Aging in autism: Symptomatology, co-occurring psychopathology, and cognitive functioning across the adult lifespan

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Chapter 7

Summary and general discussion
SUMMARY

Main findings
The current thesis provides a first series of large cross-sectional cohort studies on adults with ASD including individuals up to 80 years of age. While ASDs are heterogeneous, neurodevelopmental disorders characterized by difficulties in social communication and social interaction, and restricted, repetitive patterns of behavior, interests, or activities (American Psychiatric Association, 2000; American Psychiatric Association, 2013), the developmental trajectory of individuals with ASD across the adult lifespan is not well charted (Happé & Charlton, 2012; Perkins & Berkman, 2012; Piven & Rabins, 2011; Wright et al., 2013). In this thesis, we aimed at filling this gap. We focused on three essential domains, either for ASD or typical aging: symptomatology (Chapter 2), co-occurring psychopathology (Chapter 3), and cognitive functioning (Chapter 4, 5, 6). Taken together, the results converge to four major conclusions. First, the burden of ASD symptomatology and depression is high and particularly perceived in middle adulthood. Second, in the specific cohort of adults with ASD included in the current thesis, there was no evidence for an accelerated age-related decline (i.e., double jeopardy); the effect of age was even smaller in adults with ASD on some cognitive domains (i.e., safeguard) and parallel on most domains. Third, differences between adults with and without ASD on cognitive functioning are, if present, subtle and not pronounced. Fourth, there are important discrepancies between measures and between informants. While we need to be careful with drawing strong conclusions in this stage, we observed some interesting findings that will be discussed in further detail below. We will first summarize the findings of each investigated domain, followed by a critical discussion of the main results and we will end with implications and avenues for future research.

Symptomatology
In Chapter 2, we examined age-related differences in ASD symptoms in a large sample of intellectually able individuals with and without clinical ASD ($N_{\text{max}} = 435$). We obtained information about ASD symptomatology, including general symptoms, cognitive and affective empathy, and sensory sensitivity, by means of both self-report and proxy-report questionnaires. The symptomatology findings can be clustered into three major conclusions.

First, in line with the suggestion that ASD symptoms are likely to fluctuate over the lifespan, we found age-related differences in general ASD symptoms and sensory sensitivities. However, unlike previous longitudinal studies among younger adults that demonstrated improvement of symptoms over time (e.g., Howlin et al., 2013; Woodman et al., 2015), older
adults reported more general ASD symptoms and sensory sensitivities than young adults, while middle-aged adults reported more of these symptoms than young and older adults. A similar pattern was observed on sensory sensitivity, but age-related differences in cognitive and affective empathy were not detected.

Second, adults with ASD reported more ASD symptoms (e.g., Baron-Cohen et al., 2001; Ruzich et al., 2015), higher sensory sensitivity (Crane et al., 2009; Minshew & Hobson, 2008), and lower perspective taking and fantasy tendencies, similar empathic concern, and higher personal distress in reaction to the emotions of others (Rogers et al., 2007) than individuals without ASD. Moreover, we replicated earlier findings that females with ASD had more sensory issues and reported more ASD characteristics than males (Lai et al., 2011), whereas females without ASD manifested fewer ASD traits than non-ASD males (see Ruzich et al., 2015, for an overview). The high number of self-reported general ASD symptoms and sensory sensitivities and the persistence of these symptoms across the adult lifespan, emphasize the impact of this neuropsychiatric condition up to late adulthood.

Third, proxies who have known the participants for a long time did not report similar age-related differences in ASD symptoms. Furthermore, they reported no gender differences on ASD traits. Comparing self- and other-report of adults with ASD revealed that the proxies reported more ASD symptoms and fewer empathy and sensory sensitivities than participants themselves. Indeed, there were relevant discrepancies between self- and proxy-report. Nevertheless, poor agreement was not only observed among individuals with ASD: Also individuals without ASD showed inconsistencies with their proxies in the amount of reported symptoms.

