remains whether the results of Siebes et al. (2018)[95] are replicable and if so, what could this hypothetical discrepancy of self-assessed and observed symptoms mean. How do individuals of a heterogeneous clinical control group evaluate their autistic traits depending on their age and are there differences in self-assessment compared to individuals with an ASD?

2.2.3 Influence of intelligence on the self-assessment of autistic traits

At first, the difference between the psychological concept of intelligence and the parameter intelligence quotient (IQ) should be explained. One possible and widespread definition of intelligence is: "Intelligence is a very general mental capability that, among other things, involves the ability to reason, plan, solve problems, think abstractly, comprehend complex ideas, learn quickly and learn from experience" (Gottfredson 1994)[96]. Correspondingly, the IQ

is the numerical and standardized parameter which is supposed to represent these cognitive functions by means of intelligence tests.[97] In general, the IQ can be based on different scales, but in the following the quotient refers always to the Wechsler intelligence scale including the subtests Verbal- (VIQ) and Performance-IQ (PIQ). At this point, it must be emphasized that, next to this definition, other aspects of intelligence are also being discussed, such as the multiple intelligences by Howard Gardener and the emotional intelligence.[97,98] These aspects are not represented in the IQ measured with instruments mentioned in this study.

Regarding ASD, Bishop et al. (2012)[25] found in their study with 65 adults with autism, that individuals with a normal to high IQ scored significantly higher in the AQ than individuals with a reduced IQ. But no correlation was found between IQ and the severity of symptoms observed by the caregivers (using ADI-R), so the question arose whether the IQ is a confounding variable and interfere with self-assessment. Given that the AQ was originally designed for normal to highly intelligent individuals, this study will investigate whether the IQ has an influence on the AQ for this range. So far it has not been investigated whether IQ has an effect on AQ in adults without intelligence impairment where a diagnosis was excluded. Furthermore, it will also be determined whether the IQ differs significantly between the autistic and the non-autistic group, also in order to choose the adequate statistical method for the other calculations. In addition, this study will investigate whether Verbal- and Performance-IQ (VIQ and PIQ) vary within the groups. There are several studies suggesting that there are significant differences between VIQ and PIQ in individuals with an ASD. Nevertheless, Ambery et al. (2006)[99] state in their study with adults that the “VIQ-PIQ discrepancy” (“VIQ>PIQ or PIQ>VIQ”) can be shifted in both directions. Similar results were found in the study of Ozonoff et al. (2000)[45] with 35 children with AS and HFA and Black et al. (2009)[100] with highly functional children with an ASD.[101] Regarding adults with an ASD, in the study by Lehnhardt et al. (2016)[24] with 38 females and 69 males with an ASD, the VIQ>PIQ discrepancy could only be detected in males. This leads to the question how the ratio between VIQ and PIQ is in this sample (with normal to high intelligent individuals), since results do not appear to be consistent in this respect.

2.2.4 Influence of depressive symptoms on the self-assessment of autistic traits

As already mentioned in the previous chapter ‘Comorbidity or differential diagnosis?’, depressive disorders are not only the most common comorbidity but also an important differential diagnosis. In this study, several aspects of depressive symptoms respectively their self-report using the BDI will be investigated in the context of a sample of an autism outpatient clinic. Initially, it should be determined how severe the depressive symptoms are in the individuals who undergo the diagnostic process in our outpatient clinic. Up to this date there is hardly any data on whether the self-assessment of depressive symptoms differs significantly between people with an ASD and those with an excluded diagnosis. Furthermore, there is only limited data on whether self-assessment of depressive symptoms and autistic traits correlate.

Due to overlapping symptoms (see chapter 'Comorbidity or differential diagnosis?') and the cognitive aspect of depression that can lead to a distorted self-image, the question remains whether (and if so in which direction) depressive symptoms influence the self-assessment of autistic traits in adults with ASD or exclusion of this diagnosis. In the study by Berthoz et al. (2013)[102] including 125 adults with ASD and 47 healthy individuals of the control group, no significant correlation between BDI and AQ-50 was found. In their calculation, however, mean scores of AQ-50 and BDI of the entire sample were correlated and not divided into an exclusion group and an ASD group. On the other hand, Liew et al. (2015)[103] found significant positive correlations between autistic traits and depressive symptoms in their study. These findings, however, are based on 252 healthy students from the National University of Singapore who completed the AQ-50 to measure autistic traits and the Inventory of Depression and Anxiety Symptoms (IDAS), also a self-assessment questionnaire to measure depressive symptoms. Findings do not appear to be clear in this respect, especially in a clinical population.

2.2.5 Sensitivity and Specificity

Sensitivity and specificity are statistical probabilities in order to describe the quality of a diagnostic test from the researcher's point of view.[104, 105]

The sensitivity should predict the number of affected individuals identified as true positive (true positive rate), in case of the AQ: the proportion of individuals with an ASD above the cut-off (the letters A, B, C, D refer to the contingency Table 2.3).[106]

Sensitivity = $\frac{A}{(A+C)}$

Specificity is the probability with which healthy individuals should be predicted to be true negative (true negative rate), meaning in terms of the AQ: individuals below the cut-off and without an ASD.[106]

Specificity = $\frac{D}{(D+B)}$

As already described in the introduction, varying sensitivities (0.77 – 0.95) and specificities (0.20 – 0.98) of the AQ-50 were assessed in the different studies, especially depending on the population (healthy vs. clinical control group) and the cut-off (≥32 or ≥26) on which the investigators based their research.[5] In this study, only individuals who scored above the cut-off ≥26 in the AQ-50 went through the diagnostic process (see below in 'Methods'). Therefore, no actual sensitivity and specificity can be determined here for the general population or adults suspected of having an ASD, who have not already completed the AQ-50 or scored above this threshold. In order to be able to compare the quality of the questionnaires in the different calculations, sensitivity and specificity are calculated in the following, although they do not correspond to 'real' but relative probabilities.

It will be investigated how the relative sensitivity and specificity of AQ-50 changes within this population after splitting the sample according to patient characteristics gender and age, in

order to control these variables. If different items for the 'new' AQ-10 result from the item analysis of the AQ-50 (see chapter 'On the need for a screening tool and an adequate item analysis of the AQ'), relative sensitivity and specificity should also be determined here.

Table 2.3 *Contingency table, compare Harris and Taylor (2003)*[106]

	Condition present	**Condition absent**
Test positive	A (true positive)	B (false positive)
Test negative	C (false negative)	D (true negative)

2.2.6 An explorative-quantitative study

At this point it should be emphasized that this is a retrospective and explorative-quantitative study, intended primarily to generate further hypotheses.[107] In contrast to a confirmatory (hypothesis-testing) study, where the hypotheses are formulated before the actual examination, here the hypotheses are formally established at the end of the study.[108] Before a hypothesis can be established, some kind of observation or exploration of the object must have taken place and in a next step this hypothesis can be tested in further investigations.[84] Concerning research on autism in adulthood, there are hardly any studies available on the basis of a clinical population and there is no study with a comparable sample size dealing with these questions. In particular, the highly heterogeneous control group presented here, which includes adults who were initially suspected of having an ASD, but where the diagnosis could be ruled out in a complex diagnostic process, is vastly underrepresented in previous research, but is of great relevance for clinical practice. By comparing a group of individuals with an ASD with this control group, hypotheses are expected to be developed that may explain the limited ability of previous screening and, if possible, eventually improve the pre-selective potential of a screening-tool for ASD in adulthood in the future.

3. Methods

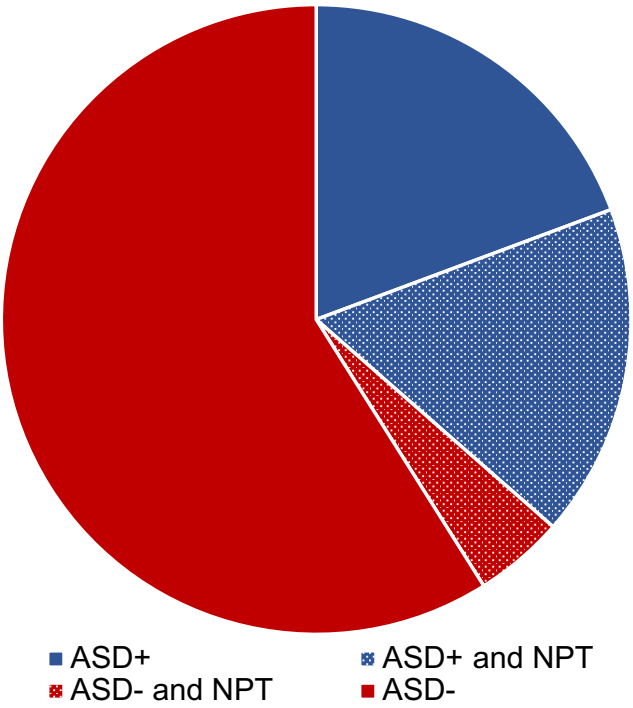
In this chapter the sample of this study will be presented first, followed by the self-assessment questionnaires AQ-10, AQ-50 and Beck Depression Inventory (BDI) along with the testing of the intelligence by means of the Wechsler-Adult-Intelligence-Scale-III (WAIS-III). At the end of this chapter, the applied statistical methods are described.

3.1 Participants

A total of 1814 adults were registered in the data acquisition, who completed the diagnostic process at the Autism Outpatient Clinic for Adults Department of Psychiatry and Psychotherapy, University Hospital of Cologne between the years 2007 and 2018. Only individuals over 18 years of age, who were assigned to the outpatient clinic by a psychiatrist with a suspected ASD and also scored above the cut-off of ≥26 in the AQ-50 were accepted for further diagnostics and thus for this study. The diagnostic process includes two independent clinical interviews. In addition to the ICD-10[12] and DSM-IV[43] diagnostic criteria, information about symptoms with social relevance that persists time and situation were obtained if available. For example close relatives or spouses have been interviewed regarding social development during childhood and adolescence, based on the ADI-R.[80] An extensive neuropsychological-testing (NPT) was performed in the period between the two interviews with regards to intelligence, executive functions, mentalizing abilities or suspected depressive symptoms.[109] In patients where an ASD already could be ruled out after the first interview, no NPT was performed.

Due to the item analysis, only patients who completed the AQ-50 questionnaire without missing items could be considered, so that 1382 of the initial 1814 individuals were included in this study. 528 of these 1382 patients (38%) were first-time diagnosed with ASD (here ASD+) and in 854 patients (62%) ASD diagnosis was ruled out, representing the clinical control-group (here ASD-). NPT was performed on 315 of the 1382 patients in this study and data on IQ (WAIS-III) and BDI were included here. Individuals with intellectual impairment (IQ<70) were excluded, since it must be assumed that they have problems with self-report and would not answer the questionnaire on their own.[25] For a graphical explanation of the division of the participants see Figure 3.1. Sending the AQ-50 as a screening-tool and data storage with given informed consent began in 2007.

Figure 3.1 *Distribution of the participants: 1382 adults (whole sample); 528 ASD+ (blue with and without texture), 248 ASD+ and NPT (only blue with texture); 854 ASD- (red with and without texture), 67 ASD- and NPT (only red with texture).*



3.2 Measures

3.2.1 The AQ

The full-length Autism-Spectrum Quotient (AQ-50) is a self-assessment questionnaire by Baron-Cohen et al. (2001)[5] consisting of 50 items covering 5 different domains, with 10 items each: 'social skills' (items: 1,11,13, 15, 22, 36, 44, 45, 47, 48); 'attention switching' (items: 2, 4, 10, 16, 25, 32, 34, 37, 43, 46); 'attention to detail' (items: 5, 6, 9, 12, 19, 23, 28, 29, 30, 49); 'communication' (items: 7, 17, 18, 26, 27, 31, 33, 35, 38, 39); 'imagination' (items: 3, 8, 14, 20, 21, 24, 40, 41, 42, 50).

One point can be scored for each item if the response is characteristic for autistic-like behaviour, so that the AQ range from a minimum of 0 to a maximum of 50 points and higher scores suggesting more autistic traits.[5]

These 5 factors and respective items were selected according to the psychopathology of ASD (see also above in chapter 'Classification, Symptoms and Diagnostic criteria,' or Table 2.2), so individuals who score highly have few social skills, few communication skills, poor imagination, outstanding attention to detail and poor attention switching.[5] Patients are instructed to choose between the four responses: "definitely agree", "slightly agree", "definitely disagree" and "slightly disagree". However, these responses are summarized only to either "agree" or "disagree" to achieve a dichotomous result.

In order to reduce a response-bias, the questions were formulated that one half of the items produced a score with the response “disagree” and the other half with “agree”. For the following items one point is scored in case of agreement (“definitely agree”, “slightly agree”): 2, 4, 5, 6, 7, 9, 12, 13, 16, 18, 19, 20, 21, 22, 23, 26, 33, 35, 39, 41, 42, 43, 45, 46. For the following items one point is scored in case of disagreement (“definitely disagree” and “slightly disagree”): 1, 3, 8, 10, 11, 14, 15, 17, 24, 25, 27, 28, 29, 30, 31, 32, 34, 36, 37, 38, 40, 44, 47, 48, 49, 50. Because participants were recruited in Germany, the German version of the AQ was used, translated by Freitag et al. in 2007.[110]

In the Autism Outpatient Clinic for Adults in Cologne the cut-off of ≥26 proposed by Woodbury-Smith et al. (2005)[7] was applied, which achieved in their study a sensitivity of 93% and a specificity of 52% in a clinical sample (with 100 adults suspected of having autism). Allison et al. (2012)[6] analysed the AQ-50 on the basis of individuals with autism and a mentally healthy control group and selected 2 items per subscale (5 subscales, as described above), which best distinguished between the groups. With these 10 most discriminating items (5, 20, 27, 28, 31, 32, 36, 37, 41, 45) they formed the short-version AQ-10 and reached a sensitivity of 0.88 and a specificity of 0.91 with a cut-off of ≥ 6 in a validation sample (419 individuals in the healthy control group, 225 adults with autism).[6] In the following study, we calculated AQ-10 scores from values of these 10 items of the AQ-50 in this sample. The complete AQ-50 questionnaire can be found in the appendix (Table 7.2).

3.2.2 The IQ

Intelligence was tested as part of neuropsychological assessment with the German version of the Wechsler-Adult-Intelligence-Scale-III (WAIS-III), the “Wechsler Intelligenztest für Erwachsene” (WIE).[111,112]

The traditional 11-subset combination with “Information”, “Digit Span”, “Vocabulary”, “Arithmetic”, “Comprehension”, “Similarities”, “Picture Completion”, “Picture Arrangement”, “Block Design”, “Matrix Reasoning”, and “Digit-Symbol-Coding” was tested, but only Full-Scale (FSIQ), Verbal- (VIQ) and Performance-IQ (PIQ) were taken into account in this study.[112]

3.2.3 The BDI

The Beck Depression Inventory (BDI) was used to record accompanying depressive symptoms and is also a self-reported screening-tool compromising 21 items.[113] Each item is rated with 0-3 points, which gives a maximum of 63 points and a minimum of 0 points.

Furthermore, the score can be divided into the categories “no depression” (0-9 points) and the severity levels of mild to moderate depressive symptoms (10-17 points) and clinically relevant depressive symptoms (>17 points).[113]

3.3 Statistics

Statistical analysis of the data was performed using Microsoft Excel 2016 and IBM SPSS Statistics 25 for Mac ("Statistical Product and Service Solution"). Graphs were created with IBM SPSS Statistics 25 and Microsoft PowerPoint 2016. As mentioned above, only individuals who completed the questionnaire without missing items and without intellectual impairment (IQ≥70) were included in this study. All *p*-values shown are two-tailed and are assumed to be statistically significant from ≤ 5%.[114]

3.3.1 The exploration of possible influences of the variables diagnosis, gender, age, IQ and BDI on the psychopathological self-assessment of autistic traits

In order to decide which tests should be conducted to explore possible influences of the above-mentioned variables, it was first examined whether the assumptions for parametric procedures were met. The assumption of normality for the AQ-50 and its subscales, the AQ-10, the BDI and age was considered as not fulfilled, so that only non-parametric tests could be utilised for these issues. Figure 3.2 illustrates the comparison of a normal distribution (black curve) with the distribution of the AQ-50 scores (blue histogram). The distribution of age of the entire sample is shown in Figure 4.1. To assess the influence of the diagnosis ASD on the self-assessment of autistic traits, the Mann-Whitney *U* test was selected. As a non-parametric test, it assigns ranks to the measured values and compares the distribution of the scores between the groups using these ranks.[115]

To explore the influence of gender on the AQ also in connection with the diagnosis of an ASD, several Mann-Whitney *U* tests were performed. Thus, the sample was first split into ASD+ and ASD- and subsequently scores from the AQ-50, AQ-10 and the subscales were compared between males and females.

