Aging in Autism

Anne Geeke Lever

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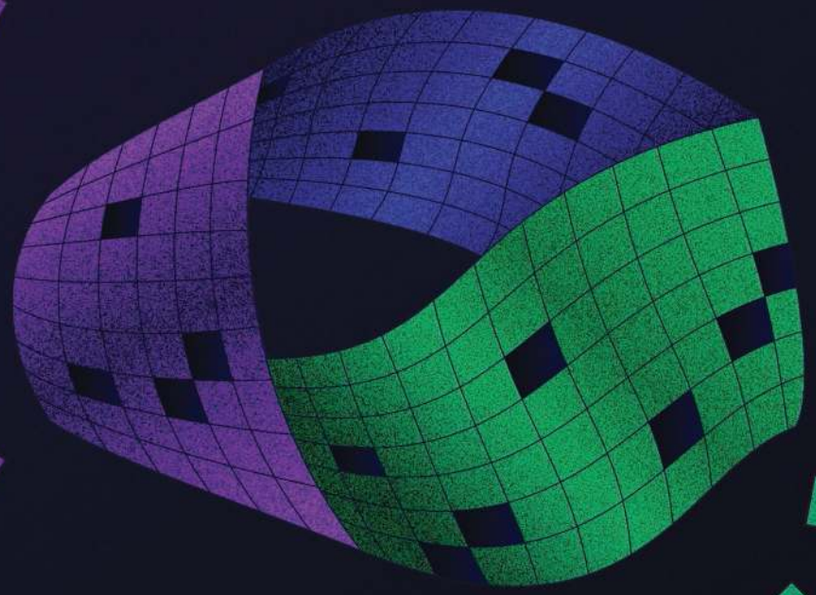
Symptomatology, co-occurring psychopathology, and cognitive functioning across the adult lifespan



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Chapter 1

General introduction

In the 1940s, Leo Kanner described several cases of children suffering from "inborn autistic disturbances of affective contact" or "early infantile autism". The behavior of these children was mainly characterized by an inability to relate to people, but also included an unusual desire for aloneness, an insistence on sameness, echolalia, and disturbance by loud noises and moving objects (Kanner, 1943; Kanner, 1944). In the same period, Hans Asperger noticed analogous peculiarities in children labeled as "autistic psychopaths" (Asperger, 1944). In addition to the observed commonalities, both Kanner and Asperger mentioned considerable differences between children in the severity and quality of manifested symptoms. Although the concept of autism has been subject to several changes throughout the years, both authors described features that are still considered at the core of the disorder. Currently, we use the term "autism spectrum disorder" (ASD) to refer to lifelong, heterogeneous, neurobiological developmental disorders characterized by persistent deficits in social communication and social interaction, and restricted, repetitive patterns of behavior, interests, or activities, which cause clinically significant impairments in daily functioning (American Psychiatric Association, 2000; American Psychiatric Association, 2013; Volkmar, Lord, Bailey, Schultz, & Klin, 2004).

Although it was initially described as a childhood disorder (Kanner, 1943; Kanner, 1944) and research has mainly focused on ASD in children (Mukaetova-Ladinska, Perry, Baron, & Povey, 2012), the persistence of autistic behavior into adulthood has been recognized (Gillberg & Steffenburg, 1987; Kanner, 1971; Rumsey, Rapoport, & Sceery, 1985) and evidence exists for the lifelong nature of the condition. For example, the prevalence rate found in an adult population is similar to the estimates reported in children and adolescents, namely approximately 1% (Brugha et al., 2011), and the diagnostic status of ASD has been proven to be relatively stable (see Magiati, Tay, & Howlin, 2014, for an overview; Billstedt, Gillberg, & Gillberg, 2011; Cederlund, 2008; Howlin, Moss, Savage, & Rutter, 2013; Piven, Harper, Palmer, & Arndt, 1996). Even when diagnostic criteria are no longer met, ASD-like behavior and significant difficulties often continue to be present (Piven et al., 1996). Being a relatively 'modern' diagnosis (Happé & Charlton, 2012), those children described in the 1940s are now approaching an advanced age. For example, Donald T., the first case described by Leo Kanner (1943), is currently 82 years old. However, knowledge on ASD in late adulthood is limited and, yet, needed (Happé & Charlton, 2012; Perkins & Berkman, 2012; Piven & Rabins, 2011; Wright, Brooks, D'Astous, & Grandin, 2013).

Research into aging and ASD is warranted for various reasons. Firstly, aging adults with ASD are likely to face challenges associated with their own condition, but also with those related to the aging process (Mukaetova-Ladinska et al., 2012), possibly leading to increased difficulties, lower well-being, and a greater reliance on health services. Secondly, the aging population is

rising. According to the World Health organization (WHO), in 2050, more than 1 in 5 individuals will be 60 years or older. This would also translate to an increased number of older adults with ASD. Furthermore, independently from the growing aging population, the number of ASD diagnoses is increasing. Although it is unclear whether the incidence of ASD has augmented, at least diagnostic criteria have been broadened, awareness of the condition has increased, and ascertainment has improved (Fombonne, 2009; Rutter, 2005). Thirdly, lifetime incremental societal costs for individuals with ASD are extremely high and mainly due to lost productivity and adult care (Ganz, 2007), but those costs necessary for the care or treatment of individuals with ASD in the sixth decade of life or older are not yet estimated. As these costs are expecting to rise, the need to adopt a life course perspective and to identify and anticipate older adults' requirements for support and service in order to alleviate the societal burden of ASD becomes evident (see Perkins & Berkman, 2012; Totsika, Felce, Kerr, & Hastings, 2010; Wright et al., 2013). These potential implications on an individual and clinical, as well as societal level indicate that it is worthwhile to study a developmental process such as aging in a developmental disorder such as ASD.

Aging is a dynamic process associated with several changes. While some of these changes are related to growth, such as a gain of knowledge and wisdom, other changes involve losses, such as a decline in physical and cognitive functioning (Baltes, Staudinger, & Lindenberger, 1999). As ASD in late adulthood is largely under-examined, it seems reasonable to focus on basic issues. Therefore, we will first investigate ASD symptomatology and its cross-sectional developmental trajectory. Given that psychiatric disorders such as depression and anxiety are commonly associated with ASD, the second emphasis is on co-occurring psychopathology. Thirdly, as typical aging is associated with an age-related decline in several cognitive domains, we will examine cognitive functioning in ASD. We do not only consider late adulthood, but also young and middle adulthood. Development is a continuous process of acquisition, maintenance, transformation, and attrition that encompasses the entire life course (Baltes et al., 1999). Examining ASD over the adult lifespan should allow us to identify more subtle age-related differences. Within this chapter, we provide an overview of the described three main themes (i.e., ASD symptomatology, co-occurring psychopathology, and cognitive functioning) and conclude with an outline of this dissertation.

Symptomatology of ASD

Given that the diagnosis of ASD is based on the presentation of certain behavioral symptoms and the developmental trajectory of these symptoms over the adult lifespan is largely unknown, this will be the first focus of this dissertation. While at the start of the studies described in the

following chapters the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 2000) was in use, clinicians and researchers currently refer to the fifth edition (DSM-5) (American Psychiatric Association, 2013). Important changes of this revision include the abolition of various subtypes (i.e., autistic disorder, Asperger's syndrome, pervasive disorder not otherwise specified) and the formation of one overall autism spectrum diagnosis (i.e., ASD), the shift from a triad of impairments (i.e., social deficits, communication deficits, and restricted, repetitive behaviors and interests [RRBIs]) to a dyad (i.e., social-communication impairments and RRBIs), and the addition of atypical sensory behavior as a RRBI subdomain. In line with the former edition, we refer to the three diagnostic subtypes of the DSM-IV in the next chapters (i.e., participants were diagnosed according to DSM-IV criteria). However, in order to also meet the amendments of the diagnostic criteria, we mainly describe ASD symptomatology as currently defined by the DSM-5 and we also investigate a newly relevant subdomain in the DSM-5 (i.e., sensory sensitivity).

As aforementioned, core symptoms of ASD include qualitative impairments in social communication and social interaction, and restricted, repetitive patterns of behavior, interests, or activities (American Psychiatric Association, 2000; American Psychiatric Association, 2013). More specifically, atypicalities in social-emotional reciprocity, nonverbal communication, establishing and maintaining relationships, and sensory sensitivity are observed. The severity and quality of the symptoms varies across individuals (American Psychiatric Association, 2013). Some individuals with ASD are non-verbal, have an intellectual disability (ID), and require substantial support. Others possess good language and intellectual abilities, are able to live independently, have a partner, and maintain a job. Although milder ASD symptoms, early language development, and higher intellectual abilities predict better outcomes (Howlin & Moss, 2012), outcome of the majority of individuals with ASD is rather poor (see Henninger & Taylor, 2013; Howlin & Moss, 2012; Levy & Perry, 2011; Magiati et al., 2014, for reviews).

The onset of ASD lies within childhood, but symptoms may not become fully manifest until the requirements of the environment exceed an individual's ability (American Psychiatric Association, 2013). For instance, an adult may run into difficulties when starting a romantic relationship in which emotional reciprocity is required or when retiring from work after which daily structure falls away. Among adolescents and adults with ASD there is much more variability in the presentation of ASD symptoms and functional impairments when compared to children with ASD (Lai & Baron-Cohen, 2015). Furthermore, throughout the years, individuals may develop coping or camouflaging strategies to mask specific social difficulties (Lai et al., 2011). Hence, in addition to behavioral heterogeneity across individuals, symptoms may also change over the lifespan (Geurts & Jansen, 2012; Howlin et al., 2013; Piven et al., 1996).

An increasing number of studies focused on severity of ASD symptomatology and its changes over time. There is evidence that some ASD symptoms abate over time (Howlin et al., 2013; Piven et al., 1996; see Magiati et al., 2014; Seltzer, Shattuck, Abbeduto, & Greenberg, 2004, for reviews). For example, repetitive behavior seems to improve with increasing age (Esbensen, Seltzer, Lam, & Bodfish, 2009; Howlin et al., 2013; Shattuck et al., 2007) as well as social functioning (Bastiaansen, Thioux et al., 2011). Nevertheless, the oldest individuals included were 64 years old. Knowledge of ASD symptomatology in (middle and) late adulthood is, thus, still limited, even though crucial in elucidating the magnitude and specificity of age-related challenges (Piven & Rabins, 2011). There are, however, several diagnostic pitfalls when studying older individuals with ASD. For example, assessing and diagnosing ASD in older adults is challenging because the developmental history that is needed for the diagnosis is difficult to obtain (Fombonne, 2012; Happé & Charlton, 2012), there is unawareness about ASD in those working with older adults (van Niekerk et al., 2011), and individuals may have acquired strategies to camouflage ASD symptoms (Lai et al., 2011). In the current thesis, we will investigate ASD symptomatology across the adult lifespan and age-related differences herein (Chapter 2).

Co-occurring psychopathology in ASD

ASD is associated with high rates of co-occurring psychiatric disorders. Approximately 70% of the ASD population has to deal with psychiatric problems at least once in their lives (e.g., Buck et al., 2014; Hofvander et al., 2009; Simonoff et al., 2008), even though rates are lower among individuals with ASD and an ID (Matson & Cervantes, 2014). Not only is psychopathology a common phenomenon, many individuals who contact mental health services with associated psychopathology are later diagnosed with ASD (Geurts & Jansen, 2012). Furthermore, older adults with mood disorders may have high ASD traits and suffer from undiagnosed ASD (Geurts, Stek, & Comijs, 2016). The presence of psychiatric disorders has a great impact on quality of life and emotional well-being, future outcome, and demands for professional help (Lainhart, 1999; Matson & Cervantes, 2014; Seltzer et al., 2004; Vannucchi et al., 2014; Wood & Gadow, 2010).

The study of psychopathology in adults with ASD has recently received more attention and a substantial number of studies indicated high rates of co-occurring psychiatric disorders not only in childhood (de Bruin, Ferdinand, Meester, de Nijs, & Verheij, 2007; Leyfer et al., 2006; Lundström et al., 2015; Mattila et al., 2010; Mukaddes, Hergüner, & Tanidir, 2010; Simonoff et al., 2008; Sinzig, Walter, & Doepfner, 2009; van Steensel, Bögels, & de Bruin, 2013) but also in adulthood (Buck et al., 2014; Croen et al., 2015; Ghaziuddin & Zafar, 2008; Hofvander et al., 2009; Joshi et al., 2013; Lugnegård, Hallerbäck, & Gillberg, 2011; Roy, Prox-Vagedes, Ohlmeier,

& Dillo, 2015). Nevertheless, the majority of these studies focused on young adulthood and knowledge of middle and late adulthood is still scarce. In the general population, psychopathology rates are lower in older adults (Bijl, Ravelli, & Van Zessen, 1998; Kessler et al., 2005) and while there is some evidence that this pattern is also present in adults with ASD (Totsika et al., 2010), this might be related to the inclusion of adults with ASD combined with an ID. A small study including adults with ASD without ID described, however, more psychiatric cases in older than in younger adults (Roy et al., 2015). We will compare psychopathological symptoms and disorders in a large sample of cognitively able young, middle, and older adults with and without ASD and explore several risk factors that may affect psychopathology (Chapter 3).

Cognition functioning in ASD

In addition to behavioral symptoms and frequently co-occurring psychopathology is ASD associated with cognitive difficulties. Three main cognitive theories have been proposed to explain the challenges that individuals with ASD encounter (e.g., see Brunsdon & Happé, 2014; Frith, 2012, for an overview). The theory of mind (ToM) deficit hypothesis originally stated that a core problem in ASD is the limited ability to identify, attribute and manipulate mental states in self and others in order to predict and explain behavior (Baron-Cohen, Leslie, & Frith, 1985). More recently, this idea have been refined and studies have suggested intact explicit knowledge of mental states in cognitively able adults with ASD, but specific problems in spontaneous, implicit ToM (Senju, Southgate, White, & Frith, 2009). The weak central coherence account originally postulated that individuals with ASD present a deficit in global information processing (Frith & Happé, 1994; Frith, 1989; Happé, 1999). However, in a more recent version of this theory, a different processing style characterized by superior local processing rather than a deficit in extracting global information is proposed (Happé & Frith, 2006; Happé & Booth, 2008). Individuals with ASD would prefer to process incoming information in a fractionated and local way, but are able to perceive global coherence when instructed to do so (Happé & Frith, 2006) or when receiving sufficient time (Van der Hallen, Evers, Brewaeys, Van den Noortgate, & Wagemans, 2015). Finally, the executive dysfunction theory originally claimed an underlying deficit in executive functions (EF) (Pennington & Ozonoff, 1996; Russell, 1997), but the primacy of EF problems in ASD is currently not assumed anymore (Hill, 2004). In this thesis, although we also assess ToM, the main focus is on EF.

EF is an umbrella term referring to various cognitive functions involved in control and coordination that are necessary for complex, goal-directed behavior. An alternative term used to indicate a similar concept is cognitive control (Solomon, Ozonoff, Cummings, & Carter, 2008).

Cognitive control refers to those processes that allow for monitoring and regulating goal-directed behavior in order to flexibly adapt behavior to environmental requirements (Botvinick, Braver, Barch, Carter, & Cohen, 2001). These functions are essential for our daily life functioning. Both terms are interchangeably used in the current dissertation.

Individuals with ASD demonstrate deficits in various EF domains, including working memory and inhibition (Geurts, van den Bergh, & Ruzzano, 2014; Hill, 2004; O'Hearn, Asato, Ordaz, & Luna, 2008; Russell, 1997). However, not only EF has been found to be deficient. Children and adolescents with ASD also present difficulties in other cognitive domains, such as episodic memory (Boucher, Mayes, & Bigham, 2012) and ToM (Yirmiya, Erel, Shaked, & Solomonica-Levi, 1998). Cognitive challenges encountered by young individuals with ASD how large overlap with those faced by typically developing older individuals. For example, typical aging is associated with decline in various cognitive domains, such as EFs (Borella, Carretti, & De Beni, 2008; Friedman, Nessler, Cycowicz, & Horton, 2009; Hasher & Zacks, 1988; Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012; Park et al., 2002; Park & Reuter-Lorenz, 2009; Salthouse & Meinz, 1995; Salthouse, 1996; Verhaeghen & Cerella, 2002), episodic memory (Goh, An, & Resnick, 2012; Hultsch, 1998; Nyberg et al., 2012; Park et al., 2002), and advanced ToM (Charlton, Barrick, Markus, & Morris, 2009; Duval, Piolino, Bejanin, Eustache, & Desgranges, 2011; Kemp, Després, Sellal, & Dufour, 2012; Maylor, Moulson, Muncer, & Taylor, 2002; Moran, 2013; Wang & Su, 2013). Given the overlap between cognitive difficulties at younger ages in ASD and in typical senescence, the question is what will happen to cognition when individuals with ASD grow old: Will the cognitive difficulties in ASD become worse during aging, will they remain stable, or will they diminish?

In the ASD literature only a few studies investigated cognition in older adults. Persistence of cognitive difficulties has been reported (Geurts & Vissers, 2012; James, Mukaetova-Ladinska, Reichelt, Briel, & Scully, 2006), but the developmental trajectories of individuals with ASD compared to typically developing older adults did differ across cognitive domains (Geurts & Vissers, 2012; Ring, Gaigg, & Bowler, 2016). In some domains (e.g., verbal episodic memory), older adults with ASD showed a similar age-related pattern compared to typical older adults, whereas in other domains they demonstrated an aggravated pattern (e.g., visual episodic memory) or an attenuated pattern (e.g., generativity). Therefore, based on the first, exploratory ASD group study in older adults (Geurts & Vissers, 2012), we will examine three possible cross-sectional developmental trajectories in this thesis. First, individuals with ASD could present similar or parallel age-related differences compared to individuals without ASD, most likely characterized by an age-related decline in cognitive functioning. Second, individuals with ASD could demonstrate a divergent or aggravated pattern in which age-related

differences are increased compared to controls. In this hypothetical situation, ASD and aging could be two factors that jeopardize cognitive functioning (i.e., double jeopardy). Third, individuals with ASD could show a convergent or attenuated pattern, characterized by reduced age-related differences compared to controls. ASD would then represent a 'safeguard' against age-related decline. Thus, we aim to elucidate whether the developmental trajectory of adults with ASD follow a different age-related pattern compared to those without ASD, in addition to a comparison of cognitive performance between adults with and without ASD (Chapter 4, 5, 6).