**Comorbidity**

In Chapter 3, we compared psychological symptoms and psychiatric disorders between young, middle, and older adults with and without ASD by administering a neuropsychiatric interview (MINI) and self-reported questionnaires (N_max = 344). Furthermore, we explored several risk factors that potentially predicted psychopathology, specifically anxiety and depression, in individuals with ASD or in the general population. Our first main finding was that, comparable to other studies involving slightly younger adults (Hofvander et al., 2009; Lugnegård et al., 2011; Roy et al., 2015), 79% of the adults with ASD met diagnostic criteria for a psychiatric diagnosis at least once in their lives. As expected, most frequent disorders were mood (57%) and anxiety (54%) disorders, followed by ADHD (30%). Secondly, when examining potential differences between young, mid, and older adults, we found that older adults with ASD less often met diagnostic criteria for a psychiatric diagnosis than young and middle-aged adults. This pattern
has also been observed in large typical aging studies (Bijl et al., 1998; Kessler et al., 2005). While depression was most common in middle-aged adults with ASD, social phobia occurred less often in older adults with ASD than in younger adults with ASD. Thirdly, despite the fact that adults with ASD experienced many feelings of depression, anxiety, and psychological distress, these elevated rates were comparable to those reported by other psychiatric patients. Fourthly, more severe self-reported ASD symptoms and ASD symptoms as observed by an expert were both risk factors for (self-reported) depression and anxiety symptoms. While self-reported ASD symptoms and lower age constituted risk factors for the adherence of any lifetime anxiety disorder, as revealed by the neuropsychiatric interview, female gender was a risk factor for any lifetime mood disorder (including depression and dysthymia) after young adulthood.

**Cognitive functioning**

Typical aging is associated with age-related deterioration in cognitive functioning (e.g., Friedman et al., 2009; Hasher & Zacks, 1988; Hultsch, 1998; Park & Reuter-Lorenz, 2009; Salthouse, 2009). As there is overlap in the cognitive challenges encountered by typically developing older adults and young individuals with ASD, we examined in the remaining chapters several cognitive functions among adults with and without ASD by means of an extensive neuropsychological test battery (Chapter 4) and experimental paradigms (Chapter 5 and 6). We hypothesized three possible cross-sectional age-related trajectories. First, individuals with ASD could present a similar developmental trajectory compared to individuals without ASD, most likely characterized by an age-related decline in cognitive functioning. Second, individuals with ASD could demonstrate a divergent pattern in which age-related differences are increased compared to controls. In this hypothetical situation, ASD and aging would be two factors that jeopardize each other. Third, individuals with ASD could show a convergent pattern, characterized by reduced age-related differences compared to controls. ASD would then provide a ‘safeguard’ against age-related decline. Thus, we aimed to elucidate whether the developmental trajectory of adults with ASD followed a different age-related pattern compared to those without ASD.

**Memory, generativity, and theory of mind**

In Chapter 4, we examined age-related differences and strengths and weaknesses in verbal and visual episodic memory, generativity, and ToM of adults with and without ASD by means of a neuropsychological test battery and we explored the relation between objective and subjective cognitive functioning ($N_{max} = 236$). The main finding of Chapter 4 was that age-related differences in ASD were similar or reduced, but not increased, compared to typically developing controls. We demonstrated that this pattern was parallel (verbal memory, generativity, ToM) or
less pronounced (visual memory) in individuals with ASD compared to those without ASD. Hence, we found, like Geurts and Vissers (2012), mainly evidence for a parallel developmental trajectory and some evidence for the safeguard hypothesis. However, we did not replicate their findings that led to the hypothesis that age-related differences in cognition could be increased in ASD.

Secondly, cognitive strengths and weaknesses occurring in adulthood were still present in old age, although ToM impairments seem to be less apparent in late adulthood. Across the adult lifespan, individuals with ASD demonstrated relatively intact abilities in verbal episodic memory, outperformed the adults without ASD on visual memory, and showed difficulties in generativity. On ToM, a domain generally considered impaired in children and adolescents and young adults with ASD (Boucher, 2012; Yirmiya et al., 1998; but see Scheeren, de Rosnay, Koot, & Begeer, 2013), we found ToM difficulties in ASD when considering the whole adult lifespan. However, when focusing on only 50+ adults, these impairments were no longer observed. Finally, adults with ASD reported many cognitive failures in daily life. However, we found that these self-reported cognitive failures and neuropsychological test performance were unrelated in both adults with and without ASD.

In addition to the findings obtained with tasks frequently used within clinical neuropsychology, we assessed cognitive functioning more in depth by focusing on two EF domains: working memory and interference control.

**Working memory**

In Chapter 5, we examined working memory (WM) performance by means of an \( n \)-back task and compared the performance of adults with and without ASD, investigated age-related differences and inter-individual differences herein (\( N = 275 \)). The first finding was that \( n \)-back performance did not differ between adults with and without ASD on neither load level, even though individuals with ASD needed more time to respond. Being contrary to our expectations, we proposed that this result could be due to the task not being sufficiently challenging, the involvement of verbal WM to a greater extent than expected, or to individual differences. Even though children with ASD showed impaired WM performance on a similar task, only a minority accounted for this group difference (de Vries & Geurts, 2014). Hence, not all individuals with ASD presented WM deficits, and this could also be the case in adults.