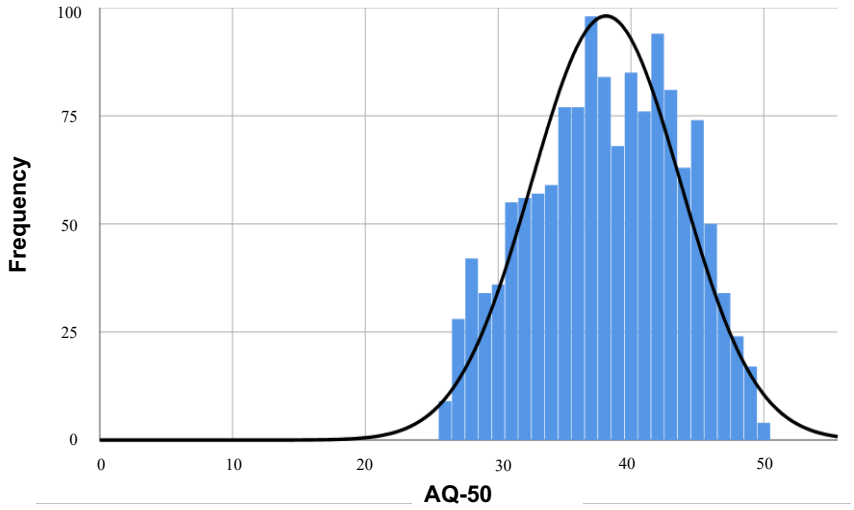
In order to investigate possible relationships between age, ASD and the AQ, several Spearman's correlations were performed. Spearman's correlation also belongs to the non-parametric statistics and operates over ranked data.[114] Here, the sample was also first divided into ASD+ and ASD- and then age was correlated with the AQ scores. The same approach was chosen for the exploration of possible influences of IQ and depressive symptoms on the AQ depending on the diagnosis of an ASD.

To explore whether depressive symptoms have an impact on the IQ in this sample, the BDI was correlated with the FSIQ.[109] According to the definition of the BDI, "clinically relevant depressive symptoms" are present, if the score is above the cut-off (BDI >17).[113] Therefore, a biserial correlation with the dichotomous variable 'clinically relevant depressive symptoms' and the metric variable FSIQ was calculated. For the dichotomous variable the values 'not present = 0' (BDI score ≤ 17) and 'present = 1' (BDI score > 17) were defined. Since the variables FSIQ, PIQ and VIQ were considered to be normally distributed, the parametric independent-samples *t*-test could be chosen for the comparison of these values between ASD+ and ASD-.

3.3.2 Item and Receiver Operating Characteristic (ROC) analyses

To ascertain how well the items distinguish between ASD+ and ASD-, the Discrimination Index (DI) was calculated for each item. These indices were computed by subtracting the percentage of ASD- that scored one point for an item, from the percentage of ASD+ that also scored a point for the same item and then this value was divided by 100.[6] The DI ranges from -1 to 1 and 0 means that an item was answered identically by both groups. According to Gillis et al. (2011)[116] and Allison et al. (2012)[6], items of a test are found to be good if the DI is between 0.3 and 0.7 (respectively between -0.3 and -0.7). In determining how well the AQ would differentiate between ASD+ and ASD-, if we divide the sample according to gender and age in this study, receiver operating characteristic (ROC) were carried out and the area under the curve (AUC) were determined. The ROC curve is plotted on a graph where the sensitivity is represented on the y-axis and "1-specificity" on the x-axis (see Figure 4.13 – Figure 4.16).[117] This curve can be used to visualize the performance of a diagnostic procedure. The AUC is the measure that is calculated from the area under this curve and can be used to compare the quality of different diagnostic tests among each other. The closer the AUC tends towards 1, the better the test. An area of 0.5 would correspond to a completely random decision and thus the worst possible test.[118] A test with an AUC of 0.9 - 0.99 is defined as an "excellent test", with 0.8 - 0.89 a "good test", with 0.7 - 0.79 a "fair test" and with 0.51 - 0.69 a "poor test" according to Carter et al. (2016)[119]. As already mentioned above (chapter 'Sensitivity and Specificity'), no 'real' sensitivities and specificities can be calculated in this study, but relative probabilities due to the pre-selection (only individuals with a score ≥26 were included here). However, these relative sensitivities and specificities allow a comparison of the different tests in this study, as they were investigated using the same sample.

Figure 3.2 *The distribution of AQ-50 scores (blue histogram) of the 1382 individuals included in this study, compared to a curve of a normal distribution (black curve).*



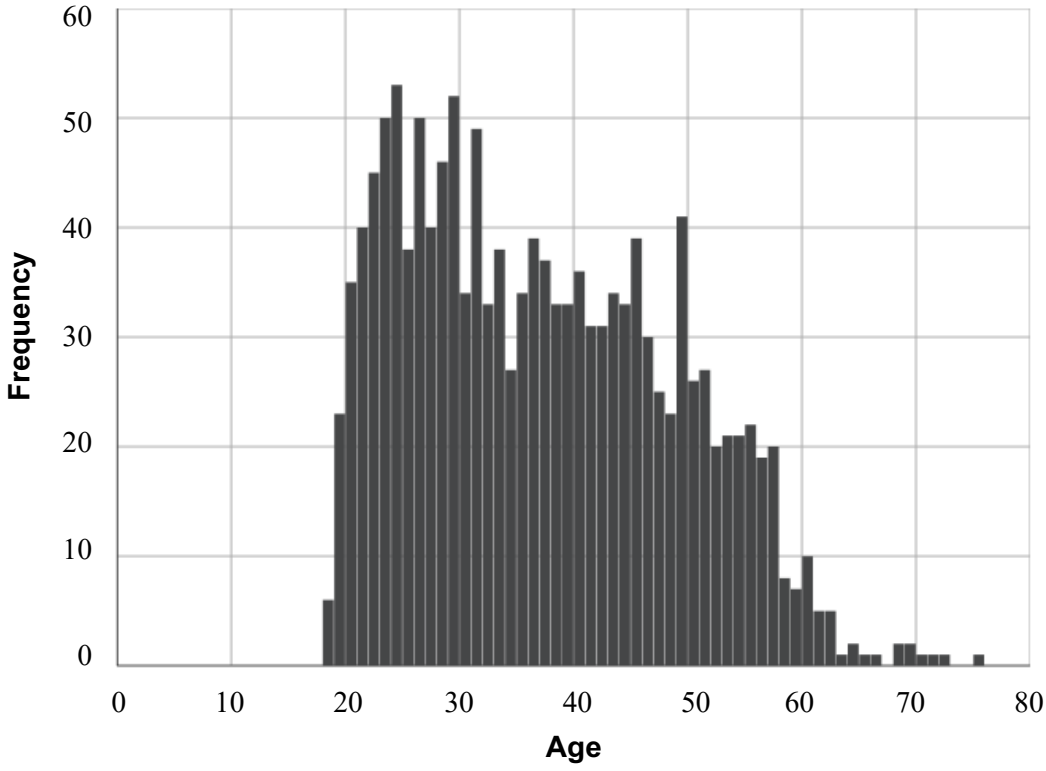
x-axis = AQ-50 scores; y-axis = Frequency as absolute values; N = 1382; Total Median = 38; skewness = - 0.151; kurtosis = -0.814

4. Results

4.1 Patient characteristics

The age of the 1382 included individuals ranged from 18 to 75, with a median of 35 years of age. Of these adults, 25% were younger than 27 years old and another 25% were older than 45 (see Figure 4.1 and Figure 4.7). The sex ratio between men and women in the whole sample and in ASD+ and ASD- was about 2:1 (Table 4.1 and Figure 4.3). 315 individuals had neuropsychological assessment (ASD+ *n* = 248; ASD- *n* = 67) with a median age of 33. Of these 315 adults, 217 were males (ASD+ *n* = 176; ASD- *n* = 41) and 91 were females (ASD+ *n* = 65; ASD- *n* = 26).

Figure 4.1 *Age distribution - whole sample.*



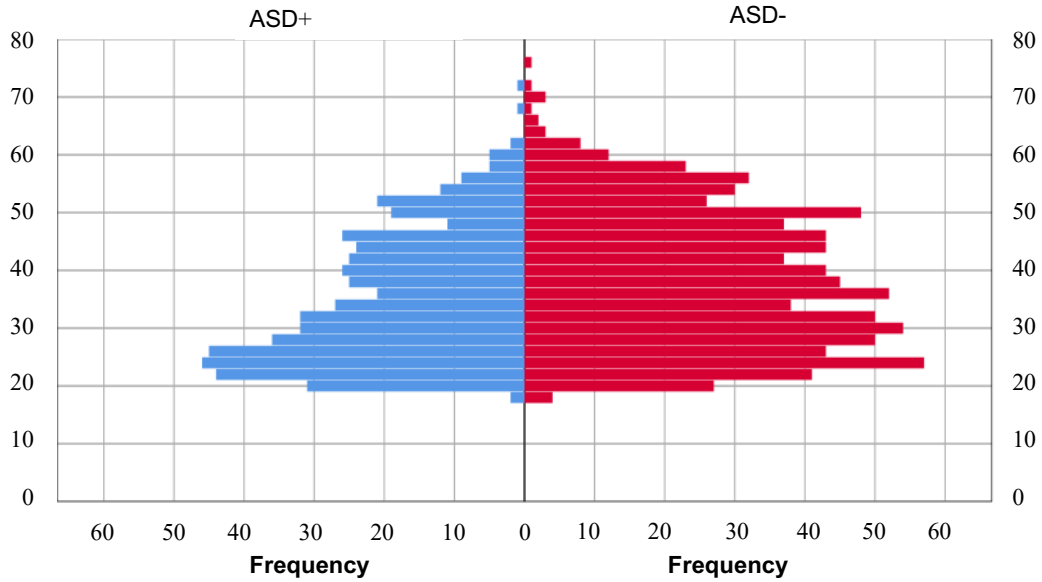
x-axis = Age; y-axis = Frequency as absolute values; N = 1382; Total Median = 35

Table 4.1 *Patient characteristics, mean AQ-50/ AQ-10 and subscale scores (AQ-50).*

	Mean age (S.D.)	Median age	Male/ Female	Mean AQ-50 (S.D.)	Mean AQ-10 (S.D.)	Social skills (S.D.)	Attention switching (S.D.)	Attention to detail (S.D.)	Communication (S.D.)	Imagination (S.D.)
All (*N*=1382)	36.6	35	910/ 472	38.1	7.7	8.6	8.6	7.0	7.5	6.4
100%	(11.6)			(5.6)	(1.9)	(1.5)	(1.4)	(2.2)	(1.8)	(2.1)
ASD+ (*n*=528)	34.4	32	366/ 162	39.0	8.0	8.8	8.6	7.1	7.8	6.8
38%	(11.0)			(5.7)	(1.8)	(1.6)	(1.4)	(2.2)	(1.8)	(2.1)
ASD- (*n*=854)	38.0	37	544/ 310	37.6	7.6	8.4	8.6	6.9	7.4	6.2
62%	(11.7)			(5.5)	(1.9)	(1.6)	(1.4)	(2.2)	(1.8)	(2.1)

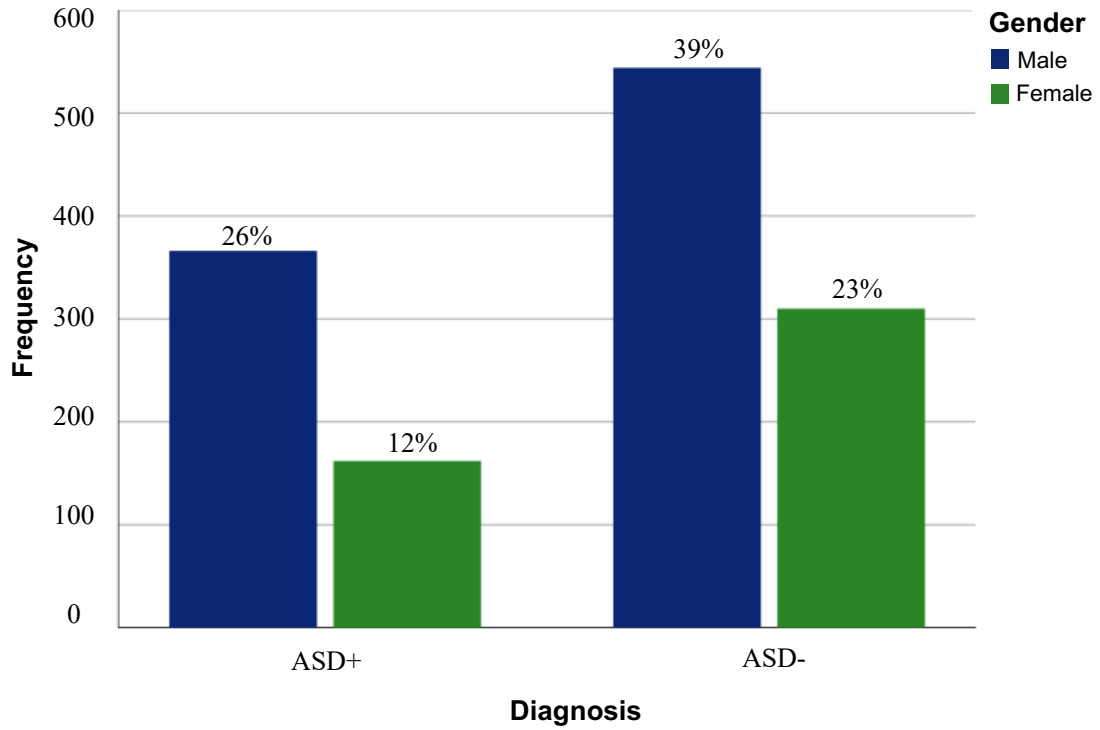
S.D. = standard deviation

Figure 4.2 *Age distribution: ASD+ (blue) vs. ASD- (red).*



x-axis = Frequency as absolute values; y-axis = Age; ASD+ n = 528; ASD+ Median age= 32; ASD- n = 854; ASD- Median age = 37

Figure 4.3 *Grouped bar chart for diagnosis and gender.*



y-axis = Frequency as absolute values; percentages above the bar charts refer to the total sample

4.2 Relationship between Diagnosis and AQ

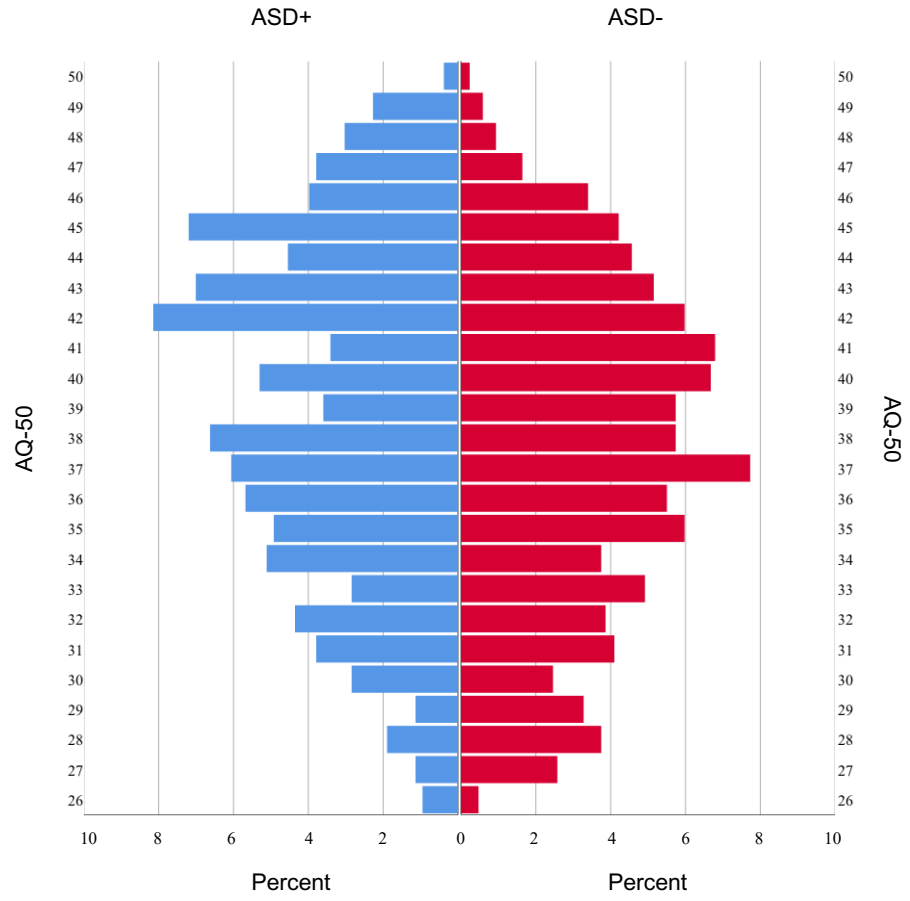
ASD+ had higher AQ-50 values (median = 39) than ASD- (median = 38). This difference was significant $p<0.001$ (Mann-Whitney *U* test, asymptotic significance 2-sided) so, the null hypothesis that the distribution of the AQ-50 is the same across ASD+ and ASD- could be rejected. This difference was minor with only one point difference in the median and represented a small effect size ($r = -0.12$), '*r*' was calculated according to Rosenthal (1991) $r = \frac{z}{\sqrt{N}}$.[114, 120] A comparable result could be found for the subscale 'imagination' (see Table 4.2). In the AQ-10 and the subscale 'communication' the median did not differ, but the first quartile was higher for ASD+ than ASD-; according to the Mann-Whitney *U* test the distribution of values between the groups was significantly different (see Table 4.2). In the subscale 'social skills' quartiles were equal, but the distribution was significantly different according to the Mann-Whitney *U* test ($p < 0.001$). 43.4% of ASD+ scored 10 points in this subscale, compared to 32.8% of ASD-, which indicates that ASD+ tends to score higher in 'social skills' (meaning that they rated their social skills lower than ASD-). For subscales 'attention switching' and 'attention to detail' the distributions of values were comparable between ASD+ and ASD-. For results see Table 4.2, for a graphical comparison see Figure 4.4 and for the interpretation of effect sizes see Table 7.1 in the appendix.