In Chapter 4, we investigate whether we can replicate and extend the previous findings in a much larger sample by means of frequently used neuropsychological measures. While general neuropsychological studies are helpful for translating the findings into clinical practice, they may not capture more fine-grained aspects of cognitive functioning. Therefore, we also use experimental paradigms to examine two EFs more in-depth: working memory (WM; Chapter 5) and inhibition (Chapter 6). These two domains are both associated with the temporal integration of information, essential for goal-directed action, served by the prefrontal cortex and are, therefore, often considered two sides of the same coin (Fuster, 2002).

Working memory

WM is the ability to maintain and manipulate information online in the absence of actual sensory information in order to guide goal-directed behavior (e.g., Baddeley, 2003; Cowan, 2014). Individuals with ASD generally show WM impairments in the visual-spatial domain (Steele, Minshew, Luna, & Sweeney, 2007; Williams, Goldstein, Carpenter, & Minshew, 2005; Williams, Goldstein, & Minshew, 2006; but see Ozonoff & Strayer, 2001), and in complex WM tasks (Koshino et al., 2008; Steele et al., 2007; Williams et al., 2006), but not on verbal WM tasks (Koshino et al., 2005; Williams et al., 2005). Results are, however, rather inconsistent (see Barendse et al., 2013, for an overview). These inconsistencies have been explained by the age range studied (Happé, Booth, Charlton, & Hughes, 2006; Luna, Doll, Hegedus, Minshew, & Sweeney, 2007; but see Rosenthal et al., 2013), by the type of task used (Steele et al., 2007), or by differences between individuals. Considerable inter-individual differences have not only been found within the ASD population (de Vries & Geurts, 2014; Geurts, Sinzig, Booth, & Happé, 2014; Towgood, Meuwese, Gilbert, Turner, & Burgess, 2009), but also within the healthy aging population (Eenshuistra, Ridderinkhof, & van der Molen, 2004; Vogel & Awh, 2008; Werkle-Bergner, Freunberger, Sander, Lindenberger, & Klimesch, 2012). Therefore, we investigate age-related differences in WM performance and inter-individual differences herein in order to identify possible factors accounting for inconsistencies within the literature (Chapter 5).

Inhibition

Inhibition refers to the mechanism or set of processes that result in the containment of prepotent behavioral responses when such responses are reflex-like, premature, inappropriate or incorrect (Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). A lack of inhibitory control is thought to underlie some of the core symptoms observed in ASD (Lopez, Lincoln, Ozonoff, & Lai, 2005). A specific aspect of inhibition is interference control, or resistance to distractor interference (Friedman & Miyake, 2004; Nigg, 2000). It refers to the ability to suppress irrelevant information. The existing literature on interference control in ASD is rather inconsistent, with some studies demonstrating impairments among individuals with ASD (Adams & Jarrold, 2012; Christ, Holt, White, & Green, 2007; Christ, Kester, Bodner, & Miles, 2011; Henderson et al., 2006), and others showing no differences between individuals with ASD and typically developing controls (Geurts, Luman, & Van Meel, 2008; Larson, South, Clayson, & Clawson, 2012; Schmitz et al., 2006; Solomon et al., 2008; Solomon et al., 2009). A recent meta-analysis indicated that individuals with ASD were moderately impaired in inhibitory control, but substantial heterogeneity across studies was also observed (Geurts et al., 2014). The use of rather crude measures, such as mean reaction times, was suggested to be one of the major reasons for this heterogeneity. More fine-grained models of specific aspects of cognitive control are needed to better understand whether and when individuals with ASD encounter difficulties. Therefore, we adopt the theoretical framework of the dual-route model (Kornblum, Hasbroucq, & Osman, 1990) and its extension, the activation-suppression hypothesis (Ridderinkhof, 2002), to examine whether individuals with ASD have difficulties in the underlying mechanisms of interference control and to explore how age affects interference control processes (Chapter 6).

Aim and outline of the dissertation

The literature so far demonstrates a paucity when it comes to the investigation of ASD after young adulthood. The current dissertation aims at advancing knowledge of what happens to individuals with ASD when they grow old and focuses on age-related differences in symptomatology, co-occurring psychopathology, and cognitive functioning in order to, ultimately, provide guidelines for the development of appropriate treatment and support for adults with ASD across the lifespan, including older adulthood.

Data of this cross-sectional study was collected between March 2012 and July 2014. The sample described in the current dissertation (with exception of Study 1 in Chapter 6) consisted of 241 adults with a formal clinical diagnosis within the autism spectrum, diagnosed prior to participating in the current study, and a comparison group comprising 199 adults without ASD. All individuals were between 19 and 79 years of age and had an estimated IQ

above 80. The ASD group was recruited through several mental health institutions across the Netherlands, and by means of advertisements on client organizations' websites. We obtained additional diagnostic information from all participants based on subjective reports of ASD characteristics (Autism-spectrum Quotient; n = 237) and/or standardized observations of the participants' behavior (Autism Diagnostic Observation Schedule; n = 142). The comparison group was recruited via advertisements on the university website and social media, and through the social environment of the researchers. All participants filled out a series of questionnaires on ASD symptomatology, co-occurring psychopathology, and cognitive functioning, providing data for mainly chapters 2 and 3. A subsample was selected and underwent an extensive (neuro)psychological assessment described in chapters 4, 5, and 6. The final sample size described in each chapter varies according to the measures of interest involved and the research aims (ASD group: n = 118-237; COM group: n = 118-198).

In **Chapter 2**, we investigate ASD symptoms. It has been suggested that symptoms may abate with age, but examination of symptoms in late adulthood is largely missing. Furthermore, we compare self-report with proxy-report as it has been suggested that individuals with ASD lack self-awareness and have difficulties reflecting on their own functioning. In addition to ASD symptomatology, individuals with ASD suffer from co-occurring psychiatric symptomatology such as depression and anxiety. Therefore, **Chapter 3** elucidates whether co-occurring psychopathology is as prevalent in older adults with ASD as it is in younger adults with ASD. Furthermore, we explore several risk factors that may be associated with psychopathology. Given that cognition is highly sensitive to aging and ASD is already associated with cognitive deficits at younger ages, the remaining chapters focus on cognitive functioning in adults with ASD. The exploratory analyses from the pioneering study on older individuals with ASD (Geurts & Vissers, 2012) preceding the current studies, suggested that these older individuals with ASD may show accelerated cognitive decline in late adulthood, even though some cognitive functions are spared and not subject to an aggravated trajectory. We aim to replicate these findings in a much larger and better defined sample in **Chapter 4**. In this chapter, a neuropsychological assessment of visual and verbal episodic memory, generativity, and ToM is described. To further and more specifically investigate cognitive functioning, we study two EFs that are often found to be impaired in ASD by means of two experimental paradigms. In **Chapter 5,** we focus on working memory and explore whether inter-individual differences may explain age-related differences in working memory decline. **Chapter 6** describes a study on interference control in which we examine processes underlying reactive and proactive control. In addition to conventional statistical analyses, we apply Bayesian hypothesis testing in order to

substantiate the evidential strength for our findings in Chapter 5 and 6. Finally, in **Chapter 7** we summarize and discuss the main findings and elaborate on clinical implications.

Chapter 2

Lifelong lasting? Self- and other-reported ASD symptoms across adulthood

Based on: Lever, A. G. & Geurts, H. M. (2016). Lifelong lasting? Self- and other-reported ASD symptoms across adulthood. *Manuscript submitted.*

ABSTRACT

Autism spectrum disorder is a lifelong neurodevelopmental disorder and the diagnosis is based on behavioral symptoms. There is some evidence that ASD symptomatology might abate over time. However, whether this amelioration protracts until late adulthood is largely unknown. Therefore, we investigated general ASD symptoms, and also social-emotional reciprocity and sensory sensitivity, in a cross-sectional study of a large group of adults with and without ASD (N = 435, age range 19-79 years) by means of self- and other-reported questionnaires. Self-report was poorly concordant to other-report, suggesting that both measures reveal different aspects of symptomatology. Moreover, although age-related differences in social-emotional reciprocity were not observed, general and sensory symptoms increased in middle adulthood and decreased in late adulthood. The high number of self-reported ASD symptoms and the persistence of these symptoms across the adult lifespan, underline the lifelong nature of this neuropsychiatric condition.

Keywords: autism spectrum disorder, symptomatology, self- and other-report, AQ, aging

INTRODUCTION

ASD symptomatology

In (1943), Leo Kanner described the first case series of children suffering from "inborn autistic disturbances of affective contact". These children demonstrated an inability to relate themselves to people and situations and an unusual desire of *aloneness*. Moreover, among other features, the children's behavior was governed by an obsessive eager to *sameness* and by atypical reactions to sounds and movements. In the same period, independently of Kanner, Hans Asperger (1944) noticed similar peculiarities in children labeled as "autistic psychopaths". Albeit both authors recognized and even examined the developmental character of the condition and the heterogeneity in symptom manifestation, it took many years until researchers and clinicians structurally studied its development beyond childhood.

Nowadays, "autism spectrum disorder" (ASD) refers to a broad range of neurodevelopmental disorders that are characterized by persistent deficits in social communication and social interaction, and restricted, repetitive patterns of behavior, interests, or activities that cause clinically significant impairments in daily functioning (American Psychiatric Association, 2013). Symptoms of ASD include atypicalities in social-emotional reciprocity, nonverbal communication, establishing and maintaining relationships, and sensory sensitivity. ASD is considered a lifelong condition, which is also observed in the prevalence estimations of approximately 100 per 10.000 individuals meeting criteria for an ASD, independent of age (Brugha et al., 2011). Furthermore, it is acknowledged that, despite its generally early onset, symptoms can be masked until available capacities are no longer sufficient to meet environmental requirements (American Psychiatric Association, 2013). Symptoms may also change over the lifespan (Geurts & Jansen, 2012; Howlin et al., 2013; Piven et al., 1996). Knowledge on ASD symptomatology in middle and late adulthood is, however, still limited, even though critical in elucidating the magnitude and specificity of age-related changes and for recognizing ASD in adulthood (Piven & Rabins, 2011). The current study aims at investigating whether ASD symptoms abate, remain stable, or become more severe over the entire adult lifespan.

Age-related changes in ASD symptoms

Several outcome studies have indicated that adolescents and adults with ASD have rather poor outcomes, with a minority living independently, being employed or attained education, and having close reciprocal relationships (see Henninger & Taylor, 2013; Howlin & Moss, 2012; Levy & Perry, 2011; Magiati et al., 2014, for reviews). Early language development, higher intellectual

abilities, and milder ASD symptoms are predictors of a more favorable future (Howlin & Moss, 2012). Despite poor outcome, there is evidence that ASD symptoms abate over time (see Magiati et al., 2014; Seltzer et al., 2004, for reviews). For example, Shattuck and colleagues (2007) examined changes in ASD symptoms over a 4.5 years period among individuals with ASD aged 10-52 years. Overall, while nonverbal communication impairments remained stable and symptoms of verbal communication and social reciprocity ameliorated, improvement was especially observed in the repetitive behavior domain. Similarly, ASD severity decreased over an approximately 37 years period (range at follow-up 29-64 years), with, again, significant improvement on the restricted, repetitive behavior domain (Howlin et al., 2013), and older individuals with ASD (until 62 years) displayed fewer and less severe repetitive behaviors than younger individuals (Esbensen et al., 2009). With regard to social behaviors, age (range 18-54 years) was not associated with attenuation of social symptoms, even though social functioning improved (Bastiaansen et al., 2011). This latest finding is in line with anecdotal accounts stating that rather than an improvement of social symptoms, people learn how to cope with them. Learning from experiences would explain why social functioning ameliorates, while social symptoms remain stable. In sum, there is consistency in repetitive behavior improving with increasing age, whereas changes in social communication and interaction symptoms are less clear. Moreover, the oldest individuals examined were 64 years old and it is unknown whether and how in ASD symptoms change in late(r) adulthood.

Like in previous studies, we focus on general symptoms of ASD. However, we will also zoom in on the two major domains of (1) social interaction and social communication, and (2) restricted, repetitive behavior, interests, or activities. We will concentrate on one subdomain of each: (1) an important aspect of socio-emotional reciprocity, namely empathy, and (2) sensory sensitivity. Social interactions and relationships rely on the fundamental ability to empathize with others (De Waal, 2008). Empathy can be defined as the capacity to understand another person's thoughts and feelings and has a complex and multidimensional nature, including both cognitive and emotional processes (Davis, 1983). Cognitive empathy refers to the ability to understand the thoughts and emotions of others by adopting their perspective. Affective empathy refers to the ability to experience feelings elicited by the emotional experiences of others. Individuals with ASD are thought to have impaired cognitive empathy, but intact affective empathy (Jones, Happé, Gilbert, Burnett, & Viding, 2010). The effect of age in adulthood is, however, unclear. When examining the effect of age on empathy in the general population, the pattern of findings is mixed. In cross-sectional studies, there seems to be a negative effect (e.g., Bailey, Henry, & Von Hippel, 2008; Grühn, Rebucal, Diehl, Lumley, & Labouvie-Vief, 2008) or no effect (e.g., Eysenck, Pearson, Easting, & Allsopp, 1985) of age. The lack of an age effect is also revealed in

longitudinal studies (e.g., Grühn et al., 2008). However, recently, it has been demonstrated in a cross-sectional sample that both cognitive and affective components of empathy increased from young to middle adulthood and declined in late adulthood, revealing an inverted U-shape form (O'Brien, Konrath, Gruhn, & Hagen, 2013). This pattern is explained by the dynamic integration theory proposing that emotional representations become increasingly more complex through cognitive development and accumulating life experiences, and peak in middle adulthood. Thereafter, in late adulthood, these representations are challenged by age-related biological and cognitive decline (Labouvie-Vief, 2009). We will test whether an inverted U-shape is also observed in individuals with ASD, whose starting point may already be lower.

Sensory sensitivity, newly relevant in the DSM-5 (American Psychiatric Association, 2013), involves both hypo- and hyperreactivity to sensorial information, including auditory, olfactory, gustatory, tactual, visual, proprioceptive, and vestibular stimuli. Anecdotal accounts on sensory sensitivity in ASD revealed that these symptoms do not seem to abate, although one might be better able to cope with them (Grandin, 2011). In line with these accounts, self-reported sensory symptoms did not decline in the broad general population (range 16-65 years) (Robertson & Simmons, 2013) or in adults with ASD (18-65 years) (Crane, Goddard, & Pring, 2009), whereas parents reported improvements with age (Kern et al., 2006; Shattuck et al., 2007). This reveals a discrepancy between what people with ASD experience themselves and how other persons perceive it.

Current study

In the current cross-sectional study, we examine age-related differences in self-reported ASD symptoms, including social-emotional reciprocity and sensory sensitivity, in a large sample of adults with and without ASD, and we compare self-report and other-report.

We investigate general ASD symptoms with the Autism-Spectrum Quotient (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001) and hypothesize ASD symptoms to abate over age in adults with ASD (Seltzer et al., 2004), even though we do not expect such a relationship in adults without ASD (Hoekstra, Bartels, Cath, & Boomsma, 2008). Empathy is examined with the Interpersonal Reactivity Index (Davis, 1980), a widely used and well established instrument for the multidimensional investigation of empathy. We expect adults with ASD to report reduced cognitive aspects of empathy (i.e., perspective taking and fantasy), but comparable (i.e., empathic concern) or increased (i.e., personal distress) affective components (Rogers, Dziobek, Hassenstab, Wolf, & Convit, 2007). Due to contrasting evidence, we can, however, only speculate about the effect of age in adults with ASD. For example, age negatively affected face-emotion recognition from childhood to adulthood (Lozier, Vanmeter, & Marsh,

2014), whereas age did not influence cognitive reasoning on other persons' mental states and eyes-emotion recognition (Chung, Barch, & Strube, 2014). Sensory sensitivity is examined with the Sensory Sensitivity Questionnaire (SSQ) (Minshew & Hobson, 2008) and we hypothesize the role of age to be negligible (Crane et al., 2009; Minshew & Hobson, 2008; Robertson & Simmons, 2013). With regard to the self-other relationship, there is discussion whether individuals with ASD are able to provide reliable information about their behavior, feelings, thoughts, and functioning. Recently, however, it has been shown that participants and proxies provide moderate agreement on social responsiveness, with non-significant differences between adults with and without ASD, but the ASD sample was rather small (n = 24, age range 18-62 years) (De la Marche et al., 2015). Therefore, we will evaluate self- and other-report in a much larger sample. The combination of both indices can reveal unique information about symptomatology, seen from both the inside and outside perspective.

METHODS

Participants

Individuals with ASD aged 19-79 years were recruited through several mental health institutions across the Netherlands and by means of advertisement on client organization websites. Requirement upon study participation was to have a clinical ASD diagnosis based on DSM-IV criteria (autism, Asperger's syndrome, and Pervasive Developmental Disorder Not Otherwise Specified) (American Psychiatric Association, 2000), which was generally established by a multidisciplinary team including a psychiatrist and/or psychologist. Individuals without ASD (comparison group [COM]) were recruited by means of advertisement on the university website and social media and within the social environment of the experimenters. Controls were eligible for participation when a clinical diagnosis of ASD or attention deficit hyperactivity disorder (ADHD) and close relatives suffering from ASD or schizophrenia were absent. Based on these criteria we excluded four individuals with ASD and nine individuals without ASD, resulting in a sample of 440 participants (241 ASD, 199 COM).

Thereafter, 435 participants completed the AQ (98.9%; n = 237 ASD, n = 198 COM). Of this group, 352 (n = 174 ASD, n = 178 COM) participants returned also the IRI and SSQ. These questionnaires were completed by respectively 349 (99.1%; n = 172 ASD, n = 177 COM) and 336 (95.5%; n = 163 ASD, n = 173 COM) participants. A proxy (e.g., partner, family member, or friend) of the participants was asked to fill out the AQ, IRI, and SSQ. Of the 435 participants, 285 participants returned other-questionnaire data (65.5%; 136 ASD [57.4%], 149 COM [75.3%]), including 270 completed AQs (n = 125 ASD, n = 145 COM), 278 completed

IRIs (n = 130 ASD, n = 148 COM), and 141 completed SSQs (n = 65 ASD, n = 76 COM). The amount of other-SSQs is smaller than the AQs and IRIs due to its later addition to the set of questionnaires.