Second, the age-related gradual decline observed in typical individuals was differentially expressed in ASD when allowing for a non-linear pattern. Although old age in ASD seemed to be associated with better WM performance, we argued that this finding should be interpreted with caution. Furthermore, also the additional exploratory Bayesian analyses suggested that the
evidence for age-related differences in WM performance among adults with ASD was rather small and, thus, barely worth mentioning. This shows that it is of importance to not just rely on the commonly used frequentist accounts and that alternative statistical procedures, such as a Bayesian approach, may provide an interesting and valuable addition to conventional methods (see also Chapter 6). Hence, although the pattern could still fit with the idea of ASD being a ‘safeguard’ for typical age-related decline in WM performance, careful interpretation about the pattern among older adults with ASD is warranted and further research is needed.

Third, of all potential factors, only estimated IQ constituted a factor that predicted inter-individual differences in age-gradients. However, differences in age-gradients were mostly due to the large heterogeneity within the small, lower IQ group. These results should, thus, be interpreted with caution.

**Interference control**

In Chapter 6, we investigated interference control by administering a Simon conflict task to two independent adult samples (Study 1: N = 42) (Study 2: N = 278). We compared measures of reactive (i.e., the expression and suppression of action impulses after the occurrence of a conflict situation within the same trial) and proactive control (i.e., the adjustment of behavior in response to a previous conflict situation in order to anticipate and prevent interference) and applied distributional analyses to examine temporal dynamics underlying these processes in ASD. The results can be summarized into two major findings. First, across the adult lifespan, our findings do not support the idea of behaviorally impaired reactive and proactive interference control processes in ASD. Nevertheless, we observed an important difference between young adult males, and middle-aged and older adult males and females. While young adult males with ASD demonstrated comparable interference effects in both reactive and proactive control, made as many fast errors on conflict trials as neurotypical controls and showed similar suppression on slow responses (Study 1), over the adult lifespan, males and females with ASD made fewer fast errors on conflict trials, and had overall slower and more accurate responses than controls on both reactive and proactive control (Study 2). These results converge to the idea that individuals with ASD adopt a more cautious response bias over the adult lifespan, which is not yet observed among young adults.

Second, increasing age was associated with longer RTs and more accurate responses in both groups. The strength of response capture was likely to be constant across the adult lifespan, whereas the efficiency of response suppression was increased in older adults. Moreover, older adults demonstrated a larger Simon effect after congruent trials than after incongruent trials compared to younger adults on RT. These findings may suggest that middle-aged and older
adults with ASD use a quantitatively different response strategy than young adults with ASD, reflected by longer response duration, higher accuracy rates, and fewer fast errors.

**GENERAL DISCUSSION**

What happens to ASD symptomatology, co-occurring psychopathology, and cognitive functioning when people with ASD grow old?

ASD is considered a developmental disorder (American Psychiatric Association, 2000; American Psychiatric Association, 2013). Developmental disorders originate in childhood and cause a delay in one or more psychological functions. What we know about ASD is mainly based on our knowledge of the condition in childhood (Mukaetova-Ladinska et al., 2012). However, this thesis substantiates the idea that several problems are still present in adulthood. Moreover, our findings suggest different developmental trajectories across the adult lifespan in ASD.