Table 4.2 *Mann-Whitney U tests between ASD+ and ASD- concerning the AQ-50, AQ-10 and subscales.*

	First quartile		Median		Third quartile		*p*	*z*	*r*
	ASD+	ASD-	ASD+	ASD-	ASD+	ASD-			
AQ-50	35	33	39	38	44	42	<0.001	4.442	0.12**
AQ-10	7	6	8	8	9	9	0.001	3.477	0.09**
Social skills	8	8	9	9	10	10	<0.001	4.402	0.12**
Attention switching	8	8	9	9	10	10	0.817	0.231	0.01
Attention to detail	6	5	7	7	9	9	0.218	1.231	0.03
Communication	7	6	8	8	9	9	<0.001	4.516	0.12**
Imagination	5	5	7	6	8	8	<0.001	4.418	0.12**

*N (sample size) = 1382; * Significance at the 0.05 level; ** Significance at the 0.01 level; z = standardized test statistic; r was calculated according to Rosenthal (1991)* $r = \frac{z}{\sqrt{N}}$ [114,120]

Figure 4.4 *The distribution of the AQ-50 values of ASD+ and ASD- in percent.*



x-axis = Percentages refer to the respective group; y-axis = AQ-50 scores; AQ-50 Median ASD+ = 39; AQ-50 Median ASD- = 38

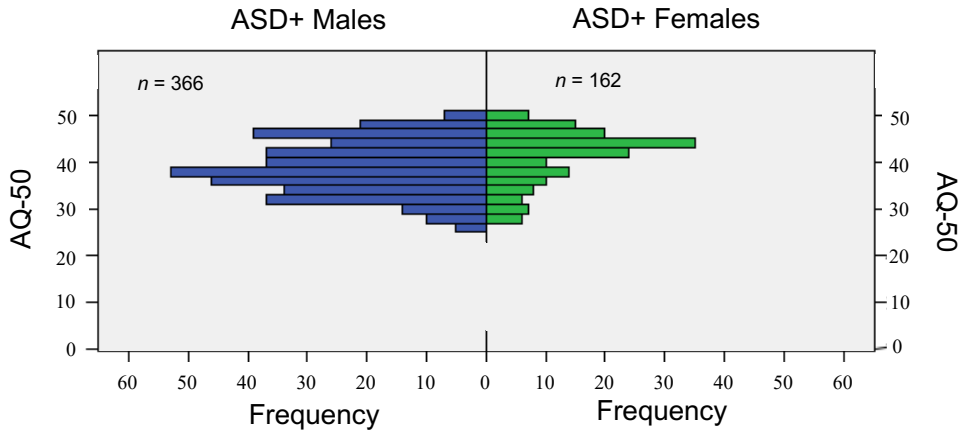
4.3 Relationship between Gender, Diagnosis and AQ

In the following, several Mann-Whitney *U* tests were conducted to explore the influence of gender on the psychopathological self-assessment of autistic traits, in relation to the diagnosis of an ASD.

In both ASD+ and ASD-, females scored higher on the AQ-50 than their male counterparts (ASD+ median difference = 4; ASD- median difference = 1.5). These differences were significant at the 0.01 level and the effect sizes (ASD+: *r* = 0.2; ASD-: *r* = 0.1) were minor,

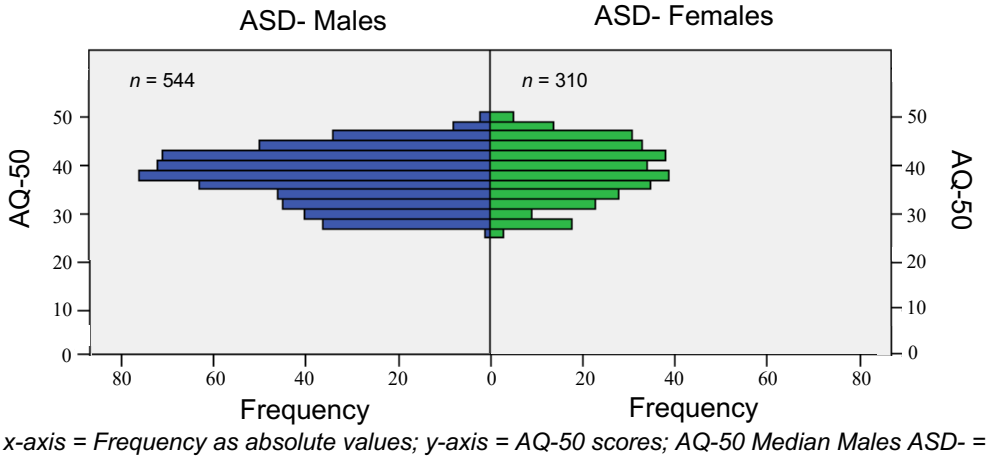
similar to that of the variable diagnosis (see above 'Relationship between Diagnosis and AQ'). The distributions of the AQ-50 scores of males and females are shown in Figure 4.5 for ASD+ and in Figure 4.6 for ASD-, for results see Table 4.3. Females also scored significantly higher than males on the AQ-10 and subscales 'social skills', 'attention switching' and 'communication', independent of the diagnosis of an ASD. Only for the subscale 'attention switching' quartiles were equal for males and females (see Table 4.3). However, the distribution of the scores shows that females scored higher than their male counterparts (42.2% of ASD+ females vs. 29.5% of ASD+ males scored 10 points; 39.0% of ASD- females vs. 27.2% of ASD- males scored 10 points). For the factor 'attention to detail' only a significant difference (significant at the 0.05 level) was found in ASD+. In the subscale 'imagination', no significant differences between genders could be explored, neither in ASD+ nor in ASD-.

Figure 4.5 *The distribution of AQ-50 values compared between males and females in ASD+.*



x-axis = Frequency as absolute values; y-axis = AQ-50 scores; AQ-50 Median Males ASD+ = 38; AQ-50 Median Females ASD+ = 42

Figure 4.6 *The distribution of AQ-50 values compared between males and females in ASD-.*



x-axis = Frequency as absolute values; y-axis = AQ-50 scores; AQ-50 Median Males ASD- = 37; AQ-50 Median Females ASD- = 38.5

Table 4.3 *Mann-Whitney U tests between Males and Females concerning the AQ-50, AQ-10 and subscales in ASD+ and ASD-.*

				AQ-50	AQ-10	Social skills	Attention switching	Attention to detail	Communication	Imagination
ASD+	Males/ Females	**First quartile**	Males	34	7	8	8	5.75	6	5
***n*=528**	*n* =366/ 162		Females	37	8	9	8	6	7	5
		Median	Males	38	8	9	9	7	8	7
			Females	42	9	10	9	8	9	7
		Third quartile	Males	43	9	10	10	9	9	8
			Females	45	10	10	10	9	10	9
			p (2-tailed)	<0.001	<0.001	<0.001	<0.001	0.017	<0.001	0.217
			z	4.647	3.808	3.547	3.939	2.39	4.733	1.100
			r	0.20**	0.17**	0.15**	0.17**	0.10*	0.21**	0.05
ASD-	Males/ Females	**First quartile**	Males	33	6	7	8	5	6	5
***n*=854**	*n*=544/ 310		Females	34	7	8	8	5	7	5
		Median	Males	37	8	9	9	7	7	6
			Females	38.5	8	9	9	7	8	6
		Third quartile	Males	41	9	10	10	9	9	8
			Females	43	9	10	10	9	9	8
			p (2-tailed)	0.004	0.008	<0.001	<0.001	0.151	0.001	0.191
			z	2.864	2.657	3.513	3.686	1.435	3.354	-1.309
			r	0.10**	0.09**	0.12**	0.13**	0.05	0.11**	-0.04

*n = group size; * Significance at the 0.05 level; ** Significance at the 0.01 level; z = standardized test statistic; r was calculated according to Rosenthal (1991)* $r = \frac{z}{\sqrt{N}}$ [114,120]

4.4 Relationship between Age, Diagnosis and AQ

The median age of ASD+ was 32 and that of ASD- was 37 (total median = 35), this difference was significant according to the Mann-Whitney *U* test ($p < 0.001$; $r = 0.15$; see also Figure 4.7). For the exploration of possible relationships between age, diagnosis and the AQ, the sample was again split into ASD+ and ASD- first, then the variable age was correlated with the different scores. In this sample, a significant influence of age on the AQ-50 was observed in ASD+ ($p < 0.001$) and in ASD- ($p < 0.001$). As can be seen from the positive correlation coefficient *r* (ASD+ $r = 0.33$; ASD- $r = 0.13$) and also in the scatterplots and the corresponding regression lines (Figure 4.8, Figure 4.9 and Figure 4.10), older individuals tended to score higher in the AQ-50 than their younger counterparts. However, this influence seems to be greater in ASD+ than in ASD-, as the effect size falls in the medium range for individuals with an ASD and in the low range for patients without this diagnosis.

In the subscales 'social skills' and 'imagination', the influence of age was comparable between the two groups ASD+ and ASD- with an overall small effect size (see Table 4.4). In contrast, for the AQ-10 and the remaining three subscales 'attention switching', 'attention to detail' and 'communication', only in ASD+ a significant impact of the variable age could be explored ($p < 0.001$ for each score and *r* between 0.18 and 0.25; see Table 4.4). For all significant correlations between age and the AQ (AQ-50, AQ-10 and subscales), the correlation coefficient was positive, meaning that older individuals tended to score higher in the AQ. In other words, with increasing age between individuals, self-assessed autistic traits tended to increase as well.

Altogether, it could be observed that age seems to have a greater influence on the psychopathological self-assessment of autistic traits in patients with an ASD than in individuals without this diagnosis. The influence of the variable 'age' depending on the diagnosis ASD can be seen by comparing the scatterplots (compare Figure 4.9 with Figure 4.10), the coefficients of determination (ASD+ $R^2 = 0.10$; vs. ASD- $R^2 = 0.014$) and the corresponding regression lines. In ASD+, the variable 'age' shared 10% variation with the AQ-50 scores in contrast to ASD-, where only 1.4% variation was shared between the variables. The impact of the variable age on the AQ-50 was even greater than the impact of the variable diagnosis ASD as seen in chapter 'Relationship between Diagnosis and AQ' ('age': $r = 0.33$ vs. 'ASD': $r = 0.12$; compare Table 4.2 and Table 4.4).

Figure 4.7 *Boxplot: age compared between ASD+ (median = 32) and ASD- (median = 37).*

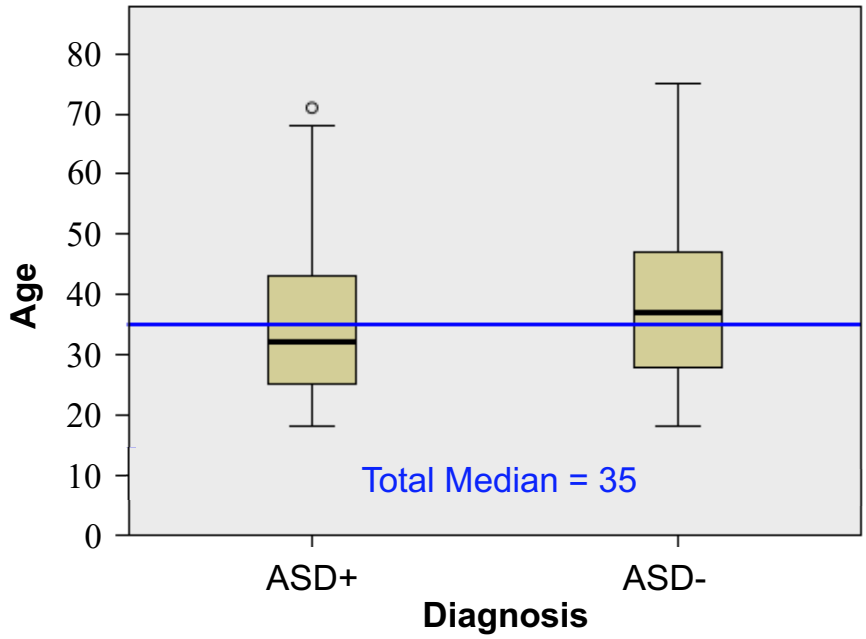
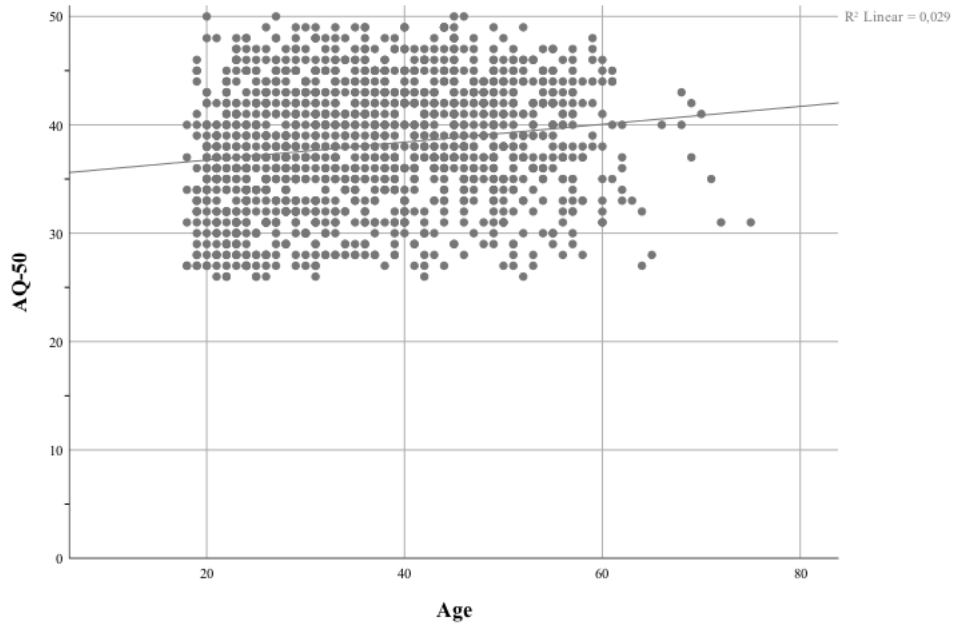


Table 4.4 *Spearman's Correlation between Age and AQ-50/ AQ-10/ subscales.*

			AQ-50	AQ-10	Social skills	Attention switching	Attention to detail	Communication	Imagination
ASD+	Age	*r*	0.33**	0.25**	0.23**	0.19**	0.18**	0.18**	0.26**
***n*=528**	(median=32)								
		p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
ASD-	Age	*r*	0.13**	0.06	0.11**	0.04	-0.03	0.04	0.21**
***n*=854**	(median=37)								
		p	<0.001	0.098	0.002	0.254	0.49	0.22	<0.001

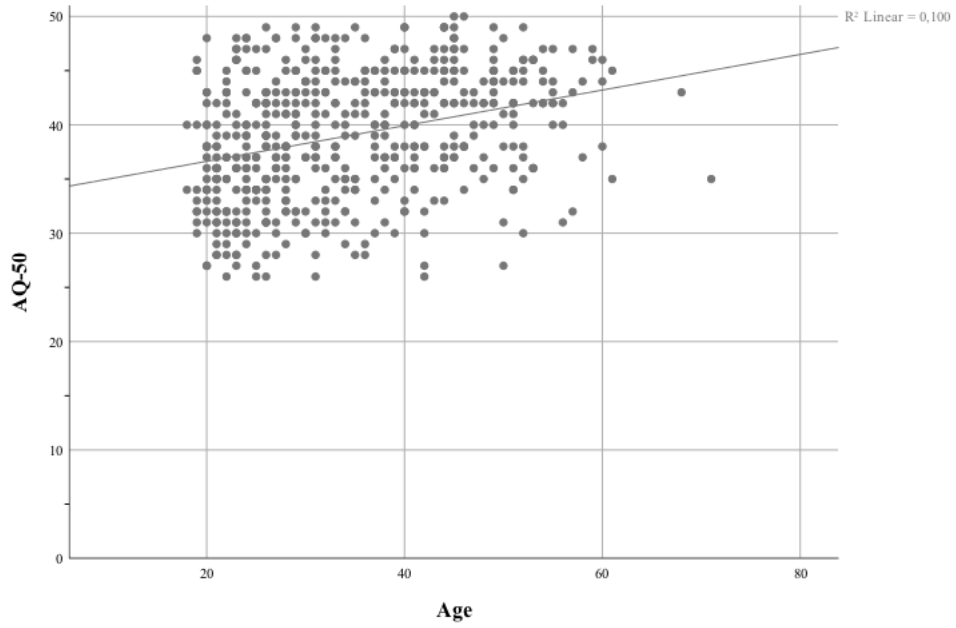
** Correlation is significant at the 0.05 level; ** Correlation is significant at the 0.01 level; n = group size*