Measures

Autism-Spectrum Quotient (AQ). The Dutch version of the AQ (Baron-Cohen et al., 2001; Hoekstra et al., 2008) was administered to identify the degree to which an intellectually able adult shows ASD traits. This self-report questionnaire comprises 50 statements about core ASD-related features and assesses five different areas: social skills, attention switching, attention to detail, communication, and imagination. Each statement is rated with 1 "definitely agree", 2 "slightly agree", 3 "slightly disagree", and 4 "definitely disagree". On half of the items, endorsement of "definitely agree/slightly agree" is indicative of ASD-like behavior, whereas on the other half "definitely disagree/slightly disagree" reveals ASD traits. These latest scores are reversed. The item scores are summed, to a maximum score of 10 per subscale and a maximum total score of 50. The other-version omits 10 items as these were labeled by the developers as being too subjective to be answered by another person (Baron-Cohen et al., 2001). Higher scores indicate more severe ASD traits. The Dutch version of the AQ has good internal consistency, test-retest reliability, and good discriminative validity (Hoekstra et al., 2008). Missing data points (maximum one per subscale) were substituted with the mean subscale score. The dependent variables are the total and subscale scores (self-report) and 40-item total score (self- and other-report).

Interpersonal Reactivity Index (IRI). The Dutch version of the IRI (Davis, 1980; de Corte et al., 2007) was administered to examine individual differences in cognitive and emotional attitude towards interpersonal situations. This self-report questionnaire consists of 28 items and four subscales assessing different aspects of empathy, which is crucial of normal social functioning, including the maintenance of social relationships and favoring pro-social behavior (de Corte et al., 2007): (a) perspective taking, the tendency to adopt another person's point of view, (b) fantasy, the tendency to identify with the feelings and actions of fictitious characters, (c) empathic concern, the tendency to experience feelings of sympathy and concern towards others, and (d) personal distress, the tendency to feel anxious and uneasy in reaction to the emotions of others (Davis, 1983). The first two subscales examine other-oriented behavior (cognitive component), whereas the latter two subscales examine self-oriented behavior (affective component). Each item is rated on a five-point Likert scale, ranging from 0 "does not describe me well" to 4 "describes me very well". The item scores are summed to a maximum of 28 per subscale. While higher perspective-taking scores and lower personal distress scores are

associated with better social functioning, correlations between social functioning and fantasy are low. Empathic concern is not consistently related to social competence, although associated with social success characteristics, such as selflessness and agreeableness. The Dutch version of the IRI has adequate psychometric properties (de Corte et al., 2007). Missing data points (maximum one per subscale) were substituted with the mean subscale score. The dependent variables are the subscale scores (self-report) and total score (self- and other-report).

Sensory Sensitivity Questionnaire (SSQ). The SSQ (Minshew & Hobson, 2008) is, after permission of the authors, translated from English into Dutch (Lever & Geurts, 2012) and back-transformed into English by an independent native English speaker. The SSQ consists of 13 statements about sensory hyper- or hyposensitivity that can be endorsed or denied, and assess low pain/temperature (2 items), high pain/temperature (2 items), tactile sensitivity (3 items), and other sensitivities (6 items). Endorsed items are summed per subscale and to a total score of maximum 13. Inter-rater reliability is good (Minshew & Hobson, 2008), but other psychometric properties of the SSQ are yet unknown. Missing data points for SSQ were not allowed due to the small number of questionnaire items. The dependent variables is the total score (self- and other-report).

Procedure

After explanation of study purposes and procedure, written informed consent was obtained for all participants. The AQ, IRI, and SSQ questionnaires were filled out. Additional measures were administered in two sessions in a selection of this sample, but will be described elsewhere (Lever & Geurts, 2015; Lever, Werkle-Bergner, Brandmaier, Ridderinkhof, & Geurts, 2015). The study was approved by the local institutional ethical review board (2011-PN-1952), and complied with all relevant laws and institutional guidelines.

Statistical analyses

First, we described our ASD group in terms of educational attainment, residential status, occupation, and relationships. The COM group was only included for comparison purposes with regard to the role of age and the self-other relationship. Second, we ran two MANCOVAs for AQ and IRI (sub)scales and an ANCOVA for the SSQ total score[i], each with group and gender as between-subject factor and (centered) age and (centered) age^2 as covariate in a model with main effects and interactions, to investigate age-related differences in ASD symptomatology across groups. We added gender as between-subject factor to these analyses, given the

[i] Data of the AQ subscales and SSQ total score were not normally distributed. However, as (M)ANOVA is thought to be robust against skewed data (Stevens, 2012), we ran parametric tests.

symptomatic differences between males and females (Lai et al., 2011; Van Wijngaarden-Cremers et al., 2014). Separate ANCOVAs on the single (sub)scales (Bonferroni correction: $\alpha = .05/6 = .0083$ for AQ; $\alpha = .05/4 = .0125$ for IRI) were used to follow-up on the omnibus MANOVA effects. When observing significant interactions, we ran planned follow-up regressions analyses (Bonferroni correction: $\alpha = .05$/number of significant interactions) per group. Third, to examine the relation between participant and proxy report, intra-class correlations coefficients (ICCs) were calculated with a two-way mixed, absolute agreement, single-measures effect model (Hallgren, 2012; McGraw & Wong, 1996; Shrout & Fleiss, 1979), overall and per group, for total scores of AQ (40 items), IRI (all items), and SSQ (all items). Levels of agreement were interpreted as poor (ICC = <0.40), fair (ICC = 0.40–0.59), good (ICC = 0.60–0.74), and excellent (ICC = 0.75–1.00) (Cicchetti, 1994). To further examine the self-other relationship, we computed three ANOVAs with Group (ASD, COM) as between-subject factors and Rater (self, other) as within-subject factor. Furthermore, to examine whether age-related differences were also observed by proxies (i.e., other-report), we ran ANCOVAs for each questionnaire's total score, with group and gender as between-subject factors and (centered) age and (centered) age^2 as covariate. Finally, we explored whether the type of proxy influenced the reported symptoms (see Supplementary material Chapter 2). Fourth, although all ASD participants had a prior ASD diagnosis, we verified these diagnoses in a subgroup of participants who were eligible to participate in a study aimed at investigating age-related differences in cognition (Lever & Geurts, 2015) by administering the Autism Diagnostic Observation Schedule module 4 (de Bildt & de Jonge, 2008; Lord et al., 2000). Therefore, we compared ASD participants who scored above the ADOS threshold for ASD (ADOS+) or autism (ADOS++) with those scoring below the threshold for ASD (ADOS-) or without ADOS (non-ADOS). All analyses were run with SPSS 22.0 (IBM Corp., 2013).

RESULTS

The descriptives of both groups (i.e., gender, age, social characteristics, years of diagnosis) are depicted in Table 2.1[ii]. The groups did not differ in mean age, but the ASD group was composed of relatively more males than females as compared to the COM group. Moreover, the participants with ASD were not as highly educated as the controls, more participants with ASD lived in a residential home, and less were in a romantic relationship. Occupation was coded according to the International Standard Classification of Occupations (ISCO-08). Of the ASD

[ii] We cross-checked whether the whole sample differed from the IRI or SSQ subsample on age, gender, and educational level. The groups did not significantly differ (all *p*s > .5).

participants, 8 had an elementary occupation, 2 were plant or machine operators or assemblers, 9 were craft workers, 1 was a skilled agricultural worker, 14 were service and sales workers, 15 were clerical support workers, 16 were technicians and associate professionals (i.e., people performing tasks related to research and the application of conceptual and operational methods, including community health workers, opticians, photographers), 62 were professionals (i.e., people providing conceptual and theoretical contributions to knowledge accumulation, including scientists, teachers, practitioners, nurses, lawyers), and 9 were managers. Moreover, there were 14 students, 3 entrepreneurs, 3 did not indicate their occupation, and 81 (34.2%) were unemployed, including 15 (18.5%) retired individuals.

ASD symptomatology

Self-reported questionnaire scores of the ASD and COM group and subscale comparisons are presented in Table 2.2. Follow-up regressions on significant interactions between age(²) and group are presented in Table 2.3.

AQ

There was a significant main effect of group (Wilks' Lambda (Λ) = 0.40, $F(5, 423) = 125.60$, $p < .001$, $\eta_p^2 = .60$) and significant interactions between group and gender (Λ = 0.97, $F(5, 423) = 3.07$, $p = .010$, $\eta_p^2 = .04$), between group and age (Λ = 0.97, $F(5, 423) = 3.02$, $p = .011$, $\eta_p^2 = .04$), and between group and age² (Λ = 0.96, $F(5, 423) = 3.21$, $p = .007$, $\eta_p^2 = .04$). Separate univariate ANCOVAs revealed, as expected, that adults with ASD reported higher AQ scores than the COM group on all (sub)scales. Significant univariate interactions were followed-up with planned regressions per group. These revealed that neither age nor age² was a significant predictor of AQ scores in the COM group. In the ASD group, age and age² were significantly associated with the total score and the attention to detail subscale score, but not with the other subscales after Bonferroni correction. The estimated coefficients of age and age² indicated that age had a positive effect and age² had a negative effect on AQ score (Figure 2.1). Furthermore, age was significantly associated with the social skills subscale, with increasing age being related to higher scores, but age² did not survive Bonferroni correction. With regard to the role of gender, females with ASD reported significantly more ASD traits than ASD males on the total score ($\beta = .19$, $p = .004$) and attention switching subscale ($\beta = .19$, $p = .004$), whereas females without ASD reported lower scores than non-ASD males on the total score ($\beta = -.20$, $p = .006$) and communication subscale ($\beta = -.23$, $p = .001$).

Table 2.1 Comparisons of descriptive variables.

	ASD (n = 237)	COM (n = 198)	Statistics
Age (years)	46.0 (SD 13.8)	45.6 (16.4)	$F(1, 433) = 0.08$, $p = .773$, $\eta_p^2 = .00$
	range 19-79	range 19-77	
Gender	163 M/74 F	109 M/89 F	Fisher's test, $p = .004$, odds ratio = 1.80
Education[a]	3/84/147	1/40/156	Fisher's test, $p < .001$
Residential status[b]	97/107/13/19/1	64/114/17/0/1	Fisher's test, $p < .001$
Relationships[c]	106/87/21/23	71/88/29/10	Fisher's test, $p = .019$
Diagnosis[d]	42/117/71/7	-	-
Time of diagnosis	4.0 (3.9)	-	-
(years)	range 0-26		

Note. ASD=autism spectrum disorder; COM=comparison group; M=male; F=female.

[a] The numbers between brackets indicate the number of participants having pre-vocational education/vocational education/higher secondary education. Four participants did not indicate their educational level (3 ASD, 1 COM).

[b] The numbers between brackets indicate living: independent/with partner or housemate/with parents/residential home/other.

[c] The numbers between brackets indicate: unmarried/married/cohabiting/other, such as being divorced or widow.

[d] The numbers between brackets indicate a diagnosis of Autism/Asperger Syndrome/Pervasive Developmental Disorder Not Otherwise Specified/ASD.

IRI

There were a significant main effect of group ($\Lambda = 0.72$, $F(4, 338) = 32.86$, $p < .001$, $\eta_p^2 = .28$) and a significant interaction between group and gender ($\Lambda = 0.97$, $F(4, 338) = 2.83$, $p = .025$, $\eta_p^2 = .03$). Neither the main effects of age nor age^2 (respectively, $\Lambda = 0.98$, $F(4, 338) = 2.21$, $p = .068$, $\eta_p^2 = .03$ and $\Lambda = 0.98$, $F(4, 338) = 1.97$, $p = .099$, $\eta_p^2 = .02$) nor the interactions between age/age^2 and group were significant (respectively, $\Lambda = 0.97$, $F(4, 338) = 1.24$, $p = .295$, $\eta_p^2 = .01$ and $\Lambda = 0.99$, $F(4, 338) = 1.29$, $p = .274$, $\eta_p^2 = .02$), indicating no significant effect of age. Separate univariate ANCOVAs revealed, as expected, that adults with ASD reported lower scores on perspective taking and fantasy, comparable scores on empathic concern, and higher scores on personal distress. The interaction between group and gender was only significant on the perspective taking and fantasy subscales: Whereas females without ASD had higher scores than males without ASD (perspective taking: $\beta = .19$, $p = .010$; fantasy: $\beta = .21$, $p = .005$), males and females with ASD did not differ (perspective taking: $\beta = -.11$, $p = .163$; fantasy: $\beta = -.05$, $p = .504$). In both groups, females indicated higher personal distress and empathic concern than males.

SSQ

There were a significant main effect of group ($F(1, 335) = 145.54$, $p < .001$, $\eta_p^2 = .31$) and significant interactions between group and gender ($F(1, 335) = 8.01$, $p = .005$, $\eta_p^2 = .02$), group and age ($F(1, 335) = 7.13$, $p = .008$, $\eta_p^2 = .02$), and group and age^2 ($F(1, 335) = 9.02$, $p = .003$, $\eta_p^2 = .03$). As expected, the ASD group reported more sensory sensitivities than the COM group. The estimated coefficients of age and age^2 indicated that age had a positive effect and age^2 had a negative effect on SSQ score in the ASD group, whereas it had no effect in the COM group (Figure 2.1). After Bonferroni correction, females had higher scores than males in the ASD group ($\beta = .39$, $p < .001$), but not in the COM group ($\beta = .16$, $p = .039$).

Self- and other-report

Proxies were partners (55.0%), family members (28.4%), friends (11.3%), or other proxies (2.8%), such as practitioners. The remaining proxies (2.5%) did not indicate their relationship with the participant. Of two participants who handed in questionnaires of two different proxies, we included data from one of these (i.e., the person who has known the participant for the longest time). The mean length of the relationship between participant and proxy was 24.1 years (SD = 13.1).

ICCs indicated fair (IRI, SSQ) to excellent (AQ) levels of agreement between self- and other-report for the total sample (see Table 2.4). Levels of agreement were fair for the COM group and poor to fair in the ASD group[iii]. Considering the 95% confidence intervals of each group, it is likely that the levels of agreement differ in the ASD and the COM group on the AQ, but not on the IRI and SSQ.

Comparison of self- and other-report revealed a main effect of rater on the AQ ($F(1, 268) = 19.93$, $p < .001$, $\eta_p^2 = .07$), with lower ratings for self-report than for other-report, but no interaction between rater and group ($F(1, 268) = 0.36$, $p = .548$, $\eta_p^2 = .00$). On the IRI, there was an interaction between rater and group ($F(1, 273) = 4.09$, $p = .044$, $\eta_p^2 = .02$). Proxies reported lower scores than participants themselves in both groups, but follow-up comparisons revealed that this discrepancy was more pronounced in the ASD group (ASD: $F(1, 128) = 24.76$, $p < .001$, $\eta_p^2 = .16$; COM: $F(1, 145) = 6.82$, $p = .010$, $\eta_p^2 = .05$). Rater and group also interacted on SSQ scores ($F(1, 132) = 5.98$, $p = .016$, $\eta_p^2 = .04$). Follow-up comparisons revealed that proxies in the ASD group tend to report less sensory symptoms than ASD participants themselves, whereas proxies in the COM group tend to report more sensory symptoms than COM participants themselves. Nevertheless, differences were too small and variability too large

[iii] ICCs for the whole group are typically larger than ICCs for subgroups.

Table 2.2 Group comparisons of the self-reported questionnaires.

		ASD	COM	Group		Gender		Group*Gender		Age		Age²		Group*Age		Group* Age²	
		M (SD)	M (SD)	*F*	η_p^2	*F*	η_p^2	*F*	η_p^2	*F*	η_p^2	*F*	η_p^2	*F*	η_p^2	*F*	η_p^2
AQ	Total score	32.9 (8.4)	12.5 (5.5)	**560.86*** **	.57	0.68	.00	**12.55*** **	.03	3.51	.01	2.48	.01	**12.92*** **	.03	**13.10*** **	.03
	Social skills	7.1 (2.5)	1.8 (1.9)	**399.62*** **	.48	0.06	.00	**8.05** **	.02	1.63	.00	0.36	.00	**7.92** **	.02	**7.36** **	.02
	Attention switching	7.5 (2.2)	2.5 (1.8)	**428.42*** **	.50	0.78	.00	**8.98** **	.02	0.06	.00	0.08	.00	**7.37** **	.02	**7.49** **	.02
	Attention to detail	6.2 (2.4)	3.6 (2.2)	**110.03*** **	.21	3.84	.01	0.57	.00	3.62	.01	6.20*	.01	**8.88** **	.02	**10.50** **	.02
	Communication	6.4 (2.4)	1.8 (1.5)	**345.84*** **	.45	0.04	.00	**9.66** **	.02	1.95	.01	0.86	.00	4.62*	.01	4.20*	.01
	Imagination	5.7 (2.2)	2.8 (1.8)	**128.07*** **	.23	0.06	.00	6.44*	.02	2.19	.01	0.83	.00	2.23	.01	2.18	.01
IRI	Perspective taking	12.6 (5.2)	18.3 (3.9)	**86.58*** **	.20	0.00	.00	**6.97** **	.02	0.63	.00	0.89	.00	1.20	.00	0.79	.00
	Fantasy	12.5 (6.1)	14.9 (5.6)	**6.25***	.02	1.20	.00	**6.65***	.02	0.85	.00	0.18	.00	0.15	.00	0.23	.00
	Empathic concern	15.6 (4.9)	17.2 (4.3)	0.99	.00	**29.29*** **	.08	1.81	.01	1.68	.01	1.31	.00	2.00	.01	2.68	.01
	Personal distress	14.9 (5.4)	10.1 (4.7)	**53.29*** **	.14	**13.92*** **	.04	0.51	.00	3.67	.01	4.36*	.01	0.59	.00	0.40	.00
SSQ	Total	5.6 (2.9)	2.4 (1.9)	145.54***	.31	27.22***	.08	8.01**	.02	6.13*	.02	7.02**	.02	7.13**	.02	9.02**	.03

Note. ASD=autism spectrum disorder; COM=comparison group; AQ=Autism-Spectrum Quotient; IRI=Interpersonal Reactivity Index; SSQ=Sensory Sensitivity Questionnaire.

* $p \leq .05$, ** $p < .01$, *** $p \leq .001$

Significant values after Bonferroni correction ($\alpha = .05/6 = .0083$ for AQ; $\alpha = .05/4 = .0125$ for IRI) are indicated in bold script. Please note that no Bonferroni correction was needed for SSQ data.

Table 2.3 Regression analyses[a] for effects of age on the self-reported questionnaires.