When focusing on ASD symptomatology and co-occurring psychopathology (Chapter 2 and 3), it becomes evident that many ASD-related symptoms and other psychopathology are experienced throughout adulthood. Furthermore, the personal burden of ASD symptomatology and depression is particularly perceived in middle adulthood. What gives rise to these elevated rates, especially in midlife? Midlife is associated with increased demands of responsibility, shifting roles, and adjustments to changes. It is a rather broad period approximately expanding from 40 to 60 years (albeit even broader ranges have been considered) in which people may need to deal with changes in multiple domains, including psychosocial, emotional, and physical changes (see Lachman, 2004, for an overview). For example, this period can be governed by the care for young children or seeing grown up children leave home; by reconsidering one’s role in relation to one’s parents, such as in case of caregiving or death; by the role of work, either paid or voluntary, such as making career or the transition to retirement; by changes in physical functioning, such as the emergence of health problems or menopause. In childhood, adolescence, and maybe also young adulthood, parents often provide support and structure, but when they pass away or they become in need of support themselves, parents will be unable to do so. This will lead to increased demands on middle-aged adults. Hence, the life events occurring in this specific stage of life may require substantial resources that could be lacking or be inefficient in adults with ASD. For example, reduced flexibility in ASD may cause difficulties in making adjustments to changes in the environment, and reduced social skills may lead to social rejection or misinterpretation. Considerable distress would be a consequence (Tantam, 2000). It has been suggested that individuals with ASD miss the coping skills to adequately deal with stressors (Groden, Baron, & Groden, 2006) and high anxiety levels were found to be related to
the ability to cope with change, anticipation, sensory stimuli, and unpleasant events (Gillott & Standen, 2007), suggesting a relationship between coping skills and coping strategies and the experience of psychological distress and symptoms. Thus, midlife challenges in combination with impairments associated with ASD and reduced coping skills (or ineffective coping strategies) may account for the high levels of experienced ASD symptoms and the increased vulnerability for psychopathology. Nevertheless, it remains unclear whether more symptoms are experienced due to the challenges of this life period or whether symptoms increase independent of these challenges. Please also note that age-related differences in the personal burden of adults with ASD are not perceived by well-known proxies (Chapter 2).

In Chapters 4, 5, and 6, we examined age-related differences in cognitive functioning and compared developmental trajectories between adults with and without ASD. In contrast to the popular idea that there might be an accelerated decline in ASD due to the presence of several risk factors (Happé & Charlton, 2012; Mukaetova-Ladinska et al., 2012; Piven & Rabins, 2011), our findings mainly supported the hypothesis of a parallel trajectory in which individuals with and without ASD showed similar age-related differences across the adult lifespan (Chapter 4 and 6). This suggests that, despite increased vulnerability, there are other factors that may protect against accelerated decline in this specific group of adults with ASD. The fact that anxiety and depression were experienced by many, but not all adults with ASD, raises the question whether there is a subgroup of adults with ASD that is at risk for accelerated decline. These potential individual differences in vulnerability are a new interesting research area.

Nevertheless, the age-related pattern in ASD seemed to fit the safeguard hypothesis in three domains by showing attenuation with age (Chapter 4 and 5). Age hardly appeared to affect performance in visual memory (immediate recall and recognition), ToM, and WM in adults with ASD. Based on these findings, we could hypothesize that adults with ASD rely on other strategies than controls. For example, as shown in Chapters 5 and 6, individuals with ASD show similar or enhanced accuracy rates compared to controls at the expense of slower responses. Their strategy seems, thus, to be featured by accuracy rather than speed. On a similar note, we could speculate that the adopted strategy by controls declines with age, whereas that of adults with ASD does not. For example, in ToM, individuals with ASD without ID mainly seem to use their verbal and reasoning skills to be able to make explicit inferences about another person’s thoughts, beliefs, intentions, and behavior, as they lack the implicit ToM abilities that enable them to quickly and intuitively understand social situations (Senju et al., 2009). Typically developing adults mainly rely on spontaneous, implicit ToM throughout their lives. Whether and how these two ToM aspects are sensitive to age-related decline is, however, unclear. Hence, it remains an issue for future research to determine whether indeed the lack of age-related effects
as observed in the aforementioned cognitive domains in individuals with ASD is due to differences in strategy use.

**How to explain the discrepancy between informants and between measures?**

In this thesis we observed discrepancies on two dimensions. Inconsistencies were detected between self and proxy informants (Chapter 2) and between objective and subjective cognitive measures (Chapter 4).

While self-report is a valuable tool to gain insight into a person’s experience and understanding of certain feelings, thoughts, and behaviors, it is sensitive to metacognitive abilities. Poor introspection has been reported in ASD (Frith, 2004; Johnson et al., 2009; Kievit & Geurts, 2011), but the reliability of self-reports from intellectually high functioning adults with ASD have also been shown (De la Marche et al., 2015). Our results indicate poor agreement between raters (Chapter 2). However, given that low agreement was observed in both the ASD group and the comparison group, it seems unsuitable to conclude that this is due to poor metacognitive abilities in ASD. Rather, a rater bias (Hirschfeld, 1993; John & Robins, 1993; Leising et al., 2010) or a different way of perceiving or experiencing behavioral traits (Carlson et al., 2013) may reflect the discrepancy between self- and proxy-report.