Figure 4.8 *Scatterplot with regression line - The distribution of individual AQ-50 values based on the age of all patients (whole sample N = 1382).*



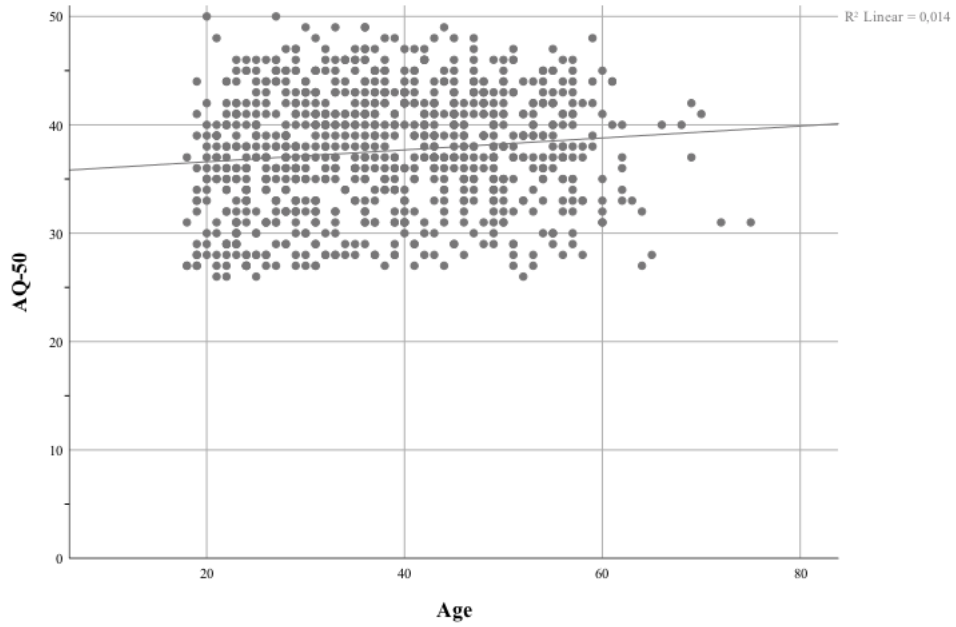
R^2= coefficient of determination. According to this calculation the variable 'age' shares 2.9% variation with the AQ-50 scores of the whole sample.[114]

Figure 4.9 *Scatterplot with regression line - The distribution of individual AQ-50 values based on the age of patients with an ASD (ASD+; n = 528).*



R^2= coefficient of determination. According to this calculation, the variable 'age' shares 10.0% variation with the AQ-50 scores of ASD+.[114]

Figure 4.10 *Scatterplot with regression line - The distribution of individual AQ-50 values based on the age of patients without an ASD (ASD-; n = 854).*



R^2= coefficient of determination. According to this calculation the variable 'age' shares 1.4% variation with the AQ-50 scores of ASD-.[114]

4.5 Correlations between Intelligence and AQ

As part of the neuropsychological assessment, 387 individuals of the total 1814 performed the German version of the WAIS-III (303 ASD+ and 84 ASD-). FSIQ ranged from 46-144 with a mean of 103.4 (S.D. = 17.8). Since the AQ was designed for people with normal to high intelligence, only patients with an IQ ≥ 70 who completed the questionnaire (total IQ ≥70: 308, ASD+: 241, ASD-: 67) were included in the following calculations (see Table 4.5).

Since a comorbid depression can possibly have a negative impact on testing the IQ, FSIQ was correlated with the dichotomous variable 'clinically relevant depressive symptoms' defined above (see 'Statistic') using a biserial correlation.[109] No significant influence of present "clinically depressive symptoms" on the FSIQ could be found neither for the total 308 individuals (p = 0.515) nor separately for ASD+ (p = 0.103) and ASD- (p = 0.093). Based on these results, individuals with a BDI above 17 could also be included in the following calculations.

Mean FSIQ for ASD+ was 106.0 (S.D. = 15.8), which was higher than the FSIQ of 102.6 for ASD- (S.D. = 13.6). According to the independent-samples t-test, this difference (3.4 points) however was not significant p = 0.111. PIQ scores showed no significant difference in this sample as well (p = 0.766). VIQ on the other hand was significantly higher (5.9 points) in ASD+ than in ASD- (p = 0.007, d = 0.31).

In both groups VIQ was significant higher (p < 0.001) than PIQ, however, the effect size was below the poor range for ASD- (d = 0.15) and medium sized for ASD+ (d = 0.54) (see Table 4.5 for results). Spearman's correlations between IQ and AQ scores were performed to ascertain

the degree to which the IQ affects the self-assessment of autistic traits. In ASD+ FSIQ, PIQ and VIQ correlated significantly with the AQ-50, indicating that the higher the IQ the higher the score in the AQ-50 (FSIQ/AQ-50: $r = 0.27$, $p < 0.001$; see Table 4.6). In contrast, FSIQ, PIQ and VIQ did not correlate significantly with the AQ-50 in ASD- (FSIQ/AQ-50: $p = 0.193$; see Table 4.6).

In ASD+ FSIQ, VIQ and PIQ correlated significantly with responses to each subscale of the AQ except for 'imagination'. No correlations were found in the clinical control group ASD-. The correlation coefficient *r* ranged between 0.1 and 0.3 in all significant Spearman's correlations, which represents a small effect size (see Table 4.6 for results).

Table 4.5 *FSIQ/ VIQ/ PIQ: Means (S.D.), Independent-samples t-test and Cohen's d.*

	FSIQ	**VIQ**	**PIQ**
Total mean (S.D.) (*N*=315)	103.4 (17.8)	106.0 (17.9)	99.3 (17.2)
Total range	46-144	53-144	50-142
IQ ≥ 70 Total mean (S.D.) (*n*=308)	105.3 (15.4)	108.0 (16.0)	100.8 (15.2)
IQ ≥ 70 Total range	70-144	65-144	63-142
ASD+ mean (S.D.) (*n*=241)	106.0 (15.8)	109.3 (16.0)	100.7 (16.0)
ASD+ range	70-144	65-144	63-142
ASD- mean (S.D.) (*n*=67)	102.6 (13.6)	103.4 (15.0)	101.3 (12.6)
ASD- range	73-136	69-139	74-136
Mean difference ASD+ and ASD-	3.4	5.9	0.5
***t*-test, *p*-value (2-tailed)**	0.111	0.007	0.766
Cohen's *d*	0.18	0.31	0.05

S.D. = standard deviation; N/ n = sample/ group size

Table 4.6 *Spearman's Correlation between FSIQ, VIQ, PIQ and AQ-50/ AQ-10/ Subscales.*

			AQ-50	**AQ-10**	**Social skills**	**Attention switching**	**Attention to detail**	**Communication**	**Imagination**
ASD+	FSIQ	*r*	0.27**	0.17**	0.23**	0.22**	0.21**	0.18**	0.00
***n*=241**		*p*	<0.001	0.007	<0.001	0.001	0.001	0.005	0.960
	VIQ	*r*	0.22**	0.12	0.17**	0.17**	0.2**	0.15*	-0.02
		p	0.001	0.061	0.009	0.009	0.002	0.021	0.794
	PIQ	*r*	0.28**	0.21**	0.25**	0.23**	0.18**	0.19**	0.02
		p	<0.001	0.001	<0.001	<0.001	0.005	0.003	0.711
ASD-	FSIQ	*r*	0.16	0.05	-0.1	0.09	0.14	-0.04	0.22
***n*=67**		*p*	0.193	0.662	0.443	0.491	0.248	0.747	0.08
	VIQ	*r*	0.11	0.04	-0.13	0.1	0.15	-0.11	0.13
		p	0.393	0.764	0.279	0.404	0.216	0.378	0.285
	PIQ	*r*	0.14	0.05	-0.05	0.01	0.07	0.04	0.23
		p	0.263	0.705	0.675	0.911	0.602	0.770	0.065

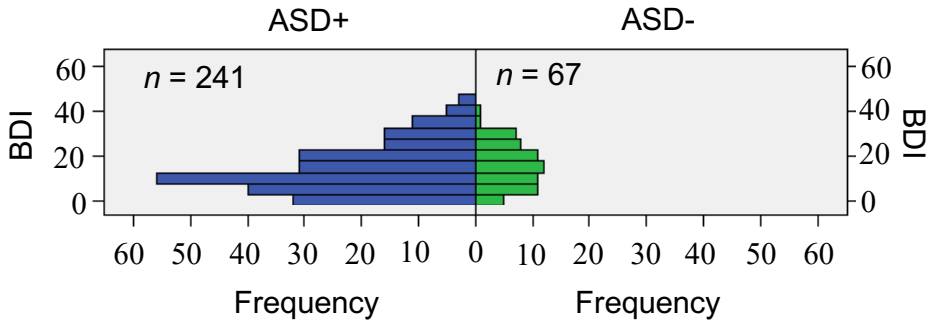
** Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed); n = group size*

4.6 Correlations between BDI and AQ

Neuropsychological testing also included self-assessment of depressive symptoms, so the 308 individuals who performed the WAIS-III also completed the BDI. Because BDI scores were not normally distributed (see also Figure 4.11), a Mann-Whitney *U* test was carried out, to explore whether the BDI differed significantly between ASD+ and ASD-. The test revealed that there was no significant difference (p = 0.192) in the BDI scores between patients with (ASD+ median = 12) and without an ASD (ASD- median = 15). For the distribution of BDI scores for ASD+ and ASD-, see Figure 4.11. BDI medians of both groups (ASD+ = 12; ASD- = 15) were within the range of mild to moderate depressive symptoms (10-17 points) and overall, 59% (10-17 points = 25%; >17 points = 34%) of the patients with an ASD and 66% (10-17 points = 24%; >17 points = 42%) of the patients without an ASD, reported severity levels of at least 'mild to moderate' or 'clinically relevant' depressive symptoms (score >17) symptoms.

To determine if there is a relationship between AQ and BDI scores, Spearman's correlations were conducted. No significant correlation was found between AQ-50/ AQ-10 and BDI, neither for ASD+ nor for ASD- (for results see Table 4.7). The only significant relationship was identified for subscale 'attention switching', which was comparable for both groups (ASD+: r = 0.14, p = 0.034; ASD-: r = 0.27, p = 0.030) with a small sized effect (r < 0.3). The positive correlation coefficients indicate that the higher the individuals rated their depressive symptoms (via the BDI), the higher they assessed their deficits in the area of 'attention switching', independent of the diagnosis of an ASD. No significant correlation could be detected for the other subscales.

Figure 4.11 *The distribution of BDI scores of ASD+ and ASD-.*



x-axis = Frequency as absolute values; y-axis = BDI scores; BDI Median ASD+ = 12; BDI Median ASD- = 15

Table 4.7 *Spearman 's Correlation between BDI and AQ-50/ AQ-10/ subscales and medians (total median = 12).*

			AQ-50	AQ-10	Social skills	Attention switching	Attention to detail	Communication	Imagination
ASD+ (*n*= 241)	BDI (median=12)	*r*	0.05	0.02	0.06	0.14*	0.01	0.11	-0.10
		p	0.406	0.820	0.377	0.034	0.911	0.085	0.136
ASD- (*n*= 67)	BDI (median=15)	*r*	0.12	0.18	0.08	0.27*	0.06	0.05	-0.08
		p	0.332	0.156	0.523	0.030	0.616	0.693	0.527

** Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed); n = group size*

4.7 Item analysis

To ascertain how well the items distinguishes between the groups ASD+ and ASD-, a Discrimination Index (DI) was calculated as described in chapter 'Statistics' (for results see Table 4.8). The mean of the DIs of all items, which is termed 'total discriminability index', was 0.028. DIs ranged from -0.080 to 0.106, so none of the items could be considered as 'good' (for the interpretation of the DI see chapter 'Statistics'). Furthermore, there were 9 items (12, 23, 25, 26, 29, 37, 43, 47, 49) in the negative range, meaning that they were answered more often by ASD- than ASD+. In order to find out if we would get the same 'Red Flags' as Allison et al. (2012)[6] for their AQ-10 (AQ-10) we also selected the two items with the best DI for each subscale. Only three items (31, 36, 41) from the AQ-10 found a place in our revised AQ-10 (AQ-10-revised). For one item of the AQ-10 (item 37), DI was even in the negative range (37).

AQ-10 (Allison et al. 2012)[6]: 5, 20, 27, 28, 31, 32, 36, 37, 41 and 45.
AQ-10-revised: 9, 15, 16, 19, 31, 34, 35, 36, 40 and 41.

In a next step, the sample was divided into different subgroups according to age and gender to examine the influence of these variables at the item level. Due to the limited number of females with ASD, the sample could only be divided into a younger (<35) and an older group (≥ 35) according to the median (35) of the entire sample. This resulted in 8 different subgroups ('Male', 'Female', '<35', '≥35', 'Male <35', 'Male ≥35', 'Female <35', 'Female ≥35'). ASD+ and ASD- were compared with each other for each subgroup and respective DIs were calculated. Total discriminability indices of the subgroups ranged from 0.018 to 0.061 and group 'Male' (0.022), '<35' (0.018), 'Male <35' (0.018) were below and group 'Female' (0.047), '≥35' (0.051), 'Male ≥35' (0.045), 'Female <35' (0.034) and 'Female ≥35' (0.061) above the entire sample (0.028). The highest DI for a single item was found in group 'Female ≥35', for item '31' (DI 0.189) and the lowest in group 'Male <35', for item '37' (DI -0.093). Maximum 18 (subgroup 'Male <35') and minimum 3 (subgroup '≥35') items had a DI in the negative range. Thus, for subgroups 'Female', '≥35', 'Male ≥35', 'Female <35' and 'Female ≥35', a better distinction

between ASD+ and ASD- could be achieved than for the entire sample. However, no item could be found in any subgroup that performed 'good' (all DIs were below 0.3). To determine if the items differ in their importance among the 4 subgroups (Male <35', 'Male ≥35', 'Female <35', 'Female ≥35'), items were ranked according their DI and Spearman's correlation was performed (see Table 4.9). The ranks between 'Male <35' and 'Male ≥35', as well as 'Female <35' and 'Female ≥35', did not correlate significantly with each other, so that the items didn't match in their relevance for discrimination between these groups. All other correlations among the groups were at least significant at the 0.05 level (see Table 4.9).

Table 4.8 *Discrimination Index (DI) for each item between ASD+ and ASD-.*

	ASD+ *n* **= (533)**			**ASD-** *n* **= (878)**			
Item	**Percentage with score = 1**	***n* with score = 1**	***n* with score = 0**	**Percentage with score = 1**	***n* with score = 1**	***n* with score = 0**	**DI**
1	93.37	493	35	90.63	774	80	0.027
2	95.83	506	22	93.91	802	52	0.019
3	35.98	190	338	31.38	268	586	0.046
4	89.58	473	55	88.06	752	102	0.015
5*	76.14	402	126	75.41	644	210	0.007
6	63.64	336	192	61.12	522	332	0.025
7	76.89	406	122	73.65	629	225	0.032
8	47.92	253	275	42.04	359	495	0.059
9	82.39	435	93	71.78	613	241	0.106
10	92.05	486	42	90.05	769	85	0.020
11	92.23	487	41	91.45	781	73	0.008
12	85.98	454	74	86.53	739	115	-0.005
13	86.55	457	71	81.15	693	161	0.054
14	62.69	331	197	59.48	508	346	0.032
15	85.98	454	74	79.63	680	174	0.064
16	75.57	399	129	73.30	626	228	0.023
17	91.10	481	47	89.93	768	86	0.012
18	55.11	291	237	48.13	411	443	0.070
19	73.11	386	142	64.99	555	299	0.081
20*	60.98	322	206	53.40	456	398	0.076
21	62.50	330	198	59.48	508	346	0.030
22	94.89	501	27	93.56	799	55	0.013
23	78.79	416	112	82.08	701	153	-0.033
24	83.90	443	85	80.56	688	166	0.033
25	85.04	449	79	86.53	739	115	-0.015
26	83.71	442	86	86.53	739	115	-0.028
27*	86.93	459	69	81.03	692	162	0.059
28*	81.25	429	99	80.56	688	166	0.007
29	60.98	322	206	61.59	526	328	-0.006
30	54.17	286	242	53.51	457	397	0.007