	AQ Total score		AQ Social skills		AQ Attention switching		AQ Attention to detail		SSQ	
	ASD	COM	ASD	COM	ASD	COM	ASD	COM	ASD	COM
	β	*β*	*β*	*β*	*β*	*β*	*β*	*β*	*β*	*β*
Age	**1.38*****	-0.89*	**1.07****	-0.73	0.86*	-1.00*	**1.34*****	-0.30	**1.54*****	0.08
Age^2	**-1.36*****	1.02*	-0.92*	0.94*	-0.92*	0.98*	**-1.60*****	0.19	**-1.76*****	-0.02
Constant	**34.54*****	**11.51*****	**7.43*****	**1.49*****	**7.80*****	**2.15*****	**6.73*****	**3.54*****	**6.39*****	**2.39*****
R^2	.05	.04	.05	.06	.03	.02	.13	.01	.12	.00
N	237	198	237	198	237	198	237	198	163	173

Note. ASD=autism spectrum disorder; COM=comparison group; AQ=Autism-Spectrum Quotient; SSQ=Sensory Sensitivity Questionnaire.

[a] Regression analyses were run per group on the scales that yielded a significant interaction between group and age(2).

* $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$

Significant values after Bonferroni correction ($\alpha = 0.05/5 = .01$) are indicated in bold script.

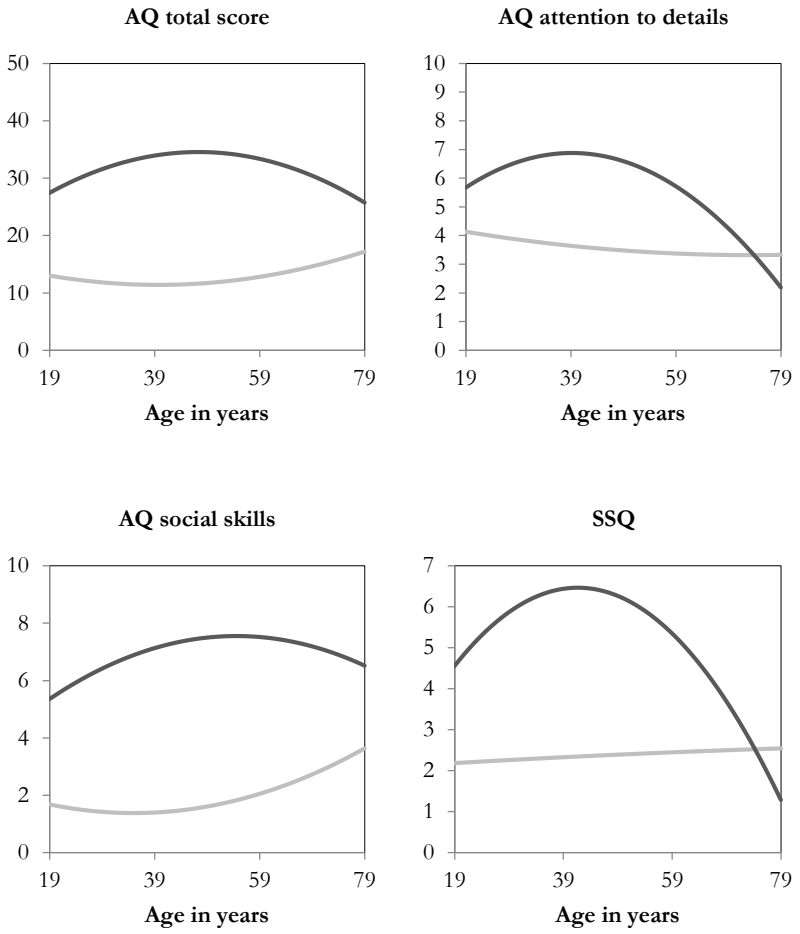

Figure 2.1 Age-related differences on the Autism-Spectrum Quotient (AQ) total score, AQ social skills subscale, AQ attention to detail subscale, and Sensory Sensitivity Questionnaire (SSQ). The darker line indicates the group with autism spectrum disorder.

to detect significant differences between self- and other-report in both groups (ASD: $F(1, 61) = 3.27$, $p = .076$, $\eta_p^2 = .05$; COM: $F(1, 71) = 2.53$, $p = .116$, $\eta_p^2 = .03$).

Age-related differences in symptoms as reported by proxies were not found to be significant on neither the AQ, IRI, nor SSQ (all ps > .07). Group differences were, however, also revealed by other-reports (all ps ≤ .009, $\eta_p^2 = .03$-$.52$). Moreover, proxies reported higher IRI ($p < .001$, $\eta_p^2 = .08$) and SSQ scores ($p = .005$, $\eta_p^2 = .06$) for females than for males, but similar AQ scores ($p = .095$, $\eta_p^2 = .01$).

Table 2.4 Intra-class correlations, confident intervals, and self- and other-reported mean scores and standard deviations for each questionnaire.

		N[a]	Cronbach's alpha	ICC	95% CI	Self M (SD)	Other M (SD)
Total	AQ[b]	270	.887	.786	.724-.834	17.9 (10.1)	19.7 (10.3)
	IRI	275	.667	.476	.359-.575	57.9 (13.4)	53.3 (14.8)
	SSQ	134	.695	.534	.400-.645	4.0 (3.0)	3.8 (2.6)
COM group	AQ[b]	145	.646	.459	.315-.581	10.1 (4.8)	11.7 (5.7)
	IRI	146	.649	.471	.334-.588	60.6 (13.1)	57.7 (13.5)
	SSQ	72	.647	.473	.275-.633	2.5 (2.0)	2.9 (2.2)
ASD group	AQ[b]	125	.328	.187	.020-.346	26.9 (6.5)	28.9 (5.4)
	IRI	129	.623	.411	.225-.561	54.7 (13.1)	48.4 (14.6)
	SSQ	62	.570	.390	.163-.580	5.6 (3.0)	4.9 (2.6)

Note. ASD=autism spectrum disorder; COM=comparison group; ICC=intra-class correlation coefficient, CI=confidence interval; AQ=Autism-Spectrum Quotient; IRI=Interpersonal Reactivity Index; SSQ=Sensory Sensitivity Questionnaire.

[a] Please note that the numbers of participants included in the analyses are slightly lower than the numbers reported in the participant section as for these analyses only those individuals were included who had completed self- and other-report.

[b] Please note that this AQ score is based on 40 items as the other-questionnaire excludes 10 items.

Comparison non-ADOS, ADOS-, ADOS+, and ADOS++

The four ADOS groups did not differ in their mean age (p = .124), gender ratio (p = .246), educational level (p = .370), time of diagnosis (p = .841*),* AQ scores (p = .457), IRI scores (p = .351), or SSQ scores (p = .347). Hence, demographics and the amount of symptoms did not differ between participants to whom the ADOS was not administered, to those scoring below the ASD threshold, and to those scoring above the ASD or autism threshold, suggesting that the results extend to the overall ASD sample.

DISCUSSION

Self-report measures are commonly used in clinical practice to obtain information about ASD symptomatology and provide a valuable tool to gain information about a person's experience of certain feelings, thoughts, and behaviors. In this study, we investigated age-related differences in self-reported ASD symptoms in a large sample of intellectually able individuals with clinical ASD across the adult lifespan. Furthermore, we evaluated both self- and other-report.

Age-related differences in ASD symptoms

Our main finding was that age-related differences are observed in self-reported general ASD symptoms and sensory sensitivity, but not in cognitive and affective empathy. With regard to general ASD symptoms, as measured with the AQ, the age-related pattern of adults with ASD was characterized by an increase in self-reported symptoms followed by a decrease. Older adults reported more symptoms than younger adults and middle-aged adults reported more symptoms than younger and older adults. Similar patterns were observed for attention to details and sensory sensitivity. Older age was associated with reduced social skills. We will discuss these findings in more detail below.

Although the diagnostic status of ASD is relatively stable over time (Billstedt, Gillberg, & Gillberg, 2007; Magiati et al., 2014; Piven et al., 1996), longitudinal studies showed that, despite some stable or even worsening individual change trajectories, the overall pattern was one of improvement with ASD symptoms abating over time (e.g., Howlin et al., 2013; Piven et al., 1996; Woodman, Smith, Greenberg, & Mailick, 2015). However, cross-sectional studies using self-report to assess ASD symptoms in adulthood did not find any association with age (Bastiaansen et al., 2011; Bishop & Seltzer, 2012). In the current cross-sectional study, the reduction of symptoms was not observed, but we did find an age-related effect. An initial increase in self-reported ASD symptoms, especially interests in details and patterns, was followed by a reduction in late adulthood. In earlier studies, only a linear age-related pattern was considered, whereas we allowed for a non-linear pattern. When we reran our analyses with only linear age, we also did not find a relation between age and symptomatology. Hence, the current results suggest that self-reported symptoms may vary over the adult lifespan in individuals with ASD, but they need replication in a longitudinal design.

Also sensory sensitivity increased from young to middle adulthood and decreased from middle to late adulthood in ASD. Reduced sensory functioning (Fozard, 1990) or better coping mechanisms (Grandin, 2011) in older adulthood may provide a suggestion for why this pattern is observed. Nevertheless, our findings are in contrast to earlier ASD studies that did not find an association between age and self-reported sensory sensitivity (Crane et al., 2009; Minshew & Hobson, 2008). Although we used the same instrument as Minshew and Hobson (2008), they included individuals between 8 and 54 years of age with a mean age of 17. Adults reported more symptoms than children, but the role of age across adulthood was not examined. The age range and mean age of the Crane study (2009) was more comparable to ours, but another instrument was used and the sample size was rather small. Our results, hence, are not necessarily discordant and future research should further investigate age-related differences or changes in sensory functioning in ASD.

Finally, empathy, an aspect of social-emotional reciprocity, was not sensitive to age-related differences (e.g., Eysenck et al., 1985) in adults with and without ASD. It has previously been demonstrated that age-related differences in perspective taking and empathic concern may follow an inverted U-shape (O'Brien et al., 2013). However, this pattern was found in a very large sample of more than 75000 individuals drawn from the general population. Our failure to replicate this finding is plausibly a power issue as the directions of estimated coefficients in the current study were comparable, even though our results fit ASD-related findings indicating that age did not affect cognitive reasoning on other persons' mental states (Chung et al., 2014).

The group and gender comparisons and age-related differences in the comparison group were in line with the literature. As expected, 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). Finally, as in previous reports about the general population, age was not associated with general ASD symptoms (Hoekstra et al., 2008; but see J. Broadbent, Galic, & Stokes, 2013) or sensory sensitivity (Crane et al., 2009; Robertson & Simmons, 2013) in the comparison group. The high number of self-reported general ASD symptoms and sensory sensitivities and the persistence of these symptoms across the adult lifespan, underline the lifelong nature of this neuropsychiatric condition.

Self- and other-report

Contrary to self-report, age-related differences in symptomatology were not perceived by the proxies. In line with this result, agreement between self- and other-report was rather poor. Although the amount of reported sensory symptoms was comparable between self- and other-report in ASD and non-ASD, participants of both groups tended to report less general ASD symptoms and more empathic tendencies than their proxies. Moreover, proxies did not indicate gender differences on general ASD features, whereas they reported more empathy and sensory sensitives for females than for males.

Albeit the agreement of the overall group was similar to those previously reported for social responsiveness (De la Marche et al., 2015), we found the agreement in both the ASD and comparison group to be rather poor. Low values are often found when there is low consensus, low consistency, or both (LeBreton & Senter, 2007). Given that Cronbach's alpha was acceptable

for all measures, except for the AQ in the ASD group, low consistency may only partially explain discrepancies between self-report and other-report. These discrepancies rather indicate a different experience of ASD-related symptoms by individuals themselves and by their proxies. Several explanations may apply.

First, it has been questioned whether individuals with ASD are able to provide reliable self-reported information as ASD has been associated with reduced introspection (Frith, 2004). Limited self-awareness of children and adolescents with ASD have indeed been demonstrated (Johnson, Filliter, & Murphy, 2009; Kievit & Geurts, 2011), but recently, it was suggested that adults with ASD are able to provide reliable information about their symptomatology (De la Marche et al., 2015). Given that either individuals with and without ASD demonstrated discrepancies in AQ scores, interpreting our findings within this framework does not hold. Furthermore, the mean difference between self and other (i.e., 1.8) was smaller than in the original Baron-Cohen sample (i.e., 2.8; 2001), which has been described as good, even though statistical analyses were lacking.

Second, in line with the previous argument, it can be argued that one of the raters is biased. A person may enhance one's own characteristics (John & Robins, 1993) or experience his or her pathological traits as more acceptable or desirable than a proxy (Hirschfeld, 1993) and, hence, underestimate the degree of behavioral symptoms, or proxies may focus more on pathological traits than on normal traits (Leising, Erbs, & Fritz, 2010) and, hence, overestimate certain symptoms.

Third, low agreement not necessarily means that there is a bias or an error in one of the raters. The self and a proxy may have different perceptions about related traits and, therefore, provide different types of information (Carlson, Vazire, & Oltmanns, 2013). The self would be more accurate about traits that describe unobservable thoughts and feelings due to privileged access, whereas a proxy would be more accurate about observable behavior (Vazire, 2010). Our findings seem to be in line with this reasoning. While discrepancies were comparable to controls on general ASD symptoms, discrepancies on empathy were larger in individuals with ASD than in controls, and discrepancies on sensory sensitivity were negative in individuals with ASD (i.e., proxies reported less symptoms than participants themselves) and positive in non-ASD (i.e., proxies reported more symptoms than participants themselves). General ASD symptoms are mostly based on behavior, whereas empathy and sensory sensitivity deal more with feelings and thoughts that are sometimes difficult to evaluate from an outside perspective.

Based on our study, we cannot disentangle these different factors. Further research is needed to examine why self- and other-report by proxies who have known the participants for a long time, provide discrepancies in ASD-related symptomatology.

Clinical implications

We believe that the current findings have several clinical implications. First, when an adult person is referred to clinical practice in order to be screened for an ASD diagnosis, often the partner initiates this process (National Institute for Health and Clinical Excellence, 2012). Moreover, during the diagnostic process, a family member is, where possible, involved to provide information about developmental history. Hence, a proxy has a crucial role. Whether the proxy is a partner, family member, or friend does not largely affect the report of ASD-related symptoms (see Table S.2.1, Supplementary material Chapter 2), despite subtle differences. Nevertheless, the disagreement between self- and other-report about symptoms is puzzling. Although we have discussed several factors that may influence this discrepancy, we cannot provide definite conclusions. Our results do suggest that it is not necessarily the case that individuals with ASD have poor introspection into their symptoms. The possibility remains that proxies and individuals with ASD provide complementary information. Observed discrepancies may provide an interesting idiosyncrasy for discussion during assessment.

Second, females with ASD reported more ASD symptoms as measured with the AQ than males with ASD, but this gender difference was not revealed by proxies. On the one hand, females with ASD might be better at masking their symptoms as they may be more motivated and more effortful to develop social skills and may present better self-referential abilities (Lai et al., 2011), resulting in high self-reported symptoms, but lower other-reported symptoms. On the other hand, albeit highly speculative, females may feel the need to report more ASD symptoms 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 symptomatic differences between males and females.

Third, since the introduction of the DSM-5 (American Psychiatric Association, 2013), sensory sensitivity has acquired importance for the diagnostic assessment of ASD. Although not all individuals with ASD experience sensory hypo- or hyperreactivity to sensory stimuli (Baranek, Parham, & Bodfish, 2005), it is an aspect that often causes extreme discomfort. As the current cross-sectional study revealed that sensory symptoms are subject to age-related differences, it would be meaningful to inquire regularly about the experience of sensory symptoms in clinical settings. This regular assessment is also relevant for general ASD symptomatology given the observed role of age in self-perceived ASD traits.

Limitations

The main limitation of the current study was its cross-sectional nature, in which age-related differences *between*-persons were taken into account. Therefore, we cannot draw conclusions on how self-reported ASD symptoms change over the years *within*-persons. Our results need a longitudinal follow-up to investigate whether age-related changes in ASD symptoms, generally examined with measures relying on other information (i.e., a parent or caregiver), such as the Autism Diagnostic Interview-Revisited or the Vineland, are also detected by individuals with ASD themselves and whether this change trajectory is one of improvement.

The convenience of self-report is also its drawback. The self has privileged access to certain feelings, and thoughts, and behaviors, but it is the interpretation and evaluation that determines how one reports about these aspects. Therefore, when examining age-related differences or age-related changes by means of self-report, a relevant aspect to evaluate is whether they indicate a change in the experience or perception of symptoms, or an observable behavioral change of symptoms. For example, the age-related differences in sensory symptoms do not necessarily indicate that older adults exhibit less symptoms than middle aged adults, as they may also indicate that older adults experience less symptoms and are better able to deal with them. Furthermore, it does not preclude that the present ones cause many discomfort, even though they experience less symptoms.

ASD is a very heterogeneous condition that affects individuals in different ways. Some individuals present symptoms that severely affect their daily functioning to such an extent that they need very substantial support. Others, mostly those with good verbal and intellectual abilities, present less severe ASD, but still encounter considerable difficulties. Our sample consisted of those latest individuals as they were intellectually high-functioning, with many having a paid job (some even high profile) and living with a partner. They were diagnosed with ASD relatively late in life and one might argue that they presented relatively mild ASD. However, they and their proxies reported many ASD symptoms (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) and many empathy difficulties, which have an impact on social functioning and are likely to be highly disabling. This shows how important it is to study this intellectually high functioning group of individuals as well.

Conclusions

In this large cross-sectional study of adults with clinical diagnoses of ASD, we demonstrated that individuals with ASD experience a significant degree of general ASD symptoms, as measured with the AQ, and empathic difficulties, as measured with the IRI, and sensory sensitivities, as

measured with the SSQ, across the adult lifespan. Self-reported general ASD symptoms and sensory sensitivities seem to increase from young to middle adulthood and diminish from middle to late adulthood, but these age-related differences were not reported by proxies who have known the participants for a long time. Indeed, the perception of ASD-related symptoms differs among self-report and other-report, with discrepancies being pronounced, suggesting that self and proxies grasp distinct aspects of symptomatology. Longitudinal follow-up studies should reveal whether self-reported ASD symptoms are experienced to change over time.

SUPPLEMENTARY MATERIAL CHAPTER 2

Effect of proxy type on symptomatology

Statistical analysis

To explore whether the type of proxy influenced the number of reported symptoms, we ran three exploratory ANOVAs with group (autism spectrum disorder [ASD], comparison [COM]) and type of proxy (partner, family, friend, or other [due to only a few cases, we clustered other proxies and unknown proxies together]) as between-subject factors for the total scores of the Autism-Spectrum Quotient (AQ), Interpersonal Reactivity Index (IRI), and Sensory Sensitivity Questionnaire (SSQ). The analyses were run with SPSS 22.0 (IBM Corp., 2013).