With regard to objective cognitive measures, we found that differences between adults with and without ASD on cognitive functioning such as memory, generativity, and ToM (Chapter 4), WM (Chapter 5), and interference control (Chapter 6) are, if present, subtle and not pronounced. When exploring individual differences in cognitive functioning, we found that only a few individuals had performances that significantly deviated from a normative mean based on performance of the neurotypical comparison group (Chapter 4). Hence, if present, cognitive impairments in ASD did not seem clinically significant. Nevertheless, adults with ASD subjectively experienced many cognitive daily challenges as revealed by self-report, which were unrelated to test performance (Chapter 4). Forty percent reported clinically significant failures (<2SD below normative mean). Importantly, there was, thus, a discordance between subjective cognitive complaints and objective test performance.

There are several potential factors that may account for this discrepancy. One could hypothesize that individuals over-report or exaggerate their symptoms. As the individuals in our sample were intellectually high functioning, they may feel the need to report many symptoms in order to get recognition of their difficulties and, in consequence, appropriate help. However, this is not a likely explanation given that proxies reported even more difficulties than those with ASD themselves on the questionnaire focusing on symptomatology (Chapter 2). Alternatively, as information is differently processed in ASD and individuals with ASD are more prone to
focus on details (Happé & Frith, 2006; Mottron et al., 2006), individuals with ASD may perceive certain feelings, thoughts, and situations as much more intense and problematic compared to individuals without such a condition or they may be excessively focused on the perceived difficulties. Also, if there are impairments in taking another person’s perspective (Chapter 2 and 4), small daily failures may be interpreted as actual difficulties rather than situations that are experienced by many people or are suited to a stage of life. The combination of a focus on details and difficulties in contextualizing perceived failures may lead to the report of many cognitive challenges.

Although these aspects can all be involved, in related research domains there have been numerous attempts to examine the clinical relevance of self-evaluations on cognitive failures. While some studies address the importance of these subjective reports to predict cognitive decline or dementia (see Jonker, Geerlings, & Schmand, 2000, for an overview), others link these complaints to personality traits, psychiatric symptoms, or physical health problems. For example, subjectively experienced cognitive failures are associated with personality traits, such as neuroticism (Comijs, Deeg, Dik, Twisk, & Jonker, 2002) and conscientiousness (Lane & Zelinski, 2003), depression (Comijs et al., 2002; Ponds, van Boxtel, & Jolles, 2000; Zimprich, Martin, & Kliegel, 2003) and anxiety symptoms (Comijs et al., 2002), and physical health problems (Comijs et al., 2002). Depression and anxiety are common in individuals with ASD (Chapter 3) and physical health problems are often reported (Croen et al., 2015). The high rates of subjectively reported cognitive complaints among adults with ASD could, thus, also be explained in light of these aspects.

Finally, according to Toplak and colleagues (2013), self-ratings reflect typical performance, whereas psychometric tests reflect optimal performance. Subjective experiences of cognitive failures may reflect daily life difficulties, which may not (yet) be captured by our selection of laboratory tasks.

**Are cognitive complaints risk factors for developing dementia?**

Even though our neuropsychological assessment did not reveal obvious cognitive difficulties in ASD (Chapter 4) and the findings did not indicate accelerated age-related decline in individuals with ASD (Chapter 4, 5, and 6), the elevated number of cognitive complaints warrant further research. Longitudinal studies show a relationship between higher cognitive complaints and a more rapid cognitive decline (Hohman, Beason-Held, Lamar, & Resnick, 2011), and an increased risk of Alzheimer’s dementia, especially in individuals with a high education (van Oijen, de Jong, Hofman, Koudstaal, & Breteler, 2007). If cognitive complaints are a true representation of (subtle) cognitive failures, rather than the result of over-reporting, hypersensitivity, personality,
or psychopathology, and are a risk factor for Alzheimer’s dementia, then we would expect a higher rate of Alzheimer’s dementia in aging individuals with ASD.