	ASD+ *n* = (533)			ASD- *n* = (878)			
Item	**Percentage with score = 1**	***n* with score = 1**	***n* with score = 0**	**Percentage with score = 1**	***n* with score = 1**	***n* with score = 0**	**DI**
31*	80.68	426	102	71.43	610	244	0.093
32*	88.07	465	63	87.94	751	103	0.001
33	70.27	371	157	69.32	592	262	0.009
34	90.53	478	50	87.47	747	107	0.031
35	63.83	337	191	56.56	483	371	0.073
36*	85.42	451	77	79.16	676	178	0.063
37*	64.96	343	185	72.95	623	231	-0.080
38	90.72	479	49	89.11	761	93	0.016
39	79.92	422	106	77.28	660	194	0.026
40	77.27	408	120	68.27	583	271	0.090
41*	82.95	438	90	74.24	634	220	0.087
42	75.19	397	131	70.96	606	248	0.042
43	87.88	464	64	88.64	757	97	-0.008
44	90.72	479	49	88.76	758	96	0.020
45*	87.69	463	65	84.19	719	135	0.035
46	90.53	478	50	90.28	771	83	0.002
47	81.63	431	97	83.72	715	139	-0.021
48	77.65	410	118	72.48	619	235	0.052
49	53.03	280	248	54.80	468	386	-0.018
50	85.98	454	74	83.49	713	141	0.025

*: Item of AQ-10 (Allison et al. 2012)[6]; **Bold**: Item of AQ-10-revised; *n = group size*

Table 4.9 *Spearman's correlation between subgroups (items ranked according their DI).*

	Male <35	**Male ≥35**	**Female <35**	**Female ≥35**
Male <35				
r	1	0.228	0.359*	0.463**
p		0.112	0.011	0.001
Male >35				
r		1	0.351*	0,344*
p			0.012	0.014
Female <35				
r			1	0.179
p				0.214
Female >35				
r				1
p				

* Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed)

4.8 Receiver Operating Characteristic (ROC)

In determining how well the AQ would differentiate between ASD+ and ASD-, if we divide the sample according to gender and age in this study, ROCs were carried out and the area under

the curve (AUC) were determined (as described in chapter 'Statistics'). Due to the limited number of females with ASD, the sample could only be divided into a younger (<35) and an older group (≥ 35) according to the median (35) of the entire sample. This resulted in 8 different subgroups, the same as in chapter 'Item analysis' ('Male', 'Female', '<35', '≥35', Male '<35', 'Male ≥35', 'Female <35', 'Female ≥35'). The AUCs were greater for subgroup 'Female' (AUC = 0.624, $p < 0.001$), '≥35' (AUC = 0.641, $p < 0.001$), 'Male ≥35' (AUC = 0.620, $p < 0.001$), and 'Female ≥35' (AUC = 0.676, $p < 0.001$) than the AUC of the whole sample (AUC = 0.571, $p < 0.001$). The AQ therefore separated better for these subgroups than for the whole sample, however, the AUCs were generally in a poor range with a maximum of 0.676 (for the interpretation of the AUC see chapter 'Statistics'). For the other subgroups, the AQ either separated more poorly ('Male': AUC = 0.551, $p = 0.009$) or did not differ significantly different from the 0.5 area (Null hypothesis) ('<35': $p = 0.075$; 'Male <35': $p = 0.143$; 'Female <35': $p = 0.053$) (see Table 4.10).

To find out which would be the best number of items for a shorter version of the AQ and how items with a weak or negative DI would affect the AQ, all items were listed according to their DI (see above in chapter 'Item analysis') and then each item was summed up according to its rank. After that, AUC was computed for the sum of the added-up items after each addition (see Table 4.11). In Table 4.11 and Figure 4.12 it can be seen that the AUC for the sum of the two highest listed items was greater than all items together ('AQ-50' AUC = 0.571 vs. AUC with two items = 0.574) and the highest AUC was reached when 14 items were added up (AUC = 0.616). The lowest AUC was achieved with only one item (AUC = 0.553).

ROC curves and AUCs were calculated for the AQ-50, AQ-10 (Allison et al. 2012)[6], AQ-10-revised, AQ-top-14 (14 added-up Items with the greatest AUC in Figure 4.12, consisting of the items: 9, 31, 40, 41, 19, 20, 35, 18, 15, 36, 27, 8, 13, 48) (see Figure 4.13 - Figure 4.16). AQ-top-14 achieved the greatest AUC (0.616), AQ-10 (Allison et al. 2012)[6] the lowest AUC (0.555) (see AUCs results in Table 4.12). Overall, each test performed poorly (AUC < 0.700).[119]

Table 4.10 *Analyses of receiver operating characteristic, AUCs (area under the curve) for different groups and subgroups.*

Group	ASD+	ASD-	N	AUC	Std. Error	Asymptotic Sig.	CI 95%	
	n	*n*					Lower	Upper
All	528	854	1382	0.571	0.016	<0.001	0.540	0.602
Male	366	544	910	0.551	0.020	0.009	0.513	0.590
Female	162	310	472	0.624	0.027	<0.001	0.571	0.678
<35	295	364	659	0.540	0.023	0.075	0.496	0.584
≥35	233	490	723	0.641	0.022	<0.001	0.597	0.685
Male <35	215	230	445	0.540	0.027	0.143	0.478	0.594
Male ≥35	151	314	465	0.620	0.028	<0.001	0.556	0.675
Female <35	80	134	214	0.579	0.040	0.053	0.500	0.658
Female ≥35	82	176	258	0.676	0.037	<0.001	0.604	0.748

Figure 4.12 *AUC (area under the curve from receiver operating characteristic curve) for the sum of the added-up items (y-axis) and the number of items added up for the whole sample (ASD+ vs. ASD-) on the x-axis. For the AUC for the respective number of added items compare Table 4.11.*

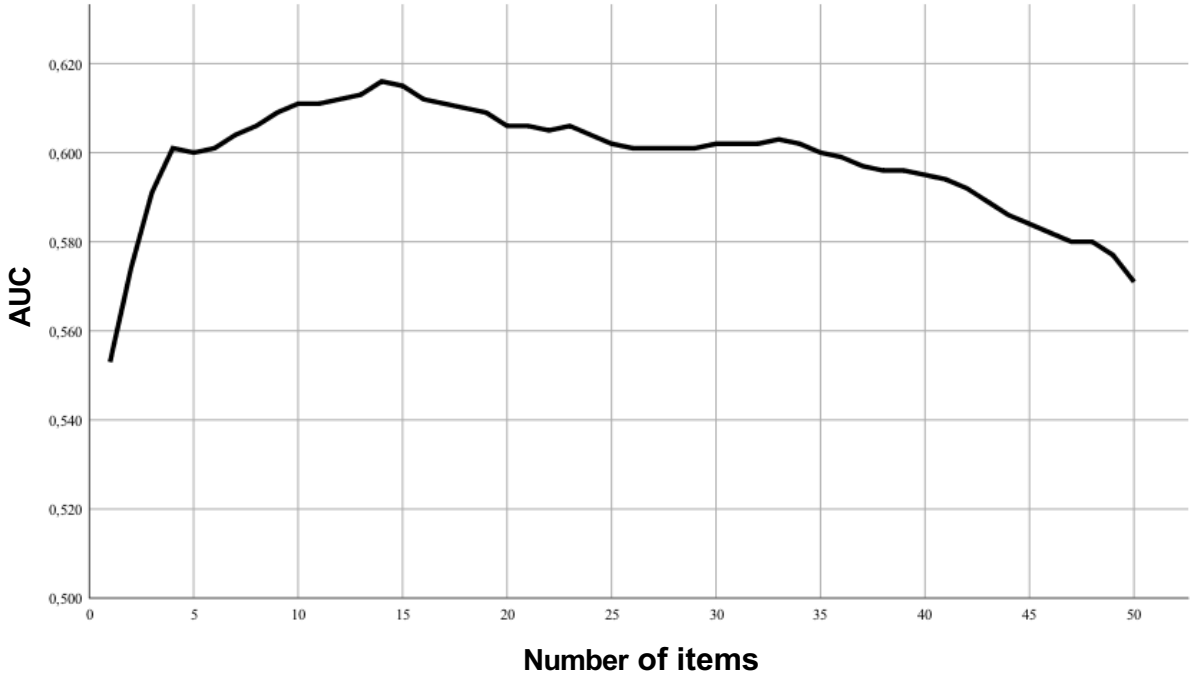


Table 4.11 *Items ranked according their Discrimination Index (DI) for the whole sample (ASD+ vs. ASD-).*

Item	Rank	DI	AUC of the sum of the added-up items
9	1	0.106	0.553
31	2	0.093	0.574
40	3	0.090	0.591
41	4	0.087	0.601
19	5	0.081	0.600
20	6	0.076	0.601
35	7	0.073	0.604
18	8	0.070	0.606

Item	Rank	DI	AUC of the sum of the added-up items
15	9	0.064	0.609
36	10	0.063	0.611
27	11	0.059	0.611
8	12	0.059	0.612
13	13	0.054	0.613
48	14	0.052	0.616
3	15	0.046	0.615
42	16	0.042	0.612
45	17	0.035	0.611
24	18	0.033	0.610
7	19	0.032	0.609
14	20	0.032	0.606
34	21	0.031	0.606
21	22	0.030	0.605
1	23	0.027	0.606
39	24	0.026	0.604
6	25	0.025	0.602
50	26	0.025	0.601
16	27	0.023	0.601
10	28	0.020	0.601
44	29	0.020	0.601
2	30	0.019	0.602
38	31	0.016	0.602
4	32	0.015	0.602
22	33	0.013	0.603
17	34	0.012	0.602
33	35	0.009	0.600
11	36	0.008	0.599
5	37	0.007	0.597
28	38	0.007	0.596
30	39	0.007	0.596
46	40	0.002	0.595
32	41	0.001	0.594
12	42	-0.005	0.592
29	43	-0.006	0.589
43	44	-0.008	0.586
25	45	-0.015	0.584
49	46	-0.018	0.582
47	47	-0.021	0.580
26	48	-0.028	0.580
23	49	-0.033	0.577
37	50	-0.080	0.571

AUC = area under the curve from receiver operating characteristics curve

Figure 4.13 *ROC-Curve for AQ-50 (ASD+ vs. ASD-).*

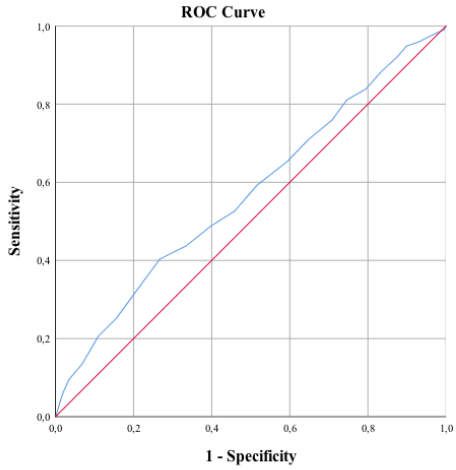


Figure 4.14 *ROC-Curve for AQ-10 (Allison et al. 2012)*[6] *ASD+ vs. ASD-.*

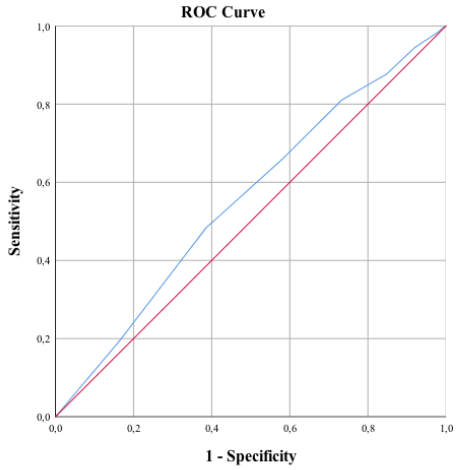


Figure 4.15 *ROC-Curve for AQ-10-revised (ASD+ vs. ASD-).*

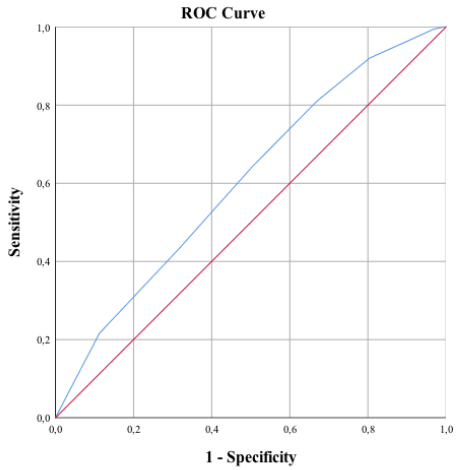


Figure 4.16 *ROC-Curve for AQ-top-14 (ASD+ vs. ASD-).*

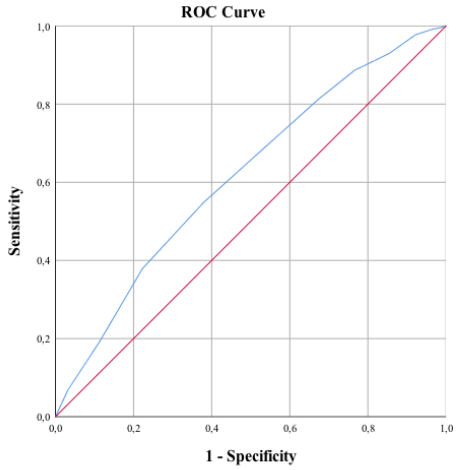


Table 4.12 *AUCs of AQ-50, AQ-10 (Allison et al.)[6], AQ-10-revised and AQ-top-14 for the whole sample (ASD+ vs. ASD-).*

Test	AUC	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower	Upper
AQ-50	0.571	0.016	<0.001	0.540	0.602
AQ-10	0.555	0.016	0.001	0.524	0.586
AQ-10-revised	0.605	0.015	<0.001	0.574	0.635
AQ-top-14	0.616	0.015	<0.001	0.586	0.647

Std. = Standard; Sig. = Significance.

5. Discussion

In a recent study, Ashwood et al. (2016)[3] revealed that the AQ-50 and its short version the AQ-10 (Allison et al. 2012)[6] predicted ASD only poorly in a large clinical sample of adults (476 adults, 346 with ASD, see Table 5.1). These results contradict earlier studies by Baron-Cohen et al. (2001)[5], Allison et al. (2012)[6], Wakabayashi et al. (2006)[121] and Booth et al. (2013)[4] where separation between groups was found to be more sufficient (see Table 5.1). The Youden Index (see Table 5.1) objectifies how poorly the AQ in Ashwood's study performed compared to the other publications (0.08 vs. 0.68 - 0.85). Ashwood et al. (2016)[3] hypothesized that the selection of the control group could explain the varying performance of the AQ. They examined on the basis of a clinical group of an "ASD diagnostic referral service for suspected ASD" instead of a non-clinical population with healthy-controls, as Baron-Cohen et al. (2001)[5], Allison et al. (2012)[6], Wakabayashi et al. (2006)[121] and Booth et al. (2013)[4] did.[3] The remarkably low specificity underlines this hypothesis (0.20 vs. 0.80 - 0.98). As already described above (see chapter 'Sensitivity and Specificity'), the specificity is the probability with which 'individuals without the disorder' are truly predicted to be negative, and thus refers only to the control group. This demonstrates again how important the choice of the control group is for the evaluation of the test quality. At this point it must be emphasised that both cases concern different conditions and are referred to as different types of screening. In the case of Ashwood et al. (2016)[3], individuals with suspected ASD are tested in a clinic for autism and this type of screening is called 'selective screening'.[122] This type of screening is more appropriate to what is required in the diagnostic process for ASD in an outpatient clinic for autism in adulthood. In the other case, testing is done proactively and is more akin to a 'mass screening'.[123] So, in the selective screening, there is a clear reason or suspicion why a person is tested and the pre-test probability (which represents the probability of having the disorder of interest before screening; in this study 38%) or 'risk' of an ASD is higher than in the second type of screening.[124] The pre-test probability of mass screening corresponds rather to the prevalence of the general population and is therefore to be placed in the range of 1-2%.[27] In the publication of the AQ-50 by Baron-Cohen et al. in 2001[5], the intention was expressed to use the questionnaire for screening, although the type of screening was not mentioned here. Nevertheless, the authors also intended to use this questionnaire for "identifying the degree to which any individual adult of normal IQ may have autistic traits".[5] It should be questioned whether one self-assessment questionnaire alone can fulfil both tasks to a sufficient extent.

However, the specificity is also higher in the publication by Woodbury-Smith et al. (2005)[7] than in the study by Ashwood et al. (2016)[3], who also used a clinical sample for screening. This is probably due to the small group size (27 patients without an ASD, 73 with an ASD), which does not sufficiently represent the usually very heterogeneous group of adults where the diagnosis ASD was ruled out (ASD-). In contrast to the control groups, ASD+ is very homogeneous

across the studies, which is evident from the comparable sensitivities, as these are calculated over the affected individuals above the cut-off (see chapter 'Sensitivity and Specificity'). This high sensitivity, which is comparable across studies (0.77 - 0.95), legitimises the use of the AQ-50 to the extent that most adults with ASD score above the cut-off. The low specificity in the study of Ashwood et al. (2016)[3] with a clinical population of an ASD diagnostic referral however, indicates that no further conclusions can be drawn about whether someone has an ASD or not, if someone scores above the cut-off in a comparable population (compare the DGPPN guideline for diagnostics of ASD, p.124)[2]. Evidence of comparable findings in a substantially larger cohort could be found in the present investigation as well. Out of 1382 individuals above the AQ-50 cut-off of 26 points, only 528 (38%) had an ASD. AQ-50 scores were only slightly higher in ASD+ than in ASD- and the effect size was minor. Furthermore, it could be shown that due to the item analysis not only scores were similar but also responses to the items.