Results

Explorations on whether the type of proxy affected the amount of reported symptoms, indicated a main effect on AQ and IRI (see Table A.1). Friends reported lower AQ scores than partners ($p < = .001$), and others ($p = .010$), but not of family members ($p = .084$). On a similar note, friends reported higher IRI scores than partners ($p = .003$), even though the comparison with family members ($p = .065$) and others was not significant ($p = 1.000$). The other comparisons were also not significant. Hence, AQ and IRI proxy scores were influenced by who filled out the questionnaire. We explored which group of proxies diverged the most from the participants. In absence of an interaction between other-type and group, we combined the ASD and COM group. The discrepancies between self- and other-report were the smallest for partners on the AQ, for friends on the IRI, and for family members on the SSQ.

Table S.2.1 Means (standard deviations) per questionnaire for each proxy type, and statistics to compare scores of the ASD and COM group and the proxy type.

		Partner	Family member	Friend	Other
Total	AQ	20.3 (10.1)	19.8 (10.3)	14.0 (9.0)	24.8 (11.2)
	IRI	51.6 (15.1)	53.1 (15.1)	61.1 (9.1)	56.3 (15.4)
	SSQ	4.1 (2.5)	3.6 (2.6)	3.2 (2.8)	4.1 (2.3)
COM group	AQ	12.6 (5.7)	11.0 (5.5)	8.6 (4.1)	13.4 (9.7)
	IRI	56.9 (14.6)	57.6 (13.1)	61.4 (10.4)	57.2 (10.0)
	SSQ	3.5 (2.3)	2.0 (1.8)	1.7 (1.0)	3.0 (-)
ASD group	AQ	29.5 (5.5)	28.5 (5.1)	24.8 (5.5)	32.0 (3.3)
	IRI	45.3 (13.1)	48.7 (15.8)	60.5 (6.3)	55.8 (18.0)
	SSQ	4.9 (2.7)	4.8 (2.6)	5.5 (3.0)	4.3 (2.4)

	Statistics								
	Group			Proxy type			Group by proxy type		
	F	*p*	η_p^2	*F*	*p*	η_p^2	*F*	*p*	η_p^2
AQ	289.81	**<.001**	.53	5.88	**.001**	.06	0.20	.894	.00
IRI	5.27	**.022**	.02	4.42	**.005**	.05	1.60	.191	.02
SSQ	9.89	**.002**	.07	1.11	.349	.03	1.47	.227	.03

Note. ASD=autism spectrum disorder; COM=comparison group; AQ=Autism-Spectrum Quotient; IRI=Interpersonal Reactivity Index; SSQ=Sensory Sensitivity Questionnaire. Significant values are indicated in bold script.

Chapter 3

Co-occurring psychopathology in young, middle-aged, and older adults with autism spectrum disorder

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ABSTRACT

Although psychiatric problems are less prevalent in old age within the general population, it is largely unknown whether this extends to individuals with autism spectrum disorders (ASD). We examined psychiatric symptoms and disorders in young, middle-aged, and older adults with and without ASD (N_{max}=344, age 19-79 years, IQ>80). Albeit comparable to other psychiatric patients, levels of symptoms and psychological distress were high over the adult lifespan; 79% met criteria for a psychiatric disorder at least once in their lives. Depression and anxiety were most common. However, older adults less often met criteria for any psychiatric diagnosis and, specifically, social phobia than younger adults. Hence, despite marked psychological distress, psychiatric problems are also less prevalent in older aged individuals with ASD.

Keywords: autism spectrum disorder, psychiatric comorbidity, aging, adults, depression, anxiety

INTRODUCTION

Psychopathology is a frequently occurring phenomenon. In the general population, approximately 40% meets criteria for a psychiatric disorder at least once in their lives (Bijl et al., 1998; Kessler et al., 2005). This rate is much higher in individuals with an autism spectrum disorder (ASD), a heterogeneous neurodevelopmental disorder characterized by atypicalities in social communication and interaction and repetitive stereotyped behavior (American Psychiatric Association, 2013). In this population, at least 69% is thought to suffer from co-occurring psychiatric disorders and symptoms (Buck et al., 2014), even though rates are lower in individuals with ASD and intellectual disability (ID) (Howlin & Moss, 2012; Matson & Cervantes, 2014). The presence of co-occurring disorders is associated with lower quality of life, greater demands for professional help, poorer prognosis, greater interference with everyday life, and worse outcome (Lainhart, 1999; Matson & Cervantes, 2014; Seltzer et al., 2004; Vannucchi et al., 2014; Wood & Gadow, 2010). Furthermore, specifically the co-occurring symptoms and disorders often constitute a target for treatment, leading to an amelioration of problems. For example, various psychotropic medications are frequently prescribed to individuals with ASD to treat associated symptoms (Aman, Lam, & Van Bourgondien, 2005; Buck et al., 2014; Esbensen et al., 2009; Logan et al., 2015; Seltzer et al., 2004). As ASD is considered a lifelong disorder (Piven et al., 1996; Seltzer et al., 2004) and symptoms of psychopathology are likely to wax and wane across the adult lifespan, knowledge regarding associated psychopathology in older adulthood is needed (Matson & Cervantes, 2014; Perkins & Berkman, 2012) to be able to provide adequate support for these older individuals. This will be the focus of the current study.

In the general population, age is a relevant factor for psychopathology. The prevalence of psychiatric disorders and their nature is different in older adulthood than in middle or young adulthood (Bijl et al., 1998; Kessler et al., 2005). While the general prevalence of psychiatric disorders is lower, the prevalence of, for example, alcohol or substance related disorders decreases sharply with increasing age, whereas depression and anxiety are still highly prevalent (Beekman et al., 1998; Wolitzky-Taylor, Castriotta, Lenze, Stanley, & Craske, 2010).

While traditionally many ASD studies mainly focused on co-occurring symptoms and disorders in childhood (de Bruin et al., 2007; Leyfer et al., 2006; Lundström et al., 2015; Mattila et al., 2010; Mukaddes et al., 2010; Simonoff et al., 2008; Sinzig et al., 2009; van Steensel et al., 2013), recently a steadily increasing number of studies have taken into account co-occurring symptoms and disorders in adulthood (Buck et al., 2014; Croen et al., 2015; Ghaziuddin & Zafar, 2008; Hofvander et al., 2009; Joshi et al., 2013; Lugnegård et al., 2011; Roy et al., 2015). These findings seem to suggest that also in the ASD population age is an important factor. In

childhood, Attention Deficit Hyperactivity Disorder (ADHD), behavioral disorder, and anxiety disorders are the most prevalent comorbid disorders (de Bruin et al., 2007; Leyfer et al., 2006; Simonoff et al., 2008; Sinzig et al., 2009), whereas in adulthood, next to ADHD and anxiety disorders, mood disorders are common (Croen et al., 2015; Ghaziuddin, Ghaziuddin, & Greden, 2002; Ghaziuddin & Zafar, 2008; Hofvander et al., 2009; Joshi et al., 2013; Roy et al., 2015; Sterling, Dawson, Estes, & Greenson, 2008). In various adult studies, older adults with ASD have been included but only a few directly compared older adults with younger individuals (Roy et al., 2015; Totsika et al., 2010). In an intellectually challenged sample, psychiatric disorders were less frequent in older adults with ASD and ID compared to younger adults with ASD and ID (Totsika et al., 2010). In contrast, in older adults with ASD without ID, co-occurring psychiatric disorders were more common than in younger adults (Roy et al., 2015). Unfortunately, the "older group" in this latest study was relatively young (age range 40-62 years), the sample was small, and a statistical comparison was lacking. A few studies focused on specific psychiatric disorders such as anxiety (Davis et al., 2011) and depression (Ghaziuddin et al., 2002). Whereas anxiety seemed to reduce from childhood to young adulthood (Davis et al., 2011), the risk for depression seemed to increase with increasing age (Ghaziuddin et al., 2002). A small study in older adults (53 to 83 years) with ASD reported high levels of psychological and somatic complaints and of psychological distress (van Heijst & Geurts, 2014). However, it has not been tested whether these participants encountered a sufficient number of psychiatric symptoms to meet diagnostic criteria, although also associated symptoms in itself may cause clinically relevant distress and impairment that may interfere with quality of life and daily functioning. Thus, the nature and prevalence of comorbid psychopathological symptoms and disorders in older adults with ASD is largely unknown. In the current study, we will, therefore, determine both the occurrence of non-ASD symptomatology and co-occurring psychiatric disorders across the adult lifespan in ASD by comparing young, middle-aged, and older adults clinically diagnosed with ASD without ID. We hypothesize psychiatric co-occurring symptoms and disorders to be substantially higher in individuals with ASD than in controls over the whole adult lifespan, but comparable to a normative group of policlinic psychiatric patients (Joshi et al., 2013). Given the mixed findings so far (Davis et al., 2011; Roy et al., 2015; Totsika et al., 2010), we will explore whether there will be differences in this co-occurrence of other psychiatric symptoms and disorders between the three age groups.

In addition to age, several other factors might affect the prevalence of comorbid psychiatric disorders in individuals with ASD, including ASD severity, gender, social economic status (i.e., education and work), living situation, and both intellectual and more general cognitive functioning. We will explore their role with respect to the co-occurring psychopathology in

adults with ASD. For example, in the general population vulnerability factors for developing anxiety or depression are, among others, cognitive decline, being female, having a lower social economic status, or not having a partner (Beekman et al., 1998). In the ASD literature the focus has been mainly on ASD severity, gender, and intellectual functioning but whether these factors are indeed risk factors for comorbid psychopathology in ASD is a topic of debate as results are rather inconsistent (Cederlund, Hagberg, & Gillberg, 2010; García-Villamisar & Rojahn, 2015; Gotham, Unruh, & Lord, 2015; Holtmann, Bölte, & Poustka, 2007; Jang & Matson, 2015; Lai et al., 2011; Lugnegård et al., 2011; Moss, Howlin, Savage, Bolton, & Rutter, 2015; Simonoff et al., 2008; Simonoff et al., 2013; Sterling et al., 2008; Tureck, Matson, Cervantes, & Konst, 2014; van Steensel, Bögels, & Dirksen, 2012). To restrict the number of analyses we will solely explore whether these aforementioned factors are indeed risk factors predictive of the most commonly co-occurring disorders in adults with ASD, which we expect to be mood and anxiety disorders (see for a similar approach in children Simonoff et al., 2008; Simonoff et al., 2013).

METHODS

Participants

Two-hundred-forty-seven adults with ASD between 19 and 79 years were recruited through several mental health institutions across the Netherlands and by means of advertisements on client organization websites. Individuals with ASD traits, but without a prior clinical diagnosis of ASD based on DSM-IV criteria (autism, Asperger's syndrome, and Pervasive Developmental Disorder Not Otherwise Specified) (American Psychiatric Association, 2000), which was generally diagnosed by a multidisciplinary team involving a psychologist and/or psychiatrist, were not eligible to participate in the study.

Two-hundred-eight adults without ASD (comparison [COM] group) were recruited by means of advertisements on the university website and on social media, and within the researchers' social environment. Individuals with a considerable amount of autistic traits, as measured with the Autism-spectrum Quotient (AQ>32) (Baron-Cohen et al., 2001), or with close family members having ASD or schizophrenia, were excluded. For both groups, additional requirement upon participation was an absent history of neurological disorders (e.g., epilepsy, stroke, cerebral contusion) or schizophrenia. Four-hundred-five individuals met these prerequisites (216 ASD, 189 COM). The study consisted of two parts. Part I included the administration of a questionnaire on psychological symptoms and distress and medication usage, which was completed by 344 individuals (172 ASD, 172 COM) who constituted the final sample of Part I. Part II included the administration of a neuropsychiatric interview to examine

Table 3.1 Descriptives of the ASD and COM group for Part I and II.

	Part I										
	ASD				Y vs M vs O	COM				Y vs M vs O	ASD vs COM
	All ages	Young	Middle	Older	Fisher's χ^2 or F	All ages	Young	Middle	Older	Fisher's χ^2 or F	χ^2
N	172	52	72	48		172	60	47	65		
Gender					4.27					1.75	4.45*
Male	116	33	45	38		97	37	23	37		
Female	56	19	27	10		75	23	24	28		
Education[a]					11.98					15.14+	9.77+
Low	1	0	1	0		0	0	0	0		
Middle	55	18	19	18		37	9	10	18		
High	115	34	51	30		134	51	37	46		
Diagnosis					6.71					-	-
Autistic disorder	26	5	12	9		-	-	-	-		
Asperger	88	27	35	26		-	-	-	-		
PDD-NOS	53	16	24	13		-	-	-	-		
ASD	5	4	1	0		-	-	-	-		
ISCO					19.29**					49.93***	7.70+
Class 1-3	62	11	37	14		80	19	36	25		
Class 4-6	21	8	10	3		22	13	5	4		
Class 7-9	11	2	4	5		4	4	0	0		
Unemployed	74	30	20	24		57	23	1	33		
Age (mean)	46.7	29.3	47.9	63.7	525.52***	46.0	26.8	47.0	63.0	711.07***	0.16
AQ (mean)	33.5	32.1	34.4	33.4	1.16	12.4	12.3	11.1	13.0	1.77	831.22***
IQ (mean)	NA	NA	NA	NA		NA	NA	NA	NA		
MMSE (mean)	NA	NA	NA	NA		NA	NA	NA	NA		
ADOS (mean)	NA	NA	NA	NA		-	-	-	-		
Psychotropic medication	87	28	38	21	1.26	6	0	2	4	3.75	96.69***
Antidepressants[b]	52	18	23	11	1.80	4	0	1	3	2.61+	49.14***
Anxiolytic/sedative/hypnotics	19	6	8	5	0.10	1	0	0	1	1.61	17.20***
Antipsychotics	24	14	7	3	9.62**	0	0	0	0	-	25.80***
Stimulants	14	4	8	2	1.73	0	0	0	0	-	14.59***
Other psychotropic medication	11	1	8	2	4.22	1	0	1	0	2.25	8.64**
Other non-psychotropic medication	58	9	27	22	10.23**	55	6	15	34	27.04***	0.12

	Part II										
	ASD				Y vs M vs O	COM				Y vs M vs O	ASD vs COM
	All ages	Young	Middle	Older	Fisher's χ^2 or F	All ages	Young	Middle	Older	Fisher's χ^2 or F	χ^2
N	138	46	47	45		170	60	46	64		
Gender					3.83					1.47	5.09*
Male	96	31	29	36		97	37	23	37		
Female	42	15	18	9		73	23	23	27		
Education[a]					10.77					13.49$^+$	8.50$^+$
Low	1	0	1	0		0	0	0	0		
Middle	43	15	11	17		36	9	9	18		
High	94	31	35	28		134	51	37	46		
Diagnosis					6.82					-	-
Autistic disorder	21	4	9	8		-	-	-	-		
Asperger	69	24	21	24		-	-	-	-		
PDD-NOS	43	14	16	13		-	-	-	-		
ASD	5	4	1	0		-	-	-	-		
ISCO					14.98*					48.84***	7.37$^+$
Class 1-3	48	10	25	13		79	19	35	25		
Class 4-6	16	7	6	3		22	13	5	4		
Class 7-9	6	1	1	4		4	4	0	0		
Unemployed	66	27	15	24		57	23	1	33		
Age (mean)	46.5	28.8	47.2	63.9	481.64***	45.9	26.8	47.2	62.9	703.46***	0.11
AQ (mean)	33.5	31.7	35.2	33.4	2.06	12.2	12.3	11.0	13.0	1.83	723.60***
IQ (mean)	113.8	112.1	116.7	112.5	1.10	113.3	111.2	114.1	114.8	0.78	0.06
MMSE (mean)	29.0	28.9	29.1	29.1	0.57	29.1	29.3	29.1	29.0	1.41	0.71
ADOS (mean)	8.6	9.5	8.5	8.0	2.43$^+$	-	-	-	-	-	-
Psychotropic medication	67	22	27	18	2.80	6	0	2	4	3.82	85.37***
Antidepressants[b]	38	12	16	10	1.65	4	0	1	3	2.65	41.02***
Anxiolytic/sedative/hypnotics	16	5	6	5	0.17	1	0	0	1	1.62	17.69***
Antipsychotics	18	11	4	3	6.46*	0	0	0	0	-	23.55***
Stimulants	9	4	4	1	2.11	0	0	0	0	-	11.42***
Other psychotropic medication	9	1	7	1	6.73**	1	0	1	0	2.28	8.54**
Other non-psychotropic medication	46	7	20	19	10.73**	53	6	14	33	26.08***	0.16

Note. ASD = autism spectrum disorder; COM = comparison group; PDD-NOS = Pervasive Developmental Disorder Not Otherwise Specified; ISCO = International Standard Classification of Occupations; AQ = Autism-spectrum Quotient; IQ = estimated intelligence quotient; MMSE = Mini Mental State Examination; ADOS = Autism Diagnostic Observation Schedule, Y = young, M = middle, O = older.

[a] One missing in both groups.

[b] Antidepressant medication refers to the use of non-selective monoamine reuptake inhibitors, selective serotonin reuptake inhibitors, and other antidepressants.

$^+p<.1$, * $p\leq.05$, ** $p\leq.01$, *** $p\leq.001$

psychiatric disorders and an analysis of potential risk factors, and was part of a larger study assessing age-related differences in cognition (Lever & Geurts, 2015). Eligible ASD individuals were selected based on age to ascertain that participants were evenly distributed across ages. IQ was estimated with two subtests of the Dutch Wechsler Adult Intelligence Scale third edition (WAIS-III) (Uterwijk, 2000; Wechsler, 1997a) and the diagnoses of the ASD participants were verified by administering the Autism Diagnostic Observation Schedule module 4 (ADOS) (de Bildt & de Jonge, 2008; Lord et al., 2000). Four individuals (2 ASD, 2 COM) had an estimated IQ below 80 and were excluded from the sample of Part II. Of the remaining 138 ASD participants, 37 scored below the ADOS cut-off for ASD (<7), 49 below the autism threshold (<10), and 52 above the autism threshold (≥10). As all these individuals had a clinical diagnosis within the autism spectrum, diagnosed independently from the present study by mental health professionals, and the sensitivity of the ADOS is poor when administered to intellectually able adults (Bastiaansen, Meffert et al., 2011), we included all these ASD participants in the current study. Furthermore, 80% scored above the threshold of 26 on the AQ (Woodbury-Smith, Robinson, Wheelwright, & Baron-Cohen, 2005). All individuals had a Mini Mental State Examination score above 26 (Folstein, Folstein, & McHugh, 1975). Hence, with respect to Part II, the final sample for the examination of co-occurring disorders was composed of 138 ASD participants and 170 COM participants.