However, it has recently been reported that individuals with ASD would suffer less frequently from Alzheimer’s dementia than a general or schizophrenia population based on a database analysis (Oberman & Pascual-Leone, 2014) but this could result from a report bias. Individuals with ASD may be more hesitant to contact preventive health services (Croen et al., 2015), there are likely many unrecognized cases of ASD among older adults (Brugha et al., 2011), and a reduced social network may cause delayed detection of initial cognitive impairment (Howlin et al., 2013). Not only in contrast to the study of Oberman and Pascual-Leone (2014) but also against this line of reasoning, is a recent study on the health status of adults with ASD that showed that dementia is more prevalent in ASD than in controls (respectively, 2.3% against 0.5%) and that females with ASD are more at risk than males with ASD for dementia compared to, respectively, females or males without ASD (Croen et al., 2015). The methodology of both studies may account for these substantial differences. While Oberman and Pascual-Leone (2014) based their prevalence rates on a database query on Harvard hospital records, Croen and colleagues (2015) based their findings on data of general health care on adults over 18 years of age. However, more importantly, Oberman based her conclusion on the comparison between people over 55 years of age with ASD (3.7%) and those without ASD (13%). This rate in the non-ASD population is far higher than those reported by large population-based cohort studies (Lobo et al., 2000) or the prevalence estimated by an expert panel (Ferri et al., 2006), suggesting that the comparison group is atypical. Finally, it should be kept in mind that 20% of the adults with ASD in the Croen study had an intellectual disability and there is an increased risk for dementia in intellectually disabled people (Strydom, Chan, King, Hassiotis, & Livingston, 2013). These considerations and inconsistent findings affirm the need for further research to examine whether ASD is an increased vulnerability factor for developing dementia, for example by studying whether and how subjective complaints have predictive value for developing dementia in ASD. Hence, even though cognitive performance difficulties in ASD may be clinically insignificant and there are several plausible explanations for the elevated perceived subjective difficulties, the discordance with subjective experiences still warrants further research.

**Strengths, limitations, and future directions**

Given the limited knowledge on ASD over the adult lifespan, and mainly late adulthood, investigating age-related differences in cross-sectional studies represents a logical initial step and provides valuable insight into ASD among older adults. However, while the current sample is unique due to the inclusion of a large group of adults over 50 years of age, a cross-sectional
design does not allow drawing conclusions about changes in symptomatology, psychopathology, and cognitive functioning over the years within individual developmental trajectories. Several longitudinal studies have examined also ASD symptoms (e.g., Howlin et al., 2013; Woodman et al., 2015), but not yet until old age and most studies are based on parent report. To overcome this gap a follow-up study to gather longitudinal self-reported data, including ASD symptomatology, cognitive failures, psychological distress, and quality of life has recently started in our lab. This new study will provide knowledge about how adults with ASD perceive their functioning over the years. Furthermore, for example, cognitive age-related changes in longitudinal studies do not always show the same patterns as age-related differences of cross-sectional designs (Nyberg et al., 2012; Raz & Lindenberger, 2011). Therefore, the examination of longitudinal changes in ASD symptomatology, psychopathology and cognitive functioning across middle and late adulthood should also constitute a next step in ASD research.

Our ASD sample consisted of individuals who already had a formal, clinical diagnosis within the autism spectrum before participating in the project, generally after thorough assessment by a multidisciplinary team. Nevertheless, we included a specific subgroup of individuals with ASD. Firstly, while 16-70% of the ASD population has an intellectual disability (Matson & Shoemaker, 2009), we included only adults with an estimated IQ above 80. Yet, estimated IQ did not differ between the ASD and comparison group (Chapter 2-6) and it did not constitute a risk factor for psychiatric comorbidity (Chapter 3), even though it appeared to be a significant predictor of age gradients in WM performance (Chapter 5). Secondly, one may argue that the ASD participants described in the current thesis presented relatively mild symptoms due to their late, mostly in adulthood, diagnoses. However, the elevated number of ASD traits reported by both self and proxy (comparable to the original sample of Baron-Cohen et al., 2001 and to the clustered sample mentioned in the recent review of Ruzich et al., 2015) (Chapter 2), the elevated number of psychological distress and many psychiatric problems (Chapter 3), the anecdotal accounts of problems with interpersonal relationships and jobs, and the lower quality of life (results not presented in the current thesis), do reveal that adults with ASD experience serious difficulties. Hence, they might be able to camouflage their symptoms until adulthood, for example due to sufficient cognitive abilities (Heijnen-Kohl & van Alphen, 2009), but perceive and experience a heavy burden of their condition later in life. Thirdly, we included a relatively large sample of females with ASD in the presented studies (males:females ratio = 3:1). While generally the ratio between males and females is estimated on 4-5:1, it has also been suggested that this proportion might be lower (2-5:1) (see Halladay et al., 2015; Lai, Lombardo, Auyeung, Chakrabarti, & Baron-Cohen, 2015, for an overview). However, in contrast to the previous idea that this ratio is especially lower in individuals with co-occurring
intellectual disability (ID), dissociations from ID have been reported (Idring et al., 2012) and the male bias seems less pronounced than formerly assumed (see Lai et al., 2015, for an overview). In this light, our proportion of females represents a strength rather than a limitation. As numbers of diagnoses in adulthood are rising, it is a possibility that the group investigated in the current thesis share many characteristics with other individuals diagnosed with ASD in adulthood. Yet, it is important to keep in mind that our conclusions might not hold for those with a lower IQ and/or with early diagnosis and/or in need of substantial support. Directions for future research include the extension of aging research to the entire autism spectrum.