These findings resulted in two major questions: first, why is the specificity in a clinical population so poor and second, is it possible to find some suggestion for a further improvement of the screening for autism in adulthood in a clinical condition. As already described above (see chapter 'Comorbidity or differential diagnosis?'), there are several differential diagnoses with symptoms similar to the ASD, in the domains of social interaction and communication or in restrictive, repetitive patterns of behaviour (which are also assessed in the AQ-50). These symptoms or traits are probably less common in the general population and are therefore not marked by a healthy individual. Unlike this, for instance, an adult with an OCD and the possible resulting depressive syndrome with social impairments could also consider some of the items to be suitable for himself. Possible items for such a scenario would be: 1, 4, 10, 11, 13, 15, 16, 17, 22, 24, 25, 26, 27, 28, 31, 32, 34, 36, 38, 39, 43, 44, 45, 46, 47, 48, 50 (see in the appendix '*The Autism-Spectrum Quotient (AQ-50) by Baron-Cohen et al. 2001*' Table 7.2)[5].

Another important aspect that complicates screening for autism on the basis of a self-assessment questionnaire in general is the presumably limited ability of self-perception of individuals with an ASD, which has been discussed in earlier studies.[3,25,125,126] It will probably be difficult for a person within the autism-spectrum to adequately assess his or her own deficits in the field of social interaction and communication, if he or she is not yet aware of them or deficits remain unidentified by the next of kin.

Another important factor to consider in the self-assessment of autistic traits is the presence of comorbidities, which can both mimic and aggravate autistic symptoms (in chapter 'Comorbidity or differential diagnosis?', the various psychiatric comorbidities and the extent to which their symptoms overlap with those of ASD have already been described in more detail). Firstly, symptoms could be mistakenly attributed to the comorbidity (probably less relevant in self-assessment than in the observation through a specialist). Secondly, Ashwood et al.

(2016)[3] found in their study that autistic adults without a comorbidity scored lower and in some cases below the cut-off in the AQ-50. Both could lead to a false negative diagnosis, meaning that a person with an ASD is not diagnosed as being affected.

In this study, the focus was on depression only. For one thing, because it is the most frequent comorbidity (in ASD+) and is often the main reason why adults with an undiagnosed ASD see a psychiatrist. For another, because it can be relevant as a differential diagnosis in ASD-. Furthermore, depression can affect the accuracy of an IQ test, which was also measured in 315 individuals in this study. But first, the influence of easily determinable and controllable variables such as gender and age were assessed and compared with the influence of the variable 'diagnosis' (ASD+ or ASD-). Then, the influence of IQ on the AQ-50 was determined for ASD+ and ASD-. On the basis of single item analyses and ROC curves, indications for an improvement of the screening were examined.

Table 5.1 *The different studies compared in terms of the control group, sample size, sensitivity, specificity and Youden J*.*

Study	Questionnaire (cut-off)	Control group	*N* (*n* ASD+; *n* Controls)	Sensitivity	Specificity	Youden J*
Baron-Cohen et al. [5]	AQ-50 (≥32)	General population	232 (58; 174)	0.79	0.98	0.77
	AQ-50 (≥26)			0.95	0.92	0.87
Allison et al. [6]	AQ-10 (≥6)	General population	643 (224; 419)	0.88	0.91	0.79
Wakabayashi et al. [121]	AQ-50-Japanese (≥33)	General population	251 (57; 194)	0.88	0.97	0.85
Booth et al. [4]	AQ-50 (≥26)	General population	283 (149; 134)	0.88	0.80	0.68
	AQ-10 (≥6)			0.80	0.87	0.67
Woodbury-Smith et al.[7]	AQ-50 (≥26)	Clinical control group	100 (73; 27)	0.95	0.52	0.47
	AQ-50 (≥32)			0.77	0.74	0.51
Ashwood et al.[3]	AQ-50 (≥26)	Clinical control group	476 (346; 126)	0.88	0.20	0.08
	AQ-10 (≥6)			0.77	0.28	0.05

* In order to compare the results of the different studies more directly, the Youden Index ("Youden J") was also calculated. This index was published 1950 by Youden for the rating of diagnostic tests and is calculated as: 'sensitivity + specificity - 1'. "Youden J" ranges from 0 to 1 and the higher the value, the more informative is the test.[127]

5.1 The influence of gender on self-assessment of autistic traits

Lai et al. (2011)[8] already discovered in a small sample with adults with an ASD (45 males, 38 females) that gender affects self-reported autistic traits. Females had significant higher scores in the AQ-50 but lower observed current symptoms in the Autism Diagnostic Observation Schedule (ADOS). Concerning the AQ-50, the present study, as well as that of Lehnhardt et

al. (2016)[24] (38 Females and 69 Males with an ASD) showed a similar influence of gender, in which females with an ASD scored significantly higher than their male counterparts.

One hypothesis which should explain the discrepancy between observed and self-assessed symptoms related to gender was, that females are more able to camouflage their symptoms because they are more aware of these traits.[8] In connection with this, females without intellectual impairments are also more susceptible being diagnosed late or even remain undiagnosed.[24] This is also reflected in the decreasing sex-ratio with increasing age: While the sex-ratio in children without any impairment of intelligence is about 5.7 - 11:1 (Males : Females)[24,128,129], the ratio equalises in their adult counterparts up to 2:1, as in this study (see 'Patient characteristics') or in the study of Hofvander et al. (2009)[18].

The results of another study by Lai et al. (2017)[93] with 60 age- and IQ-matched males and females with an ASD, in which camouflaging was further quantified and explored, underlines differences between the sexes in adults with autism. Here, camouflaging was operationalized in the quantitative discrepancy between "external behavioural presentation in social-interpersonal contexts" (measured by the ADOS) and "the internal status" ("dispositional traits" measured by the AQ and "social cognitive capability" by the "Reading the Mind in the Eyes" Test).[93] Camouflaging (or the discrepancy between "external behavioural presentation" and "the internal status") was again higher among female adults with an ASD than among their male counterparts.

Lai et al. (2017)[93] and also Kreiser et al. (2014)[130] hypothesize that "socio-cultural factors", such as gender expectations and the socialisation of women in our culture, could explain the differences between male and female individuals with autism. Lai et al. (2017)[93] suggests that gender-specific expectations, for example, may lead a girl with autism to behave "like a girl" and be "more social". Deficits, particularly in the domain of social interaction and communication, could become more or at least sooner aware to girls and women than men with an ASD and accordingly lead to more imitation of the observed behaviour (camouflaging).

In this context, the neuropsychological findings of Lehnhardt et al. (2016)[24] to the "sex-distinctive cognitive strategies in ASD diagnosed late in life" should be emphasised again (see also chapter 'Gender'). In their investigation females had higher processing speed and better executive functions than males, which could also explain their higher ability to camouflage.[24]

Interestingly not only in the ASD+ group but also in the ASD- group females had significant higher scores in the AQ than their male counterparts. In other words, whether there was an ASD or not, females in our sample population tended to value their autistic-traits higher than males.

So, the hypothesis of Lai et al. (2017)[93] also Kreiser et al. (2014)[130] could also apply to the adults in our study where the diagnosis of an ASD was ruled out (ASD-). As already described above (in chapter 'Comorbidity or differential diagnosis?'), in ASD- are, for example, individuals

with an anxiety disorder, OCD or with subclinical “autistic like traits”.[2,76] These adults also tend to suffer from difficulties in the area of social interaction and communication, which could be present since childhood. In many cases, these deficits are the reason why an ASD is suspected and why they are referred to the autism outpatient clinic for adults for diagnostics. In addition to the symptoms, gender-specific expectations could also be comparable. The hypothesis is that gender-specific expectations probably exist independently from the diagnosis and therefore that the perception (or sensitivity) of deficits in the field of social interaction and communication may be more developed among women.

Unfortunately, no data are available on the severity of the symptoms observed in our patients, as measured by the ADOS-4 module for example.[80] Therefore, it remains to be speculative whether females actually had more or less symptoms or tend more to camouflaging than males. A contrary hypothesis would therefore be that the symptoms are actually more severe in female adults in our study and that both men and women assess their deficits comparably and adequately. To further investigate these hypotheses, it would be necessary to measure and compare the already mentioned discrepancy between “external behavioural presentation in social-interpersonal contexts” (measured by the ADOS) and “the internal status” (measured by the AQ and “Reading the Mind in the Eyes” Test)[93] in individuals with ASD+ and ASD- in future studies. The question is whether “operationalized camouflaging” is specific to individuals with an ASD and without impairments in intelligence, or whether it is also common among adults with other disorders (or autistic like traits) who have comparable symptoms. This could provide further knowledge for the diagnostic of autism in adults.

However, it must be emphasized that the influence of the variable gender on the AQ was significant, but overall comparable small as the influence of the variable diagnosis on the AQ.

5.2 The influence of age on self-assessment of autistic traits

To our knowledge, the study by Siebes et al. (2018)[95] is so far the only one, that investigated the influence of age on the AQ in adults with an ASD. However, individuals in which an ASD was ruled out were not included. Similar to our study, patients of an outpatient university clinic (Radboud University Hospital, Department of Psychiatry, Netherlands) suspected of having autism received the AQ for the self-report of their autistic traits. For their statistic procedure by means of analysis of variance (ANOVA), individuals with an ASD were divided into age groups of 18-30, 30-40, 40-50, 50-60 and >60. Contrary to their hypothesis that age has an impact on the AQ and especially on the area of “repetitive and stereotyped patterns of behaviour”, a significant influence could only be found for the factor imagination (the higher the age the higher the values). In contrast, in our study population we identified an influence of age on the AQ-50 in ASD+, which was even greater than the effect of the diagnosis (medium vs. small effect size). Interestingly, here age had an opposite effect than one would have expected according to results of previous investigations on observed severity of autistic symptoms. In

our study self-assessment of autistic traits (and the subscales) increased with age in patients with an ASD, in contrast to Woodman et al. (2015)[9] who demonstrated in their prospective and longitudinal designed study that observed severity of symptoms decreases between two different time points in the same individuals (age range 10-49, mean = 21.72, SD = 9.45; average length of study period = 8.5 years). Chowdhury et al. (2010)[131], Esbensen et al. (2009)[132] and Seltzer et al. (2003)[133] also indicate an improvement in symptoms in individuals with an ASD, especially in the domain restricted and repetitive behaviour. However, these studies did not include the self-perception of autistic traits, which might not correlate to observed severity of symptoms.

Therefore, assuming that symptoms would decrease with age, it could be hypothesized that observation and self-evaluation of symptoms would be expected to occur inverse.

Lai et al. (2011)[8] stated in association with their findings on the differences between females and males with ASD in the AQ, that higher self-referential thus also higher self-awareness of autistic traits relate with less social-cognitive symptoms. In other words, in relation to our findings on the influence of age and gender on self-assessment, and on the previous results of the investigation of the observed severity of symptoms in ASD, the following hypothesis could be proposed: with decreasing autistic symptoms the perception of these increases or, vice versa, self-perception is limited by autistic symptoms.

Since, as mentioned above, data on observed symptoms using ADOS or equivalent tests were not measured and therefore could not be compared directly with the AQ. Further research should aim to test these hypotheses, as self-assessment questionnaires are essential tools in diagnostics and research and thereby results for self-reported symptoms could be biased. A suitable design would be a longitudinal study that determines and compares the self-assessment of autistic traits via the AQ-50 and the observable symptoms via the ADOS.

Limiting to this hypothesis, it must be added that this study is focused on different individuals who have not yet been diagnosed, in contrast to the study by Woodman et al. (2015)[9], in which already diagnosed patients with an ASD had their symptoms measured at two different points in time by means of the ADI-R. So, we have to distinguish between the intraindividual differences over time of the study by Woodman et al. and the interindividual differences concerning age (and other influences) of the present study.

Differences between ASD+ and ASD- could be identified here, as the correlation between the AQ-50 and age was in the medium range for ASD+ and in the low range for ASD-. Furthermore, in contrast to ASD+, there were no significant correlations in ASD- between age and the AQ-10 and subscales ‘attention switching, ‘attention to detail’ and ‘communication’. So, the influence of age seems to have a greater effect on the self-assessment of autistic traits in individuals with autism than without. Since there is no existing research on the influence of age on observed autistic traits (e.g. through the ADOS) of this group (ASD-), there is no closer context

in which these results could be embedded. Therefore, it would be reasonable to include in the longitudinal study design proposed above not only individuals with an ASD but also individuals in whom this diagnosis could initially be ruled out. Perhaps a more precise look at the various differential diagnoses would be worthwhile here, due to the great heterogeneity of this group and the not insignificant differences in symptomatology (see 'Comorbidity or differential diagnosis?').

5.3 Concerning the IQ and self-assessment of autistic traits

In our study, only Verbal-IQ (VIQ) differed significantly from the two groups, being higher in patients with an ASD. This finding is associated with the observed phenomenon that normal to highly intelligent individuals with autism have a significantly higher VIQ than Performance-IQ (PIQ).[134,135] Although VIQ was significantly higher than PIQ in ASD- as well, the difference was merely 2.1 points as opposed to ASD+ with 8.6 points (four-fold). This was also reflected in the effect sizes, as in ASD- the effect size was below the low range in contrast to ASD+ where a medium sized effect was found. Differences between VIQ and PIQ are referred to in previous research as the VIQ-PIQ "discrepancy" or "split",[136] which "could be in either direction (i.e VIQ > PIQ or PIQ > VIQ)".[99] Ambery et al. (2006)[99] stated that this VIQ-PIQ discrepancy is more common in samples of individuals with autism than in a normal population (59% vs. 25%), but is also observed in other developmental disorders.[136] Perhaps our ASD- group was in the respect of a cognitive profile more akin to the normal population than to the ASD+ group, resulting in this difference. Ankenman et al. (2014)[136] investigated the different cognitive discrepancy profiles (VIQ > PIQ, PIQ > VIQ or "no split") in their study on the basis of 1954 children with an ASD between the age of 4 and 17 (FSIQ 35-167). They were able to demonstrate that individuals with a VIQ > PIQ split were significantly older and autistic symptoms less severe than the PIQ > VIQ group (FSIQ did not differ). Based on these results, they hypothesised that these profiles correspond more to a shift from PIQ > VIQ to VIQ > PIQ with increasing age ("common developmental pathways for children with ASD") than different subtypes.[136] This may also be reflected in our ASD+ group, where adults with a VIQ-PIQ discrepancy represent the endpoint of this development.

The calculations concerning IQ and AQ revealed that Full-Scale-IQ (FSIQ) as well as VIQ and PIQ correlated significantly with the self-assessment of autistic traits in ASD+ but not in ASD-. These identified correlations were all positive, which means that among individuals with an ASD, those with a higher IQ (irrespective of FSIQ, VIQ or PIQ) also tend to score higher in the AQ-50 (or its subscales). The only exception was found for the subscale 'imagination', where no relationship between this subscale and FSIQ, VIQ or PIQ was found for ASD+.

The results pertaining to ASD+ fit well into the context of previous research of Bishop et al. (2012)[25]. In their study with 65 individuals with ASD, they likewise determined a positive relationship between IQ and AQ Scores.[25] But at the same time, there were no significant

correlations between IQ and maternal reports on the ADI-R[79] (see also in chapter 'On the need for a screening tool and an adequate item analysis of the AQ') or the 'Vineland Screener' (which is also a semi-structured interviews concerning social-communication difficulties).[25] A resulting hypothesis is that there could be a connection between difficulties (or underestimation) in the self-report of ASD symptoms and a lower IQ.

Results of Klin et al. (2007)[10] support this assumption, since they identified a negative correlation between VIQ and observed symptom severity (by means of ADOS; higher VIQ means less observed symptoms) and positive correlations between FSIQ (VIQ+PIQ) and communications skills (by means of 'Vineland Adaptive Behaviour Scale') in 187 children with ASD and IQ > 70. Correspondingly to this hypothesis, Vickerstaff et al. (2007)[126] reported in their study that 'self-perceived social competence' in children with autism also correlated negatively with the IQ. Furthermore, the relationship between IQ and AQ does not seem to be a general phenomenon and could probably be limited to autism, as no correlation was found in the clinical control group of this study.

To further test this hypothesis, AQ scores should again be correlated with an ASD assessment like the ADOS and the IQ as a confound in a clinical sample.

5.4 Correlations between BDI and self-assessment of autistic traits

Self-report of depressive symptoms, ascertained trough the BDI, did not differ significantly between ASD+ and ASD-. Overall, 59% of the patients with an ASD and 66% of the patients without an ASD, reported severity levels of at least 'mild to moderate' or 'clinically relevant' depressive symptoms (score >17). These results are probably linked to the fact that depression is the most common comorbidity in adults with ASD.[26] In the investigation by Lever and Geurts (2016)[137], 109 (79%) out of 138 adults with autism had a comorbidity and 53.6% (74) had a depression. High prevalence of depression in adults with autism were also observed in several other studies and samples.[18,138,139,140,141] Nevertheless, a comparable number of individuals without a confirmed ASD (ASD-) report depressive symptoms as well. Presumably, most of the patients in an outpatient clinic for autism have a certain degree of psychological strain, which even motivates them to participate the diagnostic process. In one part of these individuals, this distress probably manifests itself in the form of depressive symptoms. As the results of this sample indicate, the prevalence of depressive symptoms in such a population is probably even independent whether someone is diagnosed with an ASD or not.