Based on a tertile split of this ASD group, the participants were assigned to a young (19-38 years), middle-aged (39-54 years), and older (55-79 years) adult group (Table 3.1).

Measures

Psychiatric co-occurring symptoms

Symptom Checklist-90 Revised (SCL-90-R). The SCL-90-R (Arrindell & Ettema, 2005; Derogatis, 1977) is a widely used multidimensional self-report inventory consisting of 90 items to assess the presence of current psychopathological symptoms and psychological distress. Each item is rated on a five-point Likert scale ranging from 0 "not at all" to 4 "very much" and indicates how much distress was caused during the last week comprising today. The original SCL-90-R includes nine primary symptom dimensions and three global indices that cover clinically relevant psychiatric and psychosomatic symptoms. The Dutch version (Arrindell & Ettema, 2005), however, measures eight dimensions: anxiety, agoraphobia, depression, somatization, cognitive-performance deficits, interpersonal sensitivity and mistrust, hostility, and sleep difficulties. The total score, psychoneuroticism, provides a general measure of psychological distress. Higher scores indicate more symptoms and distress. The psychometric properties of the SCL-90-R,

including internal consistency, test-retest reliability, and convergent and divergent validity, are good to very good (Arrindell & Ettema, 2005).

Psychiatric co-occurring disorders

Mini International Neuropsychiatric Interview Plus (MINI-Plus). The MINI-Plus (Sheehan et al., 1998; van Vliet, Leroy, & van Megen, 2000) is a structured diagnostic interview that explores several psychiatric disorders according to DSM-IV criteria. First, two to four screenings questions are asked for each disorder. Second, if any of these is answered positively, additional questions further inquire about the presence of a disorder. We inquired about mood, anxiety, substance-related, eating, somatoform, and conduct disorders. The MINI has good inter-rater and test-retest reliability (Lecrubier et al., 1997; Sheehan et al., 1997). For the current study, we adjusted wording of a small number of questions, for example by splitting extended questions into sub questions, to make them more comprehensible to individuals with ASD and to be able of examining lifetime adherence for all disorders. Although we did not change the purport of the items, the validity of the MINI may have been reduced due to these adjustments.

ADHD rating scale. The ADHD rating scale (Kooij et al., 2005) is a 23-item self-report questionnaire to assess ADHD symptoms based on DSM-IV criteria. Using the adult scale, an individual rates the extent to which each statement illustrates his or her behavior over the past six months on a four-point Likert scale, ranging from 0 "rarely or never" to 3 "very often". Items rated with "often" or "very often" met diagnostic criteria for either inattentive or hyperactive-impulsive subtype symptoms. Following the DSM-IV (American Psychiatric Association, 2000), we considered the presence of at least six out of nine symptoms per subtype as indicative of an AD(H)D diagnosis. The validity of the ADHD rating scale is reasonable (Kooij et al., 2008).

Risk factors

ASD severity as measured with the AQ and ADOS, intellectual functioning (IQ) as estimated with a short version of the WAIS-III, general cognitive functioning as measured with the MMSE, and information on education, work situation (coded according to the International Standard Classification of Occupations [ISCO]), living situation, gender, and age as indicated by self-report constituted the risk factors.

Procedure

Informed consent was obtained from all individual participants included in the study, after which they filled out the AQ and SCL-90, among other questionnaires (Part I). Participants selected for Part II were tested in two sessions during which (1) the ADOS, shortened WAIS-III, MMSE, and MINI were administered, and (2) neuropsychological and experimental testing took place (these are described elsewhere) (e.g., Lever & Geurts, 2015). Participants who were tested in at

least one test session received compensation for their travel expenses; most COM participants also received additional compensation (max €20). The study was approved by the institutional review board of the University of Amsterdam and was in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statistical analyses

Psychiatric co-occurring symptoms. SCL-90-R variables were highly skewed and neither log, square root, nor inverse transformation lead to normality. However, as MANOVA is thought be robust against this type of violation (Stevens, 2012), we ran a MANOVA with Diagnostic group (ASD, COM) and Age (young, middle-aged, older) as between-subject factors and the total score and SCL-90-R subscales as dependent variables. Raw scores were then compared with normative data available for the general population and a policlinic psychiatric patient group (Arrindell & Ettema, 2005). Analyses were run with and without outliers (data points more than 3 SD from group mean). When the pattern of results changed by removing outliers, we report both analyses.

Psychiatric co-occurring disorders. Chi-square tests were used to compare frequencies of psychiatric disorders, as measured with the MINI-Plus and ADHD list, between the ASD and COM group. We clustered the inquired disorders into six major disorders: mood, anxiety, substance-related, eating, somatoform, and attentional and behavioral disorders and Bonferroni corrected for multiple comparisons (i.e., significance level was set on 0.05/6=0.0083). Thereafter, chi-square tests were ran per non-clustered disorder to compare the ASD and COM group and Fisher's exact test was used to compare frequencies between young, middle-aged and older adults per diagnostic group. No further correction was applied to these analyses. Results per distinct disorder are presented when group differences were significant after Bonferroni correction. Otherwise, they are presented in the supplementary material of Chapter 3.

Risk factors. Binomial logistic regressions and linear regressions were run to assess the association between risk factors and any mood or anxiety disorder and depression and anxiety symptoms, respectively. Please note that we computed these risk factor analyses on the sample of Part II (due to the inclusion of IQ and ADOS) and that we excluded the COM group from these analyses (as our focus was on the risk factors involved in the ASD group). All analyses were conducted in SPSS 22.0 (IBM Corp., 2013).

RESULTS

Psychiatric co-occurring symptoms

The SCL-90-R scores for Part I are presented in Table 3.2. The omnibus MANOVA revealed a main effect of diagnostic group, $\Lambda = 0.58$, $F(9, 330) = 26.42$, $p < .001$, $\eta_p^2 = .42$, but no main effect of age-group, $\Lambda = 0.96$, $F(18, 660) = 0.82$, $p = .672$, $\eta_p^2 = .02$, nor an interaction effect, $\Lambda = 0.94$, $F(18, 660) = 1.15$, $p = .298$, $\eta_p^2 = .03$. The ASD group had higher scores on all subscales and the total score. This is in line with the findings when we compare the scores of the ASD sample to the norms of a general population sample as over a quarter of adults with ASD had depression or anxiety scores that were considered very high (≥95th percentile). However, compared to a psychiatric patient group, only a few individuals (<5%) with ASD had scores above the 95th percentile (Table 3.3), which suggest that these high scores for individuals with ASD are common in individuals with psychiatric diagnoses.

When running the MANOVA on the subgroup sample of Part II, there was still a main effect of diagnostic group and no main effect of age-group, but now the diagnostic group by age-group interaction was significant, $\Lambda = 0.88$, $F(18, 588) = 2.16$, $p = .004$, $\eta_p^2 = .06$, with generally a decrease of reported symptoms with age in the ASD group and no such a decrease in the COM group. After removing the outliers, in addition to the already present effects, there was also a main effect of age-group, $\Lambda = 0.88$, $F(18, 542) = 1.95$, $p = .011$, $\eta_p^2 = .06$. The older age group generally had lower scores than the younger groups, even though this difference seemed more pronounced in the ASD group.

Table 3.3 Number (%) of adults with and without ASD scoring above the 95th percentile compared to a normative general population and a psychiatric patient sample.

	ASD		COM	
	NOR	PSY	NOR	PSY
Psychoneuroticism	69 (40.1%)	3 (1.7%)	5 (2.9%)	0 (-)
Agoraphobia	79 (45.9%)	1 (0.8%)	2 (1.2%)	0 (-)
Anxiety	44 (25.6%)	1 (0.8%)	2 (1.2%)	0 (-)
Depression	70 (40.7%)	1 (0.8%)	5 (2.9%)	0 (-)
Somatization	29 (16.9%)	3 (1.7%)	3 (1.7%)	0 (-)
Cognitive-performance deficits	87 (50.6%)	5 (2.9%)	6 (3.5%)	0 (-)
Interpersonal sensitivity and mistrust	67 (39.0%)	8 (4.7%)	9 (5.2%)	0 (-)
Hostility	51 (29.7%)	3 (1.7%)	6 (3.5%)	0 (-)
Sleep difficulties	42 (24.4%)	4 (2.3%)	10 (5.8%)	0 (-)

Note. ASD = autism spectrum disorder; COM = comparison group; NOR = general population; PSY = psychiatric patient sample.

Table 3.2 SCL-90-R total and subscale scores for the young, middle-aged, and older adults with and without ASD.

	ASD				COM				ASD vs COM[a]	
	All ages	Young	Middle	Older	All ages	Young	Middle	Older	*F*	η_p^2
Psychoneuroticism	174.9	183.9	173.1	167.6	113.3	111.3	115.9	113.2	192.96***	.36
Agoraphobia	11.4	12.2	11.3	10.6	7.4	7.3	7.2	7.5	116.89***	.26
Anxiety	18.3	19.8	18.1	17.0	11.8	11.4	12.1	11.8	111.28***	.25
Depression	33.6	34.8	33.9	31.8	20.6	19.8	21.1	21.0	151.71***	.31
Somatization	20.5	21.6	20.8	18.9	15.3	15.4	15.5	15.1	62.81***	.16
Cognitive-performance deficits	21.1	21.7	21.1	20.5	12.5	12.7	12.7	12.2	208.91***	.38
Interpersonal sensitivity and mistrust	37.2	38.8	36.1	37.2	23.4	22.7	24.3	23.3	152.44***	.31
Hostility	9.9	10.8	9.5	9.3	7.0	7.1	7.2	6.8	83.57***	.20
Sleep difficulties	6.6	6.9	6.7	6.2	4.7	4.6	4.7	4.8	43.21***	.11

Note. ASD = autism spectrum disorder; COM = comparison group.

[a] We do not report the effects of age-group as the overall MANOVA revealed a nonsignificant effect, as denoted in the main text.

Table 3.4 Lifetime rates of DSM-IV disorders in young, middle-aged, and older adults with and without ASD.

	ASD									COM									
	All ages		Young		Middle		Older		Young vs Middle vs Older	All ages		Young		Middle		Older		Young vs Middle vs Older	ASD vs COM
	N	%	N	%	N	%	N	%	Fisher's χ^2	N	%	N	%	N	%	N	%	Fisher's χ^2	χ^2
Any psychiatric disorder	109	79.0	38	82.6	41	87.2	30	66.7	6.02*	83	48.8	30	50.0	19	41.3	34	53.1	1.55	29.52***
Mood disorders	79	57.2	24	52.2	35	74.5	20	44.4	9.30**	31	18.2	9	15.0	9	19.6	13	20.3	0.70	50.49***
Depression	74	53.6	19	52.2	31	66.0	19	42.2	5.24+	28	16.5	9	15.0	8	17.4	11	17.2	0.20	47.47***

Dysthymia	25	18.1	6	13.0	13	27.7	6	13.3	4.04	5	2.9	1	1.7	2	4.3	2	3.1	0.86	19.95***
PDysD (only females)	9	20.9	3	18.8	3	16.7	3	33.3	5.16	2	2.7	1	4.3	1	4.3	0	-	3.00	14.34***
Anxiety disorders	74	53.6	30	65.2	25	53.2	19	42.2	4.81+	25	14.7	8	13.3	8	17.4	9	14.1	0.44	52.89***
Panic disorder	21	15.2	11	23.9	6	12.8	4	8.9	4.01	6	3.5	3	5.0	1	2.2	2	3.1	0.68	13.01***
Agoraphobia	29	21.0	10	21.7	9	19.1	10	22.2	0.20	6	3.5	1	1.7	3	6.5	2	3.1	1.77	23.12***
Social phobia	21	15.2	10	21.7	10	21.3	1	2.2	10.23**	8	4.7	3	5.0	3	6.5	2	3.2	0.86	9.87**
Specific phobia	16	11.6	5	10.9	7	14.9	4	8.9	0.84	8	4.7	1	1.7	1	2.2	6	9.4	4.11	5.03*
PTSS	4	2.9	1	2.2	3	6.4	0	-	4.66	1	0.6	0	-	1	2.2	0	-	2.28	6.36*
OCD	30	21.7	13	28.3	10	21.3	7	15.6	5.85	1	0.6	0	-	1	2.2	0	-	2.28	40.68***
GAD	22	15.9	8	17.4	9	19.1	5	11.1	3.12	5	2.9	2	3.3	2	4.3	1	1.6	1.00	17.50***
Substance-related disorders	22	15.9	9	19.6	5	10.6	8	17.8	1.60	43	25.3	20	33.3	9	19.6	14	21.9	3.10	4.00*
Eating disorders	8	5.8	4	8.7	3	6.4	1	2.2	1.79	1	0.6	1	1.7	0	-	0	-	1.74	7.29*
Somatoform disorders	8	5.8	6	13.0	2	4.3	0	-	6.72*	3	1.8	0	-	1	2.2	2	3.1	1.81	3.60+
Attentional and behavioral disorders	43	31.2	14	30.4	16	34.0	13	28.9	0.33	9	5.3	5	8.3	2	4.3	2	3.1	1.65	36.31***
ADHD[a]	42	30.4	14	30.4	15	31.9	13	28.9	0.13	9	5.3	5	8.3	2	4.3	2	3.1	1.65	34.84***
Inattentive	14	10.1	5	10.9	3	6.4	6	13.3	1.30	4	2.4	3	5.0	1	2.2	0	-	3.05	8.40**
Hyperactivity/impulsivity	18	13.0	6	13.0	8	17.0	4	8.9	1.33	5	2.9	2	3.3	1	2.2	2	3.1	0.32	11.25***
Combined	10	7.2	3	6.5	4	8.5	3	6.7	0.28	0	-	0	-	0	-	0	-	-	12.73***
Conduct disorder	3	2.2	1	2.2	2	4.3	0	-	4.46	1	0.6	0	-	1	2.2	0	-	2.28	4.35

Note. ASD = autism spectrum disorder; COM = comparison group; PDysD = premenstrual dysphoric disorder; PTSS = post-traumatic stress disorder; OCD = obsessive compulsive disorder; GAD = generalized anxiety disorder; ADHD = attention deficit hyperactivity disorder.

[a] Measured with the ADHD list instead of the Mini International Neuropsychiatric Interview Plus. Please note that we used the presence of an AD(H)D diagnosis as an exclusion criterion in the COM group, based on which three individuals were excluded. Hence, this prevalence rate is likely an underestimation.

$^{+}p<.1$, $^{*}p\leq.05$, $^{**}p\leq.01$, $^{***}p\leq.001$

Table 3.5 Frequencies and percentages of the number of lifetime diagnoses in young, middle-aged, and older adults with and without ASD.

	ASD								COM							
	All ages		Young		Middle		Older		All ages		Young		Middle		Older	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
No DSM-IV diagnoses	29	21.0	8	17.4	6	12.8	15	33.3	87	51.2	30	50.0	27	58.7	30	46.9
1 DSM-IV diagnosis	28	20.3	6	13.0	13	27.7	9	20.0	56	32.9	16	26.7	13	28.3	27	42.2
2 DSM-IV diagnoses	19	13.8	8	17.4	7	14.9	4	8.9	16	9.4	8	13.3	3	6.5	5	7.8
3 DSM-IV diagnoses	24	17.4	8	17.4	6	12.8	10	22.2	4	2.4	2	3.3	1	2.2	1	1.6
4 DSM-IV diagnoses	17	12.3	9	19.6	3	6.4	5	11.1	2	1.2	2	3.3	0	-	0	-
>4 DSM-IV diagnoses	21	15.2	7	15.2	12	25.5	2	4.4	5	2.9	2	3.3	2	4.3	1	1.6

Note. ASD = autism spectrum disorder; COM = comparison group

Psychiatric co-occurring disorders

The frequencies of the investigated lifetime DSM-IV diagnoses are presented in Table 3.4. In the ASD group, 79.0% met one or more lifetime diagnosis for a psychiatric disorder against 48.8% of the COM group. Overall, older adults with ASD less often met diagnostic criteria compared to the younger age groups, whereas there were no differences between age groups among adults without ASD. In the ASD group, while 21% did not meet criteria for any psychiatric diagnoses and 20.3% met criteria for one psychopathology, over 57% had more than one co-occurring lifetime disorder. In the COM group, the large majority did meet criteria for one or none lifetime DSM-IV diagnosis. Nevertheless, a small percentage (15.9%) of the individuals without ASD had more than one co-occurring psychopathology (Table 3.5).

As expected, in adults with ASD, mood disorders were the most common group of psychiatric disorders (57.2%) and included major depression (53.6%) and dysthymia (18.1%). Mood disorders were most prevalent in middle-aged adults and least prevalent in the oldest age-group with ASD. All mood disorders were more frequent in adults with ASD than in adults without ASD. There were no differences between age-groups in the COM group.

The second most common group of disorders in the ASD group were the anxiety disorders (53.6%) of which obsessive-compulsive disorder (OCD; 21.7%) and agoraphobia (21.0%) most often occurred. The prevalence of any anxiety disorder appeared slightly lower in older adults, but it was not statistically significant. Whereas social phobia was common in young and middle-aged adults, it was not in older adults with ASD. All anxiety disorders were more frequent in adults with ASD than in adults without ASD. In the COM group, there were no differences between age-groups.

As mood and anxiety disorders often co-occur (Beekman et al., 2000; Sartorius, Üstün, Lecrubier, & Wittchen, 1996), we explored the overlap between these two lifetime diagnoses (Figure 3.1). Over 65% of the adults with ASD meeting criteria for any lifetime mood or anxiety disorder, also met criteria for the other co-occurring disorder.

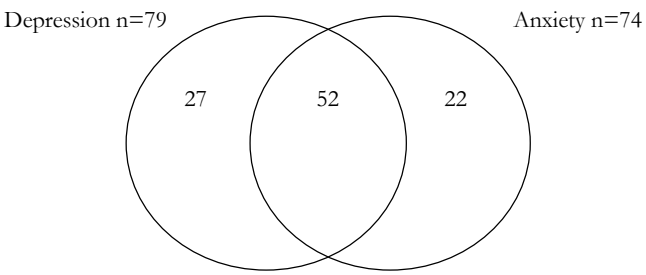

Figure 3.1 Number of ASD participants showing overlap between mood and anxiety disorders.