The large majority of the ASD participants had a psychiatric co-occurring diagnosis at least once in their lives and used psychotropic medication. On the one hand this augments the representativeness of the sample, as comorbidity and medication usage is rather common. On the other hand, psychopathology may influence cognitive functioning (e.g., Engelhardt et al., 2008; Paterniti et al., 2002) and self-reported cognitive functioning (Comijs et al., 2002; Ponds et al., 2000; Zimprich et al., 2003). A previous study in adult males with ASD demonstrated that comorbid conditions did not affect cognitive performance (Wilson et al., 2014), and in one of our studies it also was unrelated to cognitive performance (Chapter 5). However, we did not check whether this was also the case in the other studies and we only inquired about lifetime psychiatric disorders rather than current disorders. Finally, psychotropic medication may affect cognitive functioning by enhancing (e.g., Grön, Kirstein, Thielcher, Riepe, & Spitzer, 2005; Sahakian & Morein-Zamir, 2007) or reducing (e.g., Barker, Greenwood, Jackson, & Crowe, 2004; Deptula & Pomara, 1990; Tannenbaum, Paquette, Hilmer, Holroyd-Leduc, & Carnahan, 2012) it, but we did not control for this potential influence. Future research may shed light on these issues.

We used Bayesian hypothesis testing to explore the evidential strength for our findings in Chapter 5 and 6. This approach provided an interesting and valuable addition to conventional methods and it is of interest to use this statistical approach more often. While the majority of our studies investigated cognition in ASD (Chapter 4, 5, and 6), we selectively examined cognitive control and did not consider, for example, cognitive flexibility and planning. Furthermore, only one aspect of ToM was taken into account and weak central coherence was not studied at all. This represents a limitation of our study. Nevertheless, our results are in line with the idea that EF and ToM problems are not universal (Chapter 4, 5, and 6), which underlines the relevance of studying inter-individual differences and subgroups of individuals with ASD.

Finally, in line with the manual in use at the start of our study, the ASD participants were diagnosed according to DSM-IV criteria with autistic disorder, Asperger’s syndrome, or PDD-NOS (American Psychiatric Association, 2000). In the current DSM-5, this distinction is
abolished and changed into one spectrum diagnosis with a severity indication based on one’s need for support. Although we examined sensory sensitivity, a domain newly added to the DSM-5, we are not able to meet all amendments of the DMS-5 and, for example, to draw conclusions on a severity indication of the participants.

**Clinical implications**

ASD is a highly disabling disorder that affects approximately 1% of the population (Brugha et al., 2011). With the increasing number of older adults as a result of the aging population and the increasing number of diagnosed cases in (late) adulthood, this has an impact on costs for health care and use of services. Also, it requires clinicians to be aware of the ASD phenotype in late adulthood, which is often still lacking (van Nickerk et al., 2011). Furthermore, professionals working in elderly homes would benefit from more awareness about ASD in older adults. Hence, the findings presented in this thesis may have a number of clinical implications.

The age-related differences observed in ASD symptomatology (Chapter 2) suggest that it would be meaningful to regularly inquire after the experience of symptoms throughout the adult lifespan in clinical settings. Hence, not only at the time of diagnosis, but also during follow-up. Furthermore, the increased behavioral symptoms (Chapter 2) and increased rates of depression in middle adulthood (Chapter 3), suggests the importance of monitoring individuals with ASD in middle adulthood and providing adequate support to reduce stress and distress, and improving their well-being.