Concerning the influence of depressive symptoms on the self-report of autistic traits, no significant correlation between the AQ-50/ AQ-10 and the BDI was found, neither in ASD+ nor in ASD-. Based on this result, it can be hypothesized that the degree of severity of depressive symptoms didn't influence the self-assessment of autistic traits.

However, subscale 'attention switching' takes an exceptional position in both groups, where a positive relationship with the BDI score was found. Possibly single items of this subscale

overlap with depressive symptoms, since this correlation is present in ASD+ and ASD-. Perhaps questions like ‘new situations make me anxious’ (item 46) or ‘I enjoy doing things spontaneously’ (item 34) are also answered by people suffering from depression. Future research might consider these correlations.

Nevertheless, it should also be considered that the adults in this sample may not be able to adequately assess their depressive symptoms by using a self-assessment questionnaire.

The results of the systematic-review by Cassidy et al. (2018)[26] lead in a similar direction. Although instruments like the “Patient Health Questionnaire” (PHQ-9) or the BDI-II detect depression well in a general population, they presumably fail partially in patients with ASD.[26] Due to frequent difficulties in self-report in the context of limited insight on the one hand and overlapping symptoms (difficulties with sleep, flat affect, social withdrawal and reduced eye contact) of depression and autism on the other, could lead to inadequate diagnosis of depression in adults with autism on the basis of the established measures.[65]

In order to determine whether a depressive symptomatology influences the self-assessment of autistic traits, the AQ should be correlated with symptoms of depression observed by healthcare professionals in further studies.

5.5 Item and ROC analyses

Item analysis revealed that the groups ASD+ and ASD- were remarkably similar in their responses on item level, as discrimination indices (DIs) were all below the ‘good’ range (< 0.3- 0.7).[6,116] Furthermore, 9 Items of the AQ-50 were even more frequently answered by ASD- than ASD+ for the whole sample. 7 different items were found in the AQ-10-revised than in the original AQ-10 by Allison et al. (2012)[6], which was created using the same method, but here on the basis of a clinical population. These results indicate that the AQ-10 from Allison et al. (2012)[6] is probably not a suitable screening instrument even on item level. Due to the healthy control group, Allison et al. (2012)[6] probably did not find the most discriminating items for the purpose of distinguishing between ASD and its differential diagnoses, but between healthy and affected individuals. Therefore, for the purpose of clinical screening, better results could possibly be achieved with the AQ-10-revised. Further research should validate the AQ-10-revised in other clinical samples. This should be done without preselection by the cut-off of 26 in contrast to this study, to maintain sensitivity, specificity and an even revised cut-off value of the test.

When divided into subgroups according to gender and age, higher DIs indicated that ASD+ and ASD- differed here more clearly in their responses. However, no ‘good’ performance could be observed for any item here either (DI was below 0.3).[116]

For AQ-50 and AQ-10 scores, ROC analyses calculated only a very low discrimination, as the AUCs were in a weak range. Sensitivity and specificity for the cut-off of 26 could not be calculated here, since only patients above this cut-off were included. Due to this preselection,

AUCs and DIs should only be interpreted as relative and not as absolute values as well. However, in ROC analyses a better distinction has been achieved by using the same subgroups as in the item analysis. Thus, it can be hypothesized that screening could be improved by splitting into subgroups according to gender and age to control these variables. Further, it could be necessary to consider selecting different items for each subgroup, if we look at the results of Spearman's rank correlation. The findings of the rank correlation indicate that for the different subgroups each item could have a different importance for discrimination. This must be considered if short versions should be created for different subgroups based on the most discriminating items. These findings should be seen in connection with the results of the previous calculations concerning the influence of the variables gender and age on the AQ. Here, influences of the variables gender and age on the self-assessment of autistic traits could be observed. The effect was comparably sized for the variable 'gender' and even larger for the variable 'age' compared to the variable 'diagnosis' (ASD+ or ASD-). Beyond this, these findings can also be seen in the context of the theory of the different gender phenotypes. As described in chapter 'Gender', there are indications for a male and female phenotype with different "sex-related cognitive profile(s)" (Lehnhardt et al. 2016)[24]. If different phenotypes with varying cognitive strategies can be assumed, an adaptation of the screening to these should be considered and investigated in further research (with a prospective design).

Furthermore, due to the calculations with the addition of the items, there are indications that above a certain number of items, no additional discriminatory value will be obtained. As can be seen from Figure 4.12 (or Table 4.11), the AUC decreases after 14 items and reaches its lowest point at 50 items (AQ-50). The largest AUC could be achieved with the 14 best (according their DI) items, so it should be reconsidered whether the selection of 50 (AQ-50) or 10 items (AQ-10) is the most reasonable. According to the test theory, a higher number of items can lead to a higher precision, because the more items exist, the more the measurement error tends towards 0.[142] In addition, with more items the reliability (internal consistency) improves.[142] However, there are overlapping symptoms between ASD and the differential diagnoses (as already described in chapter 'Comorbidity or differential diagnosis?'), which can be seen in the similar response on item level and total scores in this study. Therefore, not only the internal consistency is relevant for this screening questionnaire, but also the discrimination index (DI), the measure that distinguishes one construct (ASD) from other constructs (differential diagnoses). Moreover, the increase in accuracy is limited because variables outside the test, such as motivation and concentration, can negatively affect the accuracy if the test is too long.[142] Therefore, Moosbrugger et al. (2012)[142] recommend that a screening test should contain less rather than more items, which probably also applies to screening for autism in adults in this context.

From the findings of the item and ROC analyses, it might be advisable revising the AQ-50 and AQ-10 based on a clinical population with suspected ASD, with a focus on excluding the 9 items with a negative DI and possibly under control of the variables gender and age. For this purpose, it would be important to have a closer look at the clinical control group as well in order to investigate the similarities and differences between ASD (ASD+) and the differential diagnoses (ASD-) in more detail. This could be achieved by further diagnosing the patients from ASD- and dividing them according to their (differential) diagnosis. Possibly, criteria C (symptoms present since childhood) and D (symptoms are clinically relevant) of the DSM-5 could be considered in a revision of the AQ. Because these criteria may be important for the differentiation between ASD and the differential diagnoses (or "autistic like traits") and were not considered in the AQ-50. As shown in Table 5.4, Criterion C seems to be important to distinguish autism from personality disorders but is only marginally considered in the AQ (only item 40).

5.6 Subscales

In the following, calculations and results are discussed with the aim of a detailed analysis of the subscales. Therefore, Mann-Whitney *U* tests, correlations and the item analysis will be considered here with a focus on the subscales. But first of all, these 5 factors should be compared in terms of their content in order to create a link from content to correlations. By taking a closer look at the single items of the subscales and the different symptom groups (or criteria) of DSM-5 or the ICD-10, 4 of these factors can clearly be allocated to the different criteria (for subscales see subchapter 'The AQ'; for items of the AQ-50 see Table 7.2; for DSM-5 and ICD-10 diagnostic criteria see Table 2.2). Criterion A or I and II ("Persistent deficits in social communication and social interaction across various contexts" from DSM-5) could include the factors 'social skills' and 'communication' and Criterion B or III ("Restrictive, repetitive patterns of behaviour, interest or activities" from DSM-5) could include 'attention switching' and 'attention to detail'.

It appears that this division of the subscales not only seems reasonable considering the allocation to the criteria, but also in terms of the influence of the variable 'diagnosis', (see Table 5.2). This leads to the hypothesis that Criterion A is more important for the differentiation between ASD+ and ASD- in screening than Criterion B, since no significant difference between ASD+ and ASD- could be found for subscales 'attention switching' and 'attention to detail'. Except for the variable 'BDI', all other variables ('gender', 'age', 'FSIQ') have a comparable influence on these 4 subscales (see Table 5.2) in ASD+. For the 'BDI' only a significant influence 'attention switching' could be found for ASD+ and ASD-, which leads to the hypothesis that there could be an overlap between the BDI or depressive symptoms and this factor. In ASD-, the influences of the variables were also found to be very consistent across

these 4 subscales. Exceptions were the influence of 'age' on 'social skills' and the lack of influence of 'gender' on 'attention to detail' (see Table 5.2). Taking into account the results of Broadbent et al. (2013)[143] with a healthy control group, it could be hypothesised that the subscale 'social skills' is influenced by age independently of any diagnosis. It is difficult to generate hypotheses on lack of influence of gender on 'attention to detail' in ASD- because, on the one hand, the individuals of ASD- are very heterogeneous and there is no further research on this group so far. On the other hand, the subscale 'attention to detail' is (like the other subscales) adapted to autism-specific deficits and not to difficulties in this area as, for example, someone with an OCD or an anankastic personality disorder would have. However, the influence of gender here seems to depend on the diagnosis of an ASD.

Overall, the subscale 'imagination' seems to have an exceptional position in the AQ-50 and this study:

1) Firstly, this factor does not seem to be clearly associated with one symptom group of DSM-5 or ICD-10. There are items (item 3, 8, 14, 20, 21 and 24; or see Table 5.3) which can be assigned to either 'A' or 'B' (or, according to ICD-10, to 'I', 'II' or 'III'). Interestingly, most items cannot be assigned to any of these criteria and therefore do not represent the core symptoms of the common diagnostic systems DSM-5 or ICD-10 (see Table 5.3, for core symptoms see Table 2.1). So, the question remains why these items (or symptoms) were included in the AQ-50 by Baron-Cohen et al. (2001)[5]. In their publication on the AQ-50, Baron-Cohen et al. (2001)[5] wrote that they based the selection of items on the "triad of autistic symptoms" and referred to publications by Rutter (1978)[144] and Wing et al. (1979)[145], as well as to the American Psychiatric Association (APA) and its DSM-IV[43]. To this triad, impairments in "social interaction, social communication and social imagination" (Wing et al. 1981)[146] are summarized and classified under Criterion B in the DSM-IV.[43] In the already mentioned NICE guideline on adults with an ASD[23] it is described how this triad has been reduced to two "core dimensions". Thus, the first two aspects were combined into one criterion "social communication and social interaction" (see Table 2.2) due to the difficulties in distinguishing these constructs from each other. However, the dimension "social imagination difficulties" was dissolved and was replaced by the Criterion B "Restrictive, repetitive patterns of behaviour, interest or activities". According to the NICE guideline, this dimension seemed not to be a necessary criterion, since there are individuals with an ASD with "great imagination in relation to the arts (drawing, in particular)".[23] Another argument for the elimination was that the construct "imagination" was difficult to operationalize. At this point it is necessary to elaborate what is understood by the term 'imagination' in this context. The author of the AQ-50 Baron-Cohen (2000)[147] writes that imagination is "relevant to theory of mind since it involves building an unreal world that exists purely in your own mind". The "theory of mind" again refers to the ability of an individual to attribute the appropriate mental

state (e.g. certain feelings or thoughts) to itself or others, with the aim of explaining or anticipating the corresponding behaviour.[61,148] This ability is essential for a functioning social interaction and is thus also connected to the core symptoms (Criterion A of DSM-5) and the related subscales of AQ-50 ('social skills' and 'communication'). Impaired imagination in children with an ASD can be observed in the so-called "pretend play" and the painting of unreal or impossible objects (e.g. "two-headed people").[147] In adults with an ASD, the inability to tell or create a story and the missing interest in fiction are also included (see Table 5.3 for the items of this subscale).[149]

2) Secondly, despite the first point, 'imagination' is the only subscale in this study which contains only items with a positive DI (see Table 4.8 or Table 4.11). In other words, this is the only subscale in which every item was answered on average more often by ASD+ than by ASD-. In line with this hypothesis-generating study, the following consideration can be derived: The reduced imagination seems to be more specific for individuals with an ASD in the form in which it is presented in the AQ-50 compared to the other symptom groups (or subscales). This hypothesis is supported by a theoretical comparison of the ICD-10 diagnostic criteria of the most relevant differential diagnoses of ASD with the different subscales and their corresponding items (see Table 5.4). As can be seen in Table 5.4, only in 'imagination' there is no anticipated overlap (no red triangles) between these ICD-10 diagnostic criteria of the differential diagnoses and the items of this subscale. However, this hypothesis and argumentation is limited due to the fact that subclinical "autistic like traits" in ASD- (see chapter 'Comorbidity or differential diagnosis?') could not be included because they are not operationalized in the ICD-10.[2,76] Nevertheless, it would be interesting to investigate on the basis of item analyses whether the assumed overlaps are accurate in further research.
3) Besides the variable 'diagnosis', only the variable 'age' had an influence on this factor. 'Imagination' was therefore robust against the influences of 'gender', 'FSIQ' and 'BDI' compared to the other factors (see Table 5.2). Based on these results the following hypotheses can be generated: In this subscale, the items do not represent the gender-specific expectations (see chapter 'The influence of gender on self-assessment of autistic traits') and are therefore assessed equally by both sexes.[93] Furthermore, impairments in imagination could be perceived as less deficient or stressful, so that gender-specific cognitive compensation mechanisms might not be necessary here. Perhaps this factor is the only one that could be independent of intelligence (in the normal to high-intelligence spectrum), or these items require less introspection than the other subscales, in line with the hypothesis in chapter 'Concerning the IQ and self-assessment of autistic traits', that the ability for an adequate self-report is connected with the IQ. Age could have an influence on imagination (or the self-assessment of imagination) in general, as this

influence was independent of the diagnosis ASD in this study. So far there are no studies on how imagination changes with age. If imagination is understood as part of the "theory of mind" as described above (quote from Baron-Cohen 2000)[147], the results of Maylor et al. (2002)[150] could be mentioned in this context. In their study with three different age groups (16-29, 60-74, 75-89), each consisting of 25 mentally healthy participants, the youngest group scored significantly better in the "theory of mind"-tasks (stories) than the older groups.[150]

Table 5.2 *Summary of influences of the variables on the subscales of the AQ-50 analysed in this study using 'Mann-Whitney U tests' and 'Spearman's Correlations' (see chapter 'Results').*

	Diagnosis	**Gender ASD+**	**Gender ASD-**	**Age ASD+**	**Age ASD-**	**FSIQ ASD+**	**FSIQ ASD-**	**BDI ASD+**	**BDI ASD-**
Social skills	+	+	+	+	+	+	0	0	0
Attention switching	0	+	+	+	0	+	0	+	+
Attention to detail	0	+	0	+	0	+	0	0	0
Communication	+	+	+	+	0	+	0	0	0
Imagination	+	0	0	+	+	0	0	0	0

+ = influence of variable on subscale; 0 = no influence of variable on subscale

Table 5.3 *Comparison and allocation of the items of the subscale 'Imagination' (AQ-50)*[5] *and the diagnostic Criteria A and B (DSM-5)*[11] *as well as I, II and III (ICD-10)*[12]

	Criterion A or I and II	**Criterion B or III**	**No conformity with DSM-5 or ICD-10**
Item 3: "If I try to imagine something, I find it very easy to create a picture in my mind" (disagree = score)			X
Item 8: "When I'm reading a story, I can easily imagine what the characters might look like" (disagree = score)			X
Item 14: "I find making up stories easy" (disagree = score)			X
Item 20: "When I'm reading a story, I find it difficult to work out the characters' intentions" (agree = score)			X
Item 21: "I don' t particularly enjoy reading fiction" (agree = score)			X
Item 24: "I would rather go to the theatre than a museum" (disagree = score)			X
Item 40 "When I was young, I used to enjoy playing games involving pretending with other children" (disagree = score)	"Lack of varied spontaneous make-believe play or (when young) social imitative play" (ICD-10 Criterion II.d)		
Item 41 "I like to collect information about categories of things (e.g. types of car, types of bird, types of train, types of plant, etc.)." (agree = score)		"Highly restricted, fixated interests that is abnormal in intensity or focus" (DSM-5 Criterion B.3)	
Item 42: "I find it difficult to imagine what it would be like to be someone else" (agree = score)	„Deficits in social-emotional reciprocity" (DSM-5 A.1)		
Item 50: "I find it very easy to play games with children that involve pretending" (disagree = score)	"Lack of varied spontaneous make-believe play or (when young) social imitative play" (ICD-10 Criterion II.d)		

Table 5.4 *Overlap between the subscales 'social skills', 'attention switching', 'attention to detail', 'communication' and 'imagination' of the Autism-Spectrum Quotient of Baron-Cohen et al. (2001)[5] and the diagnostic criteria of the relevant differential diagnoses of ASD in adulthood. Modified from Lehnhardt et al. (2013)[17], the content in quotation marks was directly quoted from the ICD-10 [12].*