Associations between risk factors and mood and anxiety symptoms

ASD severity by both self-report and ADOS was predictive of the amount of depression and anxiety symptoms as measured with the SCL-90-R. None of the other risk factors was significantly associated with these symptoms (Table 3.6).

Table 3.6. Risk factors associated with depression and anxiety symptoms (SCL-90-R) in adults with ASD.

	Depression				Anxiety			
	B	SE	t	95% CI	B	SE	t	95% CI
Age	-0.05	0.07	-0.75	-0.18-0.08	-0.10	0.06	-1.62	-0.23-0.02
Gender	4.24	2.33	1.82	-0.37-8.84	3.85	2.25	1.71	-0.61-8.31
Education	-1.98	2.23	-0.89	-6.40-2.44	-3.04	2.16	-1.41	-7.31-1.24
Living situation	-0.53	1.06	-0.50	-2.63-1.58	-0.93	1.03	-0.91	-2.97-1.10
ISCO	0.05	0.73	0.07	-1.38-1.49	0.43	0.70	0.62	-0.96-1.83
IQ	-0.06	0.07	-0.93	-0.19-0.07	0.01	0.06	0.18	-0.11-0.14
MMSE	-0.57	1.04	-0.55	-2.63-1.49	-1.39	1.01	-1.38	-3.39-0.60
AQ	0.45	0.12	3.62***	0.20-0.69	0.40	0.12	3.33***	0.16-0.63
ADOS	0.89	0.34	2.66**	0.23-1.56	0.77	0.33	2.38*	0.13-1.42
Constant	36.94	28.45	1.30	-19.37-93.26	57.94	27.54	2.10*	3.44-112.45
R^2	20.5%				20.9%			
N	134				134			

Note. SCL-90-R = Symptom Checklist 90 revised; ISCO = International Standard Classification of Occupations; IQ = estimated intelligence quotient; MMSE = Mini Mental State Examination; AQ = Autism-spectrum Quotient; ADOS = Autism Diagnostic Observation Schedule.

*$p \leq .05$, **$p \leq .01$, ***$p \leq .001$

Associations between risk factors and any mood and anxiety disorder

Female gender was a significant predictor of any mood disorder. Lower age and more severe ASD as indicated by self-report were associated with the presence of any anxiety disorder. None of the other risk factors was associated with any mood or anxiety disorder (Table 3.7).

Table 3.7 Risk factors associated with any mood and anxiety disorder (MINI-Plus) in adults with ASD.

	Any mood disorder				Any anxiety disorder			
	B	SE	Odds Ratio	95% CI	B	SE	Odds Ratio	95% CI
Age	-0.00	.01	1.00	0.97-1.02	-0.04	.02	0.97*	0.94-1.00
Gender	1.46	.49	4.29**	1.65-11.18	0.85	0.52	2.33	0.85-6.42
Education	-0.14	.44	0.87	0.37-2.04	-0.67	.50	0.51	0.19-1.37
Living situation	0.18	.21	1.20	0.80-1.80	0.04	0.23	1.05	0.67-1.64
ISCO	-0.14	.14	0.87	0.66-1.15	0.09	.16	1.09	0.80-1.48
IQ	-0.00	.01	1.00	0.97-1.02	-0.01	.01	0.99	0.96-1.02
MMSE	-0.03	.20	0.97	0.66-1.43	0.00	.23	1.00	0.65-1.56
AQ	0.01	.02	1.01	0.97-1.06	0.15	0.03	1.16***	1.09-1.24
ADOS	0.02	0.07	1.02	0.90-1.16	0.04	0.07	1.04	0.90-1.20
Constant	-0.56	5.42	0.57		-2.18	6.07	0.11	
N	134				134			

Note. MINI-Plus= Mini International Neuropsychiatric Interview; ISCO = International Standard Classification of Occupations; IQ = estimated intelligence quotient; MMSE = Mini Mental State Examination; AQ = Autism-spectrum Quotient; ADOS = Autism Diagnostic Observation Schedule.
*$p \leq .05$, **$p \leq .01$, ***$p \leq .001$

DISCUSSION

In the current study, we examined psychiatric symptoms and disorders in young, middle-aged, and older adults with ASD and focused on the two most frequently occurring diagnoses (i.e., mood and anxiety) by testing several potential risk factors covering different domains. As expected, adults with ASD experienced more psychological symptoms and distress compared to a typically developing comparison group. These elevated levels were not only reported by older adults (for similar findings see van Heijst & Geurts, 2014), but were consistently high also in young and middle-aged adults and, thus, across the adult lifespan. Whereas at least a quarter of the adults with ASD reported symptoms within the clinical range compared to a population-based sample, only a few participants scored within the clinical range when compared to a psychiatric patient group (see also Joshi et al., 2013). These findings indicate that, as expected, adults with ASD experience many feelings of depression, anxiety, and psychological distress, but comparable to other psychiatric patients.

Consistent with the experience of many psychological symptoms, is the high proportion of individuals meeting criteria for a psychiatric diagnosis. Seventy-nine percent of the adults with ASD have experienced any psychiatric disorder once in their lives. As predicted,

most common disorders were mood (57%) and anxiety disorders (54%), which often co-occur. ADHD frequently occurred as well (30%) and notable is the high percentage of females meeting criteria for a premenstrual dysphoric disorder (21%). The estimated occurrences of psychiatric disorders in a large group of adults with ASD is comparable to those previously reported in other studies of adults without IDs using the Structured Clinical Interview for DSM-IV axis I Disorders (SCID-I) or a structured DSM-IV based clinical interview (Hofvander et al., 2009; Lugnegård et al., 2011; Roy et al., 2015). The MINI is based on both the DSM-IV and ICD-10 (Lecrubier et al., 1997) and the MINI and SCID-I are well concordant with each other (Sheehan et al., 1997). Given the consistency with previous studies involving a similar population, the current findings seem to reflect the true lifetime psychiatric problems of adults with ASD.

However, while others focused on young and middle-aged adults, we also examined older adults and we found that, also in late adulthood, psychiatric disorders were still common. Nevertheless, lifetime diagnoses for any psychiatric disorder were less often present in older than in younger adults with ASD, suggesting reduced psychopathology in late adulthood, a pattern that has been commonly observed in large typical aging studies (Bijl et al., 1998; Kessler et al., 2005). Although a recent study found the opposite (i.e., psychopathology was more common in older than in younger adults) in older adults with ASD and without ID (Roy et al., 2015), this seems mainly due to the inclusion of middle-aged adults in the "older" adult group (age range 40-62 years) in the study of Roy and colleagues. Especially in mid adulthood, psychiatric disorders such as depression seem more common than in older or younger individuals (Bijl et al., 1998; Kessler et al., 2005). While our older adult group consisted of participants until 79 years of age, participants in the Roy study were rather middle-aged, which would explain why high rates were found and why our findings were apparently discordant. We also observed that only one (2%) older adult met criteria for social phobia (i.e., social anxiety disorder) against 21% of young and middle-aged adults. There are several potential explanations for this latter finding. First, social phobia and social skills may reciprocally influence each other: individuals with poor social skills may be more likely to experience anxiety related to social interactions, but, inversely, individuals with social anxiety may less likely develop and practice their social skills (Bellini, 2004). In fact, adults with social anxiety disorder report difficulties in social skills, similarly to ASD individuals (Cath, Ran, Smit, van Balkom, & Comijs, 2008). Although social symptoms tend to remain stable over time in ASD (Magiati et al., 2014), social functioning seems to improve (Bastiaansen et al., 2011). Older adults would be more able to adjust their behavior to social situations and cope with their social difficulties, which could have a positive effect on feeling more comfortable in social situations and a negative effect on feelings of anxiety. Second, reduced social anxiety can be associated with a decrement in awareness or concern about social

situations, for example due to lower empathic skills (Bellini, 2004). However, neither empathic concern (Lever & Geurts, 2016) nor theory of mind (Lever & Geurts, 2015) declined in older adults with ASD, suggesting that this explanation does not hold. Third, older adults may have accepted their difficulties in social situations and, therefore, show less preoccupation and anxiety. Finally, it could be that older adults experience feelings of anxiety in social situations that are qualitatively different than aspects captured by this type of assessment, for example due to differential social settings and type of interactions (Ciliberti, Gould, Smith, Chorney, & Edelstein, 2011). Future research is needed to test which of these potential explanations will hold.

In line with previous studies in adults with ASD (García-Villamisar & Rojahn, 2015; Sterling et al., 2008), individuals with more depression and anxiety symptoms also demonstrated more severe self-reported and observed ASD symptoms. When focusing on psychiatric disorders rather than symptoms, higher self-reported ASD symptomatology and lower age were associated with the presence of any lifetime anxiety disorder. This latest result confirmed the already observed trend in the age-group comparisons. Furthermore, female gender was associated with any lifetime mood disorder, indicating that females are more likely to receive a diagnosis of depression or dysthymia than males. Although in line with observations in the general population (Kessler et al., 2005), no such gender differences have been detected in previous adult ASD studies (Lai et al., 2011; Lugnegård et al., 2011). The use of self-report information (Lai et al., 2011) or the inclusion of young adults (Lugnegård et al., 2011) may account for this discrepancy. As aforementioned we did not find a relation between depressive symptoms and gender by means of self-report either and when we (post-hoc) selected only young adults within our sample we also did not observe a gender difference on mood disorder. Hence, our findings do suggest that after young adulthood females with ASD are more vulnerable for mood disorder than males with ASD, just as reported in the general population. The other risk factors (i.e., intellectual and general cognitive functioning, social economic status [education and work], and living situation), selected for their consistent relationship with psychopathology in the general population, were notably not associated with depression and anxiety symptoms and disorders in the ASD group.

Our study suffers from a few limitations that are of importance to keep in mind when interpreting the findings. First, we did neither include an epidemiological sample nor did we adopt a longitudinal design. Therefore, our results can be an overestimation of prevalence rates (Howlin & Moss, 2012) and cohort effects can bias our results. Within the current design the directionality of effect cannot be determined: For example, does more severe ASD symptoms cause more psychiatric problems, or is more severe ASD inherently related to psychopathology?

Longitudinal research may shed light on this issue. Second, the structured nature of the MINI interview did not allow to disentangle whether specific symptoms were characteristic of the investigated disorder or part of the ASD phenotype (e.g., OCD or social anxiety) (see Kerns & Kendall, 2012; Wood & Gadow, 2010). Third, although prevalence rates of psychiatric disorders in adults without ASD are largely comparable to those obtained in epidemiological studies including a general population sample (Bijl et al., 1998; Kessler et al., 2005), the frequency of substance-related disorders was high. This is mainly due to the prevalence of alcohol abuse (see Table S.3.1, Supplementary material Chapter 3). Fourth, we solely focused on psychiatric comorbidities and not on medical comorbidities, although we did collect information regarding the use of non-psychotropic medication. While the percentages of prescribed psychotropic drugs are in line with the high number of observed psychiatric diagnoses, the percentages of non-psychotropic medication use in the ASD and COM group were similar. This might suggest that there are no differences between groups with regard to medical conditions, but this would be a premature conclusion. Those with ASD might report less somatic complaints to their general practitioner due to reduced sensitivity to bodily signals or they might be more reluctant to access the healthcare system due to, for example, communication and social difficulties or anxiety for medical examination as a result of sensory sensitivities. Earlier studies focusing on medical conditions in ASD, reported elevated rates compared to controls on many disorders, including gastrointestinal and sleep disorders, diabetes, and dyslipidemia (Croen et al., 2015; Kohane et al., 2012; Tyler, Schramm, Karafa, Tang, & Jain, 2011). Hence, in future research it would be worthwhile not to merely focus on psychiatric comorbidities but also on somatic comorbidities.

To conclude, in this large ASD adult cohort study including older adults, we showed that psychopathology, and specifically social phobia, less frequently occurred in late adulthood. As these findings represent just an initial step into the understanding of psychopathology across the entire adult lifespan, further research into the nature of psychiatric co-occurring symptoms and disorders and intricate risk factors in old age is needed. Given that psychiatric problems are, however, still common and psychological distress is substantial, we need adequate interventions and support to reduce the personal burden of adults with ASD.

SUPPLEMENTARY MATERIAL CHAPTER 3

Table S.3.1 Lifetime rates of substance-related, eating, and somatoform DSM-IV disorders in young, middle-aged, and older adults with and without ASD.

	ASD									COM								
	All ages		Young		Middle		Older			All ages		Young		Middle		Older		ASD vs COM
	N	%	N	%	N	%	N	%	Fisher's χ^2	N	%	N	%	N	%	N	%	Fisher's χ^2	χ^2
Substance-related disorders	22	15.9	9	19.6	5	10.6	8	17.8	1.60	43	25.3	20	33.3	9	19.6	14	21.9	3.10	4.00*
Alcohol abuse	19	13.8	7	15.2	5	10.6	7	15.6	4.66	41	24.1	19	31.7	9	19.6	13	20.3	4.28	8.31*
Alcohol dependence	7	5.1	1	2.2	4	8.5	2	4.4	1.82	7	4.1	4	6.7	0	-	3	4.7	2.97	0.16
Drugs abuse	6	4.3	4	8.7	1	2.1	1	2.2	5.07	11	6.5	10	16.7	0	-	1	1.6	18.13***	4.07
Drugs dependence	4	2.9	3	6.5	1	2.1	0	-	2.93	7	4.1	7	11.7	0	-	0	-	12.81***	1.16
Eating disorders	8	5.8	4	8.7	3	6.4	1	2.2	1.79	1	0.6	1	1.7	0	-	0	-	1.74	7.29*
Anorexia nervosa	5	3.6	3	6.5	2	4.3	0	-	4.69	0	-	0	-	0	-	0	-	-	6.29*
Bulimia nervosa	3	2.2	1	2.2	1	2.1	1	2.2	2.27	1	0.6	1	1.7	0	-	0	-	1.74	2.75
Somatoform disorders	8	5.8	6	13.0	2	4.3	0	-	6.72*	3	1.8	0	-	1	2.2	2	3.1	1.81	3.60+
Somatization	4	2.9	4	8.7	0	-	0	-	7.83**	0	-	0	-	0	-	0	-	-	6.26*
Pain disorder	3	2.2	1	2.2	2	4.3	0	-	3.61	3	1.8	0	-	1	2.2	2	3.1	1.81	1.31
Hypochondriasis	1	0.7	1	2.2	0	-	0	-	3.55	0	-	0	-	0	-	0	-	-	2.48
BDD	1	0.7	1	0.9	0	-	0	-	3.69	0	-	0	-	0	-	0	-	-	2.48

Note. ASD = autism spectrum disorder; COM = comparison group; BDD = body dysmorphic disorder.

$^{+}p<.1$, $^{*}p\leq.05$, $^{**}p\leq.01$, $^{***}p\leq.001$

Chapter 4

Age-related differences in cognition across the adult lifespan in autism spectrum disorder

Based on: Lever, A. G. & Geurts, H. M. (2015). Age-related differences in cognition across the adult lifespan in autism spectrum disorder. *Autism Research*. Advanced online publication, doi: 10.1002/aur.1545.

ABSTRACT

It is largely unknown how age impacts cognition in autism spectrum disorder (ASD). We investigated whether age-related cognitive differences are similar, reduced or increased across the adult lifespan, examined cognitive strengths and weaknesses, and explored whether objective test performance is related to subjective cognitive challenges. Neuropsychological tests assessing visual and verbal memory, generativity, and theory of mind (ToM), and a self-report measure assessing cognitive failures were administered to 236 matched participants with and without ASD, aged 20-79 years (IQ>80). Group comparisons revealed that individuals with ASD had higher scores on visual memory, lower scores on generativity and ToM, and similar performance on verbal memory. However, ToM impairments were no longer present in older (50+ years) adults with ASD. Across adulthood, individuals with ASD demonstrated similar age-related effects on verbal memory, generativity, and ToM, while age-related differences were reduced on visual memory. Although adults with ASD reported many cognitive failures, those were not associated with neuropsychological test performance. Hence, while some cognitive abilities (visual and verbal memory) and difficulties (generativity and semantic memory) persist across adulthood in ASD, others become less apparent in old age (ToM). Age-related differences characteristic of typical aging are reduced or parallel, but not increased in individuals with ASD, suggesting that ASD may partially protect against an age-related decrease in cognitive functioning. Despite these findings, adults with ASD experience many cognitive daily challenges, which highlights the need for adequate social support and the importance of further research into this topic, including longitudinal studies.

Keywords: autism spectrum disorder, aging, older adults, cognition, neuropsychology, memory, theory of mind, generativity

INTRODUCTION

Typical aging is associated with age-related decline in various cognitive domains, such as episodic memory (e.g., Goh et al., 2012; Nyberg et al., 2012), executive functions (EF) (e.g., Hasher & Zacks, 1988; Verhaeghen & Cerella, 2002), and advanced theory of mind (ToM) (e.g., Charlton et al., 2009; Maylor et al., 2002). Cognitive challenges encountered by typically aging individuals show large overlap with those faced by individuals with autism spectrum disorder (ASD) at younger ages. For example, children and adolescents with ASD, a neurodevelopmental disorder characterized by qualitative impairments in social communication and interaction and restricted, repetitive behavior (American Psychiatric Association, 2013), display difficulties in aspects of episodic memory (Boucher et al., 2012), EF (Brunsdon & Happé, 2014; Hill, 2004), and ToM (Yirmiya et al., 1998). While ASD is a lifelong condition, it is unknown (Happé & Charlton, 2012; Mukaetova-Ladinska et al., 2012) what happens to individuals with ASD when aging processes start to kick in.

Even though some are arguing that having ASD might protect against developing dementia (Oberman & Pascual-Leone, 2014), to our knowledge only two studies actually focused on cognition in older adults. A series of case-studies (67-84 years, N = 5) indicated that older adults with ASD still encounter cognitive deficits, although only three were assessed with actual memory and EF tests (James et al., 2006). In the first ASD group study on age-related cognitive differences among older adults (51-83 years, N = 46), the effect of age was not homogenous across domains (Geurts & Vissers, 2012; Goh et al., 2012). The authors postulated three hypotheses regarding age-related patterns. First, age may have a similar effect in individuals with and without ASD (parallel development hypothesis), which was observed for verbal memory. Second, ASD may have a detrimental effect (double jeopardy hypothesis), resulting in a steeper age-related decrease in cognitive functioning, as was observed for visual memory. Third, ASD may 'protect' against age-related differences (safeguard hypothesis), as a reduced pattern was observed for generativity. The relatively small sample size of the study, and lack of using a standardized diagnostic instrument to verify already existing ASD diagnoses, warrants replication (Geurts & Vissers, 2012).