Females with ASD reported more ASD traits than males with ASD, whereas this gender difference was not perceived by proxies (Chapter 2). A meta-analysis on gender differences in core ASD symptoms as reported by parents or as denoted by observational instruments, demonstrated that females with ASD show similar social and communication symptoms, but fewer restricted, repetitive behaviors than ASD males (Van Wijngaarden-Cremers et al., 2014). This latter difference may, however, be because female interests were not detected and recognized as restricted and repetitive (Halladay et al., 2015). Moreover, in presence of similar ASD symptom severity in childhood, females showed less deviant current behaviors in social interaction and communication (Lai et al., 2011). These findings and the gender comparable ASD traits as perceived by proxies in the presence of more self-reported ASD traits by females, may support the idea that females are, in general, better in camouflaging (i.e., masking or compensating for) their condition (see Lai et al., 2015). They could be more motivated by societal expectations, take more effort to develop social skills, and may have better self-referential abilities (Lai et al., 2011). However, females may also more strongly perceive their symptoms or, although highly speculative, they may feel the need to report more ASD symptoms. They might
do the latter in order to be recognized as having ASD, getting access to the mental health system and receiving appropriate treatment, as ASD in girls and women is still underdiagnosed (see Halladay et al., 2015, for an overview). Even though this latest suggestion seems unlikely given that the female participants in our study already had a clinical diagnosis, clinical professionals should be aware of possible symptomatic differences between males and females. Finally, our findings indicate that females with ASD are vulnerable for dysphoria related to the period preceding menstruation and, especially after young adulthood, for mood disorders (Chapter 3). This may require special attention in terms of support or treatment.

Diagnosing older individuals is complicated (Heijnen-Kohl & van Alphen, 2009). Often, there is no developmental history available (Geurts & Jansen, 2012; Happé & Charlton, 2012) and expression of symptoms may change over the adult lifespan. It would then be important to have an appropriate measure to observe current symptoms. The ADOS has been considered as one of the ‘gold-standard’ instruments for ASD assessment (Ozonoff, Goodlin-Jones, & Solomon, 2005). Although it was developed as a research instrument (Lord et al., 2000) and has proven its usefulness in this regard, it is currently also in use by clinicians as part of multimethod assessment. Although we did not investigate the validity of the ADOS and it was not our purpose to draw conclusions about this instrument, our experience with the ADOS, and those of others working with intellectually high functioning adults (e.g., Bastiaansen et al., 2011; Ring et al., 2016), suggests that the ADOS is not sensitive enough to detect ASD in adults who do not have an intellectual disability, are diagnosed in adulthood, and are not in need of substantial support. Therefore, we suggest, in line with the Dutch ASD guidelines (Trimbos, 2013) that clinicians should not only rely on one instrument such as the ADOS when assessing ASD, even though the ADOS can be fruitful when used in combination with other measures.

Moreover, our findings also suggest that it is important to rely on more than one source for diagnostic assessment (see again Dutch guidelines; Trimbos, 2013). This reliance on multiple sources is especially important as it is often the partner who initiates the diagnostic process (National Institute for Health and Clinical Excellence, 2012; Trimbos, 2013) and often a family member is involved in the assessment of the developmental history, if possible. Hence, a proxy has a pivotal function. Our findings indicate that whether the proxy is a partner, family member, or friend does not largely affect the report of ASD-related symptoms (see Supplementary material Chapter 2), despite subtle differences. However, clients and proxies seem to perceive different aspects of ASD symptomatology. The discrepancies observed between both informants may provide an interesting contrast to discuss during assessment.

The findings indicate that the neuropsychological profile of adults with ASD without intellectual disability does not reflect severe cognitive difficulties (Chapter 4, 5, 6). Clinicians,
thus, should be aware that cognitive problems may not be pronounced in adults with ASD. Moreover, the observed strengths represent useful targets for treatment. Although age may have a negative impact on the cognitive functioning of individuals with ASD, as it does in the general population, this does not seem to lead to a more severe trajectory in ASD.

Even though cognitive functioning does not appear severely impaired as measured with neuropsychological and experimental tests, adults with ASD report poor well-being. Cognitive failures are often experienced, severity of self-reported symptoms is pronounced, psychological distress is high, co-occurring psychopathology is common, and medication use is frequent. Exploratory analyses on available data also indicate that quality of life is low in adults with ASD. Although interventions for adults with ASD are limited (Brugha, Doos, Tempier, Einfeld, & Howlin, 2015), these poor subjective experiences underline the need for adequate interventions and support to reduce the personal burden of adults with ASD. Guidelines indicate that psychoeducation is a first step in providing this support. The results presented in this thesis provide a basis for the development of such a psychoeducation for older adults with ASD, which is currently being tested for its effectiveness.

To conclude, the findings of the large pioneering study presented in this doctoral thesis indicate that for the majority of the examined adults with ASD, who are referred to mental health services and who are intellectually high functioning, relatively independent, and diagnosed later in life, experience of ASD-related and psychiatric symptoms and cognitive failures is substantial. However, no evidence for accelerated cognitive decline has been found, which may provide some reassurance to individuals with ASD across the adult lifespan.