	ASD	Schizoid PD	Schizotypal PD	Avoidant PD	Social phobia	Anankastic PD	Narcissistic PD	Dissocial PD	Borderline PD	Affective disorders*1 4	Psychotic disorders*1 4	OCD	ADHD
Social skills	▲	▲ *3	▲ *5	▲ *7	▲ *8	▲ *9	▲ *11	▲ *12	▲ *13	▲	▲	▲ *15	▲ *17
Restricted, repetitive, stereotyped patterns of behaviour and interests*1	▲	▲ *4	▲ *6	▲	▲	▲ *10	▲	▲	▲	▲	▲	▲ *16	▲
Communication	▲	▲ *3	▲ *5	▲ *7	▲ *8	▲	▲ *11	▲ *12	▲ *13	▲	▲	▲ *15	▲ *17
Imagination	▲	▲ *4	▲ *6	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲
Social interaction in childhood*2	■	■	■	■	■	■	■	■	■	■	■	■	■
Biographical stress factors*2	■	■	■	■	■	■	■	■	■	■	■	■	■

ASD = autism spectrum disorder; PD = personality disorder; OCD = obsessive-compulsive disorder; ADHD = attention deficit-hyperactivity disorder;
▲ = anticipated overlap; ▲ = potential overlap; ▲ = usually no overlap; ■ = (impairments) usually present; ■ = (impairments) potentially present; ■ = (impairments) usually not present;
*1 subscales 'attention switching' and 'attention to detail' were summarized into the criterion III of the ICD-10 criteria for autism; *2 due to Lehnhardt et al. (2013) and the ICD-10;
*3 "social withdrawal", "marked insensitivity to prevailing social norms and convention is unintentional"; *4 "excessive preoccupation with fantasy and introspection"; *5 "eccentric behaviour", "social withdrawal"; *6 "odd beliefs or magical thinking, influencing behaviour and inconsistent with subcultural norms"; *7 "avoidance of social activities"; *8 : "these fears are manifested in social situations";
*9 "excessive pedantry and adherence to social conventions"; *10 "preoccupation with details, rules, lists, order, organization, or schedule"; *11 "lack of empathy"; *12 "reduced empathy";
*13 "major difficulties in interpersonal relationships"; *14 depending on degree of severity and type of disorder; *15 "the obsessions or compulsions cause distress or interfere with the patient's social or individual functioning"; *16 the obsessions or compulsions "are repetitive"; *17 "the symptoms causes clinically significant distress or impairment in social, academic, or occupational functioning"

5.7 Limitations

Beside some strengths of this study, like the size of the sample, no missing items on the AQ-50 and the reliability of the diagnosis due to the extensive diagnostic process, there are also some important limitations. First, only individuals who scored above the cut-off of 26 were considered here. Therefore, no genuine (but relative) sensitivity and specificity could be calculated here. Probably there were individuals with an ASD below the threshold of the AQ-50 which could not be included and could have led to a bias especially in item analysis and the development of the AQ-10-revised. However, this is likely to apply to only a few individuals, as the sensitivity of the AQ-50 (cut-off $\geq$ 26) has been rated as good in various samples and studies (0.77 - 0.95).[2]

Furthermore, it must be pointed out that all calculations and results refer to the Autism Outpatient Clinic for Adults Department of Psychiatry and Psychotherapy, in Cologne and not to any other additional sample. So unfortunately, there is no validation sample here for the AQ-10-revised or the AQ-top-14. Moreover, our results are based on the German version of the AQ-50, language differences could have an effect here.

A bias concerning the calculations for the IQ and BDI could have resulted from the selection of the individuals for the NPT. Here, patients were excluded for whom an ASD could already be ruled out after the first interview, which also led to significantly more people with an ASD being included in these calculations (see also chapter 'Participants').[109] A randomized selection of the individuals would have been more appropriate in this context.

No further information about possible diagnoses in the control group (ASD-) or comorbidities in the ASD+ group were collected. It would be interesting to determine which differential diagnoses are the most similar to ASD in self-assessing autistic traits. In the study by Lehnhardt et al. (2012)[21] in which the psychosocial functioning of adults with an ASD from the same population was investigated, a comorbid "clinical relevant depression" was estimated to be about 30% (with the BDI), which was at a similar level as in our study (34%). As discussed above, it is questionable whether the BDI is a suitable instrument for detecting comorbid depression in ASD (see also chapter 'Correlations between BDI and self-assessment of autistic traits'). To date, however, there is no study that has examined the frequency of the differential diagnoses of ASD in an outpatient clinic for autism in adulthood. Depression as a differential diagnosis can be estimated in this study to be 42% in ASD- (with the already mentioned bias), although it must be pointed out that depression can also be a comorbidity in this group as well (e.g. a comorbid depression in a PD).[151] The common differential diagnoses were presented in chapter 'Comorbidity or differential diagnosis?', among those the anxiety disorders are the most prevalent mental disorders in the general population in Germany.[152]

Nevertheless, an anxiety disorder can also be a comorbidity in ASD- (for example in a PD) as well.[153]

An important limitation of this study is that individuals with diagnoses “other pervasive developmental disorders” (ICD-10: F84.8) and “pervasive developmental disorder, unspecified” (ICD-10: F84.9) or the equivalent of the DSM-IV “pervasive developmental disorders, not otherwise specified (PDD-NOS)” (299.80) were not included. This concerns 48 individuals and thus 3.4% of the sample (out of 1430 individuals without any missing items and without impairment in intelligence), including 31 males and 17 females (sex ratio 2:1) aged 18 to 56 (median = 27). The main argument for excluding these diagnoses from this study is that they cannot be reliably assigned to ASD+ or ASD- (as described in chapter ‘Classification, Symptoms and Diagnostic criteria’ and ‘Comorbidity or differential diagnosis?’). In diagnostics, it can be very difficult to distinguish between clinically relevant or subclinical autistic traits, which can result in false positive (for ASD+) or false negative (for ASD-) diagnoses.[51,61] This diagnostic difficulty can push the examination to the limits of its objectivity and reliability, which explains why it is essential to perform this diagnostic process with two independent examiners and examinations (at different dates).

Another possibility would have been to include these individuals in terms of a third group (next to ASD+ and ASD-). However, arguments against this approach are, that the current and future diagnostic systems (DSM-5 and ICD-11) categorically differentiate between ASD+ and non-ASD and thus exclude a third group (see chapter ’Classification, Symptoms and Diagnostic criteria’). This demonstrates the problem of “fluid transitions” between a diagnosis and exclusion of an ASD. On the other hand, the interpretation of the statistics would only have a considerably limited informational value due to the extreme group size differences (for example 544 ASD- males vs. 17 females of the “third group”).

Regarding gender, only the binary gender identities (males and females) were assessed and accordingly individuals of the non-binary gender identity were not taken into account. According to the guideline of the “German Society for Sexual Research (DGfS)” (“Deutsche Gesellschaft für Sexualforschung”)[154], the prevalence of potential gender incongruence in the normal population ranges between 0.6% and 2.2%, whereby there can be significant differences due to the heterogeneous terminology. Van der Miesen et al. (2018)[155] reported a higher prevalence of “wish to be of the opposite gender” in adolescents and adults with an ASD (1380 individuals) compared to a sample (1862 individuals) of the general population (3-5% in general population vs. 6.5-11.4% in ASD). Possibly, the lack of consideration of experienced gender identity, which may differ from the assigned gender, may have led to a bias in the interpretation of the findings concerning gender and the AQ and could be considered in future research.

What limits the findings concerning the AQ-10 is, that they only refer to a calculated score from the corresponding items of the AQ-50, possibly the AQ-10 would perform slightly differently. This also applies to our AQ-10-revised and the AQ-top-14. However, this corresponds to the method used in other important studies on the AQ-50 and AQ-10, including the studies of Ashwood et al. (2016)[3], Allison et al. (2012)[6] and Sizoo et al. (2015)[156].

As already mentioned, no data for the observation of autistic symptoms were collected in our study, for example with the ADOS or comparable tools. So, it may be intriguing and the task of further research to see, if people with a higher AQ really have more observable symptoms or not, including a focus on the influences of the variables gender, age and IQ.

In conclusion, it must be mentioned that this was an exploratory data analysis which was intended to generate new hypotheses for future research. This study was not intended to confirm or reject existing hypotheses and therefore post-hoc calculations were not taken into account (see also chapter 'An explorative-quantitative study').

5.8 Conclusions

Despite the limitations mentioned above, this exploratory data analysis of the largest clinical sample of adults with late diagnosed ASD to date provides important implications and hypotheses for screening, diagnostics and phenomenology of autism. By comparing the distributions of scores, it could be demonstrated that the AQ-50 separates poorly between individuals with an ASD (ASD+) and patients where an ASD could be ruled out (ASD-). As already stated in the DGPPN guidelines on screening of autism[2], if the cut-off of 26 is passed, no further information can be derived whether an ASD is likely or not. Nevertheless, the AQ-50 can still be used as a screening instrument due to its consistent and sufficient sensitivity over several studies. A central hypothesis of this investigation is that screening using a self-assessment tool is presumably complicated due to the limited self-perception of individuals with an ASD. Females or older adults with an ASD, who were expected to have fewer observed autistic symptoms according to the current state of research, assessed their autistic traits here as significantly more severe than their respective counterparts (males or younger individuals). Possibly, also the IQ has an influence on the self-perception of people with an ASD exclusively, since the AQ-50 correlated positively with the IQ only in ASD+, as opposed to age and gender. There was a significant influence of the variables gender and age on the AQ-50, therefore controlling these variables seems to be reasonable. This hypothesis was supported by the findings of the ROC analyses, since a better discrimination could be achieved by this approach. Therefore, this hypothesis could be tested in a future study, for example with a prospective design, comparing the current standard (via the AQ-50) with a screening that is controlled for gender and age.

There were no significant differences in full-scale IQ and the severity of depressive symptoms between ASD+ and ASD-. BDI scores did not correlate with those of the AQ-50, only the

subscale ‘attention switching’ possibly overlap with symptoms of depression in ASD. Further evidence for the ineffectiveness of the short version AQ-10 by Allison et al. (2012)[6] for the screening of autism could be found. Based on the same method as Allison et al. (2012)[6] used to select their 10 items from the AQ-50, here 7 other items could be identified for a new AQ-10-revised. Item analysis also revealed that for 9 items of the AQ-50, adults without an ASD scored more frequently than their counterparts with an ASD. For subscales ‘attention switching’ and ‘attention to detail’ no significant differences between ASD+ and ASD- could be found. These findings suggest a revision of the items of the AQ-50, possibly with more attention to criteria C (symptoms present since childhood) and D (symptoms are clinically relevant) of the DSM-5. In turn, limited imagination capabilities seem to be underrated in the ICD-10 and DSM-5, since scores in the corresponding subscale were significantly higher in ASD+ than ASD- and were not affected by gender and IQ. Overall, this study suggests that a detailed investigation of ASD- will be indispensable. Moreover, the comparison between observation and self-assessment of autistic symptoms will be essential to test the generated hypotheses.

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Mit Unterstützung von meinem Doktorvater Privatdozent Dr. Fritz-Georg Lehnhardt und Prof. Dr. Dr. Kai Vogeley habe ich vor der Dissertation ein Teil der Ergebnisse im Rahmen des Kongresses der „deutschen Gesellschaft für Psychiatrie und Psychotherapie, Psychosomatik und Nervenheilkunde“ (DGPPN) am 26.11.2021 als Präsentation vorgetragen.

7. Appendix

Table 7.1 *Effect sizes, compare Field (2015)*[114]

	Small effect	**Medium effect**	**Large effect**
Cohen's *d*	0.2	0.5	0.8
Correlation coefficient *r*	0.1	0.3	0.5

Table 7.2 *The Autism-Spectrum Quotient (AQ-50) by Baron-Cohen et al. (2001)*[5]

1.	I prefer to do things with others rather than on my own.	definitely agree	slightly agree	slightly disagree	definitely disagree
2.	I prefer to do things the same way over and over again.	definitely agree	slightly agree	slightly disagree	definitely disagree
3.	If I try to imagine something, I find it very easy to create a picture in my mind.	definitely agree	slightly agree	slightly disagree	definitely disagree
4.	I frequently get so strongly absorbed in one thing that I lose sight of other things.	definitely agree	slightly agree	slightly disagree	definitely disagree
5.	I often notice small sounds when others do not.	definitely agree	slightly agree	slightly disagree	definitely disagree
6.	I usually notice car number plates or similar strings of information.	definitely agree	slightly agree	slightly disagree	definitely disagree
7.	Other people frequently tell me that what I've said is impolite, even though I think it is polite.	definitely agree	slightly agree	slightly disagree	definitely disagree
8.	When I'm reading a story, I can easily imagine what the characters might look like.	definitely agree	slightly agree	slightly disagree	definitely disagree
9.	I am fascinated by dates.	definitely agree	slightly agree	slightly disagree	definitely disagree
10.	In a social group, I can easily keep track of several different people's conversations.	definitely agree	slightly agree	slightly disagree	definitely disagree
11.	I find social situations easy.	definitely agree	slightly agree	slightly disagree	definitely disagree
12.	I tend to notice details that others do not.	definitely agree	slightly agree	slightly disagree	definitely disagree
13.	I would rather go to a library than a party.	definitely agree	slightly agree	slightly disagree	definitely disagree
14.	I find making up stories easy.	definitely agree	slightly agree	slightly disagree	definitely disagree

15.	I find myself drawn more strongly to people than to things.	definitely agree	slightly agree	slightly disagree	definitely disagree
16.	I tend to have very strong interests, which I get upset about if I can't pursue.	definitely agree	slightly agree	slightly disagree	definitely disagree
17.	I enjoy social chit-chat.	definitely agree	slightly agree	slightly disagree	definitely disagree
18.	When I talk, it isn't always easy for others to get a word in edgeways.	definitely agree	slightly agree	slightly disagree	definitely disagree
19.	I am fascinated by numbers.	definitely agree	slightly agree	slightly disagree	definitely disagree
20.	When I'm reading a story, I find it difficult to work out the characters' intentions.	definitely agree	slightly agree	slightly disagree	definitely disagree
21.	I don' t particularly enjoy reading fiction.	definitely agree	slightly agree	slightly disagree	definitely disagree
22.	I find it hard to make new friends.	definitely agree	slightly agree	slightly disagree	definitely disagree
23.	I notice patterns in things all the time.	definitely agree	slightly agree	slightly disagree	definitely disagree
24.	I would rather go to the theatre than a museum.	definitely agree	slightly agree	slightly disagree	definitely disagree
25.	It does not upset me if my daily routine is disturbed.	definitely agree	slightly agree	slightly disagree	definitely disagree
26.	I frequently find that I don't know how to keep a conversation going.	definitely agree	slightly agree	slightly disagree	definitely disagree
27.	I find it easy to "read between the lines" when someone is talking to me.	definitely agree	slightly agree	slightly disagree	definitely disagree
28.	I usually concentrate more on the whole picture, rather than the small details.	definitely agree	slightly agree	slightly disagree	definitely disagree
29.	I am not very good at remembering phone numbers.	definitely agree	slightly agree	slightly disagree	definitely disagree
30.	I don't usually notice small changes in a situation, or a person's appearance.	definitely agree	slightly agree	slightly disagree	definitely disagree
31.	I know how to tell if someone listening to me is getting bored.	definitely agree	slightly agree	slightly disagree	definitely disagree
32.	I find it easy to do more than one thing at once.	definitely agree	slightly agree	slightly disagree	definitely disagree

33.	When I talk on the phone, I'm not sure when it's my turn to speak.	definitely agree	slightly agree	slightly disagree	definitely disagree
34.	I enjoy doing things spontaneously.	definitely agree	slightly agree	slightly disagree	definitely disagree
35.	I am often the last to understand the point of a joke.	definitely agree	slightly agree	slightly disagree	definitely disagree
36.	I find it easy to work out what someone is thinking or feeling just by looking at their face.	definitely agree	slightly agree	slightly disagree	definitely disagree
37.	If there is an interruption, I can switch back to what I was doing very quickly.	definitely agree	slightly agree	slightly disagree	definitely disagree
38.	I am good at social chit-chat.	definitely agree	slightly agree	slightly disagree	definitely disagree
39.	People often tell me that I keep going on and on about the same thing.	definitely agree	slightly agree	slightly disagree	definitely disagree
40.	When I was young, I used to enjoy playing games involving pretending with other children.	definitely agree	slightly agree	slightly disagree	definitely disagree
41.	I like to collect information about categories of things (e.g. types of car, types of bird, types of train, types of plant, etc.).	definitely agree	slightly agree	slightly disagree	definitely disagree
42.	I find it difficult to imagine what it would be like to be someone else.	definitely agree	slightly agree	slightly disagree	definitely disagree
43.	I like to plan any activities I participate in carefully.	definitely agree	slightly agree	slightly disagree	definitely disagree
44.	I enjoy social occasions.	definitely agree	slightly agree	slightly disagree	definitely disagree
45.	I find it difficult to work out people's intentions.	definitely agree	slightly agree	slightly disagree	definitely disagree
46.	New situations make me anxious.	definitely agree	slightly agree	slightly disagree	definitely disagree
47.	I enjoy meeting new people.	definitely agree	slightly agree	slightly disagree	definitely disagree
48.	I am a good diplomat.	definitely agree	slightly agree	slightly disagree	definitely disagree
49.	I am not very good at remembering people's date of birth.	definitely agree	slightly agree	slightly disagree	definitely disagree

50.	I find it very easy to play games with children that involve pretending.	definitely agree	slightly agree	slightly disagree	definitely disagree

7.1 Figures

7.2 Tables