The current study was designed to test the three hypotheses by determining whether these earlier findings for episodic memory (visual and verbal) and generativity (fluency) can be replicated, but also by focusing on ToM. ToM is a highly relevant cognitive domain for ASD, which was ignored in the previous study. Besides using standardized assessment and including a much larger, independent, age-comparable group (50-79 years, n = 113), we extended the age range (20-79 years, N = 236) to study cognition not only in old age, but also across the adult

lifespan. Please note that recently, in another ASD group study exploring age-related differences over the adult lifespan (20-61 years) in relational memory, a safeguard pattern on a specific aspect of relational memory was found (Ring, Gaigg, & Bowler, 2015). Finally, as elderly with ASD experienced more cognitive challenges in everyday life than typical older individuals (van Heijst & Geurts, 2014), we explored whether subjective cognitive failures are related to objective test performance.

We expected decreased performance in the ASD group compared to age-, gender-, and IQ-matched controls on phonemic (e.g., Bramham et al., 2009; Geurts & Vissers, 2012; Rumsey & Hamburger, 1988) and semantic (Spek, Schatorjé, Scholte, & van Berckelaer-Onnes, 2009) fluency, and advanced ToM (Chung et al., 2014), but not on visual and verbal memory (Boucher et al., 2012; Geurts & Vissers, 2012). We hypothesized age-related effects in ASD to be (a) increased on visual memory, (b) parallel on verbal memory, (c) reduced on phonemic and semantic fluency, and (d) reduced on ToM, given that ToM abilities decline in typical aging (e.g., Duval et al., 2011) and social abilities seem to improve with age in adults with ASD (Bastiaansen et al., 2011).

METHODS

Participants

Individuals with ASD between 20 and 79 years were recruited through several mental health institutions across the Netherlands, and by means of advertisements on client organization websites. We applied the following exclusion criteria: (a) no prior clinical ASD diagnosis according to DSM-IV (American Psychiatric Association, 2000) criteria; (b) history of neurological disorders (e.g., epilepsy, stroke, cerebral contusion) or schizophrenia, or having experienced more than one psychosis; (c) Autism Diagnostic Observation Schedule < 7 (ADOS) (Lord et al., 2000) and Autism-spectrum Quotient < 26 (AQ) (Baron-Cohen et al., 2001); (d) IQ < 80 or Mini Mental State Examination < 26 (MMSE) (Folstein et al., 1975); (e) current alcohol or drugs dependency. Based on these criteria, we excluded 50 of the initial 168 individuals with ASD (see Figure 4.1) and included the remaining 118 participants.

Individuals without ASD (i.e., comparison group [COM]) were recruited by means of advertisements on the university website and on social media, and within the researchers' social environment. The following exclusion criteria were applied: (a) clinical diagnosis of ASD or Attention Deficit Hyperactivity disorder (ADHD); (b) history of neurological disorders or schizophrenia, or having ever experienced a psychosis; (c) ASD or schizophrenia in close family members (i.e., parents, children, brothers, and sisters); (d) AQ > 32; (e) IQ < 80 or MMSE <

26; (f) current alcohol or drugs dependency. We excluded 26 of the initial 193 individuals without ASD. Of the remaining 167 participants, 118 were selected based on gender, age (within seven years, mean difference = 0.05, SD = 2.2), and IQ (within 22 points, mean difference = -0.5, SD = 10.0) to match the 118 ASD participants on these variables (Table 4.1).

Individuals were approximately evenly distributed across the age range per 10-year-bin (i.e., n ranges from 38 [19-29 years] to 51 [50-59 years]), even though there were fewer participants in the oldest bin (i.e., 70-79 years, n = 16). Information about clinical diagnoses, medical conditions, and family members were obtained by means of self-report.

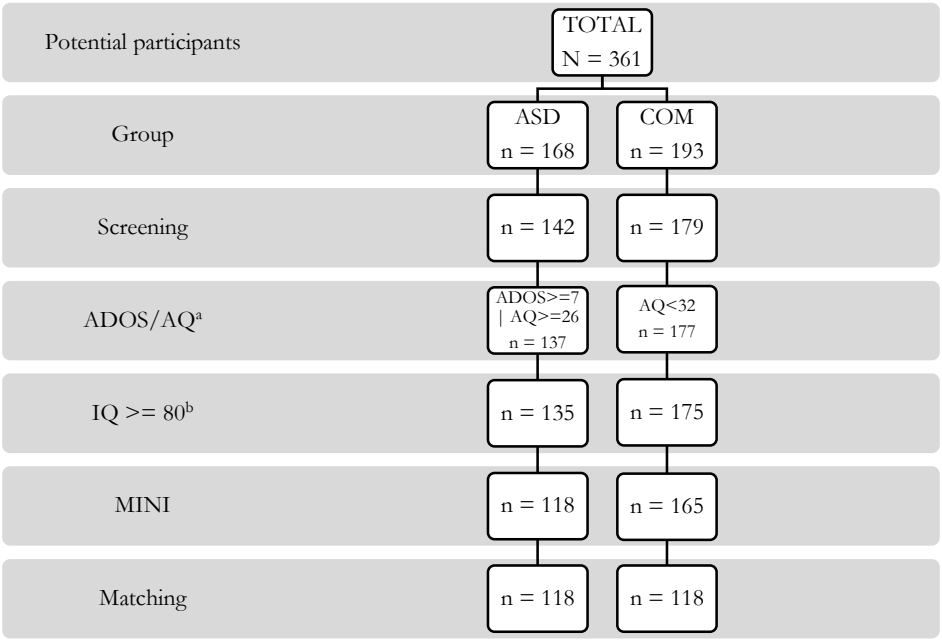

Figure 4.1 Diagram of the inclusion process.

Note. ASD = autism spectrum disorder; COM = comparison group; ADOS = Autism Diagnostic Observation Schedule; AQ = Autism-spectrum Quotient; IQ = estimated intelligence quotient; MINI = Mini International Neuropsychiatric Interview. Neuropsychological and questionnaire data was obtained from all participants except for Faux Pas (ASD: n = 117; COM: n = 116) and CFQ (ASD: n = 116).

[a] Due to low sensitivity of the ADOS when administered to intellectually able adults (Bastiaansen et al., 2011), we required ASD participants to exceed the threshold on either the ADOS or AQ. Only five participants of those scoring below the ADOS cut-off (<7; n = 35) did not exceed the AQ cut-off (<26). The majority met the ADOS threshold (n = 88).

[b] None of the participants was excluded based on the Mini Mental State Examination (i.e., no scores <26 were observed).

Materials

ASD assessment

The ADOS module 4 (de Bildt & de Jonge, 2008; Lord et al., 2000) is the most commonly used, instrument to assess the current presence of ASD symptoms within the domains of communication, reciprocal social interaction, imagination, and restricted and repetitive behavior, during a standardized, semi-structured observation. Exceeding a specific cut-off (i.e., 7) on the combined communication/social interaction domain, is indicative of an ASD (Bastiaansen et al., 2011). The AQ (Baron-Cohen et al., 2001; Hoekstra et al., 2008) is a valid and reliable self-reported questionnaire for the assessment of autistic traits consisting of 50 items. We employed a threshold of 26 for the ASD group and a threshold of 32 for the COM group, as suggested for, respectively a referred clinical sample and the general population (Baron-Cohen et al., 2001; Woodbury-Smith et al., 2005). Due to low sensitivity of the ADOS when administered to intellectually able adults (Bastiaansen et al., 2011), we required ASD participants to exceed the threshold on either the ADOS or AQ, but the majority did meet the ADOS criterion (n = 88; 74.6%).

Screening instruments

We administered the Vocabulary and Matrix Reasoning subtests of the Wechsler Adult Intelligence Scale third edition (WAIS-III) (Uterwijk, 2000; Wechsler, 1997a) to estimate IQ; the MMSE (Folstein et al., 1975; Kok & Verhey, 2002; Molloy, Alemayehu, & Roberts, 1991) to screen individuals for pathological cognitive impairment; the Mini International Neuropsychiatric Interview Plus (MINI-Plus) (Sheehan et al., 1998; van Vliet et al., 2000) to assess the presence or absence of alcohol dependence, substance dependence, and psychoses.

Neuropsychological tests

Visual memory. Visual Reproduction is a valid and reliable subtest of the Wechsler Memory Scale third edition (WMS-III) (Wechsler, 1997b), used to assess visual memory. In five consecutive trials, participants had 10 seconds to memorize a geometrical figure and reproduce it immediately thereafter and after a 30-minute delay period. Moreover, participants had to recognize the originally learned figures among 48 geometrical figures. Dependent variables are the sum of correctly recalled elements during immediate and delayed recall, and the sum of correctly recognized learned and rejected new figures (i.e., recognition).

Verbal memory. The Rey Auditory Verbal Learning Task (RAVLT) (Rey, 1964; van den Burg, Saan, & Deelman, 1985) is a commonly used, valid, and reliable instrument (Saan & Deelman, 1986) to assess verbal memory. Participants learned and recalled a list of 15 unrelated words in five consecutive trials and, after a 20-minute interval, recalled the list again and recognized the words among a list of 15 old and 15 new words. Dependent variables are the sum of correctly

Table 4.1 Means (standard deviations) of the demographic and clinical scores of the ASD and COM group for both the whole sample and a subset of participants over 50 years.

	All			50+		
	ASD (n = 118)	COM (n = 118)	Statistics	ASD (n = 57)	COM (n = 56)	Statistics
Gender	83 M/35 F	83 M/35 F		44 M/13 F	43 M/13 F	
Education[a]	0/1/0/3/35/53/26	0/0/1/3/19/59/36	Fisher's test, $p = .08$	0/0/0/1/18/22/16	0/0/1/3/9/29/14	Fisher's test, $p = .17$
Diagnosis[b]	18/60/35/5			12/30/15/0		
Age	47.6 (14.9)	47.7 (15.4)	$F(1, 235) = 0.00$, $p = .98$, $\eta_p^2 = .00$	60.8 (6.9)	61.5 (7.2)	$F(1, 112) = 0.28$, $p = .60$, $\eta_p^2 = .00$
	range 20-79	range 20-77		range 50-79	range 50-77	
IQ	114.8 (16.9)	114.3 (15.3)	$F(1, 235) = 0.06$, $p = .81$, $\eta_p^2 = .00$	116.8 (16.4)	116.1 (15.3)	$F(1, 112) = 0.05$, $p = .83$, $\eta_p^2 = .00$
	range 84-155	range 80-149		range 84-153	range 80-149	
MMSE	29.1 (1.0)	29.1 (1.0)	$F(1, 235) = 0.07$, $p = .79$, $\eta_p^2 = .00$	29.1 (0.8)	29.0 (1.1)	$F(1, 112) = 0.34$, $p = .56$, $\eta_p^2 = .00$
	range 26-30	range 26-30		range 27-30	range 26-30	
AQ	33.7 (8.3)	12.4 (5.5)	$F(1, 234)^c = 542.40$, $p < .001$, $\eta_p^2 = .70$	34.9 (8.0)	13.4 (5.0)	$F(1, 111)^c = 290.85$, $p < .001$, $\eta_p^2 = .73$
	range 8-49	range 2-26		range 8-48	range 4-25	
ADOS[d]	8.6 (3.1)			8.3 (3.0)		
	range 1-19			range 3-18		

Note. ASD = autism spectrum disorder; COM = comparison group; M = male; F = female; IQ = estimated intelligence quotient; MMSE = Mini Mental State Examination; AQ = Autism-spectrum Quotient; ADOS = Autism Diagnostic Observation Schedule.

[a] The numbers between brackets indicate the educational level based on the Verhage coding system (1964), ranging from 1 (primary education not finished) to 7 (university degree).

[b] The numbers between brackets indicate a diagnosis of Autism/Asperger/Pervasive Developmental Disorder Not Otherwise Specified/ASD.

[c] One ASD participant did not complete the AQ (but met the ADOS criterion and, hence, was included).

[d] Of the final sample, 30 participants scored below the ADOS cut-off (<7). Excluding these participants from the analyses did not alter the pattern of results (see Table S.4.2 and S.4.3, Supplementary material Chapter 4).

recalled words during the five learning trials (i.e., immediate recall) and after 20 minutes (i.e., delayed recall), and sum of correctly recognized old and rejected new words (i.e., recognition).

Generativity and semantic memory. In verbal fluency measures phonological and/or semantic cues are given to recall information from semantic memory (Goh et al., 2012). Therefore, fluency measures are often used to assess both generativity (as EF measure) and semantic memory (Schmand, Groenink, & Van den Dungen, 2008). Phonemic fluency was evaluated with the Controlled Oral Word Association Test (COWAT) (Benton & Hamsher, 1989; Schmand et al., 2008), which has good internal consistency (Schmand et al., 2008). Participants named as many words as possible starting with a provided letter in three trials of one minute each (D,A,T), but were not allowed to name proper nouns, numbers, and serial words starting with the same prefix. Semantic fluency was assessed with the Word Naming subtest of the Groninger Intelligence Test (GIT) (Luteijn & Barelds, 2004), which has good reliability and sufficient internal consistency (Mulder, Dekker, & Dekker, 2006). Participants named as many words as possible belonging to a specific category in two trials of one minute each (animals, professions). Dependent variables are the total number of correctly named words.

ToM. An abbreviated version of the Faux Pas test (Spek, Scholte, & Van Berckelaer-Onnes, 2010; Stone, Baron-Cohen, & Knight, 1998) was used to assess advanced ToM. Five stories containing a faux pas, which is a socially unintended inappropriate response (Baron-Cohen, O'Riordan, Stone, Jones, & Plaisted, 1999), and four stories without faux pas were read with the participants and questions about the faux pas were asked, together with two control questions to assure the stories were properly understood. Dependent variable is the sum of correctly answered questions on all stories minus the control questions.

Data collected through WMS-III and Faux Pas were coded by two raters (see Supplementary material Chapter 4).

Self-report cognitive failures

The Cognitive Failures Questionnaire (CFQ) (D. E. Broadbent, Cooper, FitzGerald, & Parkes, 1982; Merckelbach, Muris, Nijman, & de Jong, 1996) is a valid and reliable (Vom Hofe, Mainemarre, & Vannier, 1998) 25-item self-report questionnaire used to assess the experience of memory errors, committing blunders, and distractibility in everyday situations. CFQ total score is the dependent variable.

Procedure

Participants were informed about the study purposes and procedure and written informed consent was obtained. They filled out the AQ and CFQ and were tested in two sessions, in which (a) ASD assessment and screening took place; (b) neuropsychological tests were administered in

counterbalanced order (additional experimental tests and questionnaires were administered, but will be discussed elsewhere). Participants received compensation for their travel expenses; most COM participants also received additional compensation (max. €20). Data was collected between March 2012 and July 2014. The study was approved by the institutional review board of the University of Amsterdam (2011-PN-1952).

Statistical analyses

First, to compare the two groups on several cognitive domains, we ran three MANOVAs for visual memory, verbal memory, and generativity and semantic memory, and two ANOVAs for ToM and CFQ, each with Group (ASD, COM) as between-subject factor. Second, to investigate the effect of age, we ran linear multiple regression analyses for each domain with (centered) Age, Group, and Age×Group as predictors. If there was an Age×Group interaction, we ran follow-up regression analyses for each group separately. Third, to determine whether our results are comparable to Geurts and Vissers (2012), we reran the above mentioned analyses on a subgroup of participants, including individuals of 50 years or older. Fourth, to explore whether cognitive performance was associated with self-reported cognitive failures, we ran, per group, Spearman correlations between CFQ and each dependent measure.

As normality assumptions were violated for almost all dependent variables and transformation did not normalize the data, data were analyzed with both parametric and nonparametric tests. As both analyses yielded analogous results, we only report parametric tests. Unless removing outliers (i.e., data points more than three SD from each group mean) changed the pattern of results, analyses are reported including outliers. To reduce the probability of Type I errors, alpha was set at 0.01 for the group comparisons and regression analyses. An alpha level of 0.05 was employed for the exploratory analyses.

RESULTS

Group comparisons

The ASD group reported many more cognitive failures on the CFQ than the COM group, but group differences were absent on most neuropsychological tests (Table 4.2). However, groups differed significantly on ToM, and, after removing outliers[iv], on visual memory immediate recall, and generativity. These findings are discussed below.

[iv] There were 5 outliers on the visual memory test (3 ASD, 2 COM), 5 on verbal memory (3 ASD, 2 COM), 2 on phonemic and semantic fluency (ASD), 2 on ToM (COM).

Visual memory

ASD participants yielded higher scores on immediate recall of the WMS-III Visual Reproduction subtest than COM participants, suggesting that visual memory is a cognitive strength of adults with ASD.

Generativity and semantic memory

COM participants named more correct words starting with a given letter (phonemic fluency) and words belonging to a given category (semantic fluency) than ASD participants, indicating difficulties for adults with ASD in this domain.

ToM

COM participants had better Faux Pas performance than ASD participants. Hence, adults with ASD showed ToM problems.

Age-related differences

Age had a significant effect on all domains, except generativity. As most regression analyses did not reveal any Age×Group interaction (Table 4.3), age seemed to have a similar effect in the ASD and COM group. Yet, we observed an interaction for visual memory recognition and a borderline significant interaction for visual memory immediate recall. These findings are discussed below.

Visual memory

While age did not explain a relevant proportion of variance in the ASD group, $F(1, 116) = 2.58$, $p = .11$, $R^2 = .02$, it did in the COM group, $F(1, 116) = 39.76$, $p < .001$, $R^2 = .26$. Inspection of the beta coefficients revealed a steeper decrease in performance in the COM group ($\beta = -.51$) compared to the ASD group ($\beta = -.15$). These results indicate that recognition in adults with ASD did not significantly differ over age, whereas performance of adults without ASD deteriorated with increasing age. Similar results were found for immediate recall. Age explained a small amount of variance in the ASD group, $F(1, 116) = 3.90$, $p = .05$, $R^2 = .03$, but a considerable amount in the COM group, $F(1, 116) = 36.19$, $p < .001$, $R^2 = .24$. Again, inspection of the beta coefficients revealed a steeper decrease in performance in the COM group ($\beta = -.49$) compared to the ASD group ($\beta = -.18$).

Older adults

Selection of 50+ participants yielded a subset of 57 ASD and 56 COM participants between 50 and 79 years. The two groups did not differ on gender, age, IQ, MMSE score, or educational level (Table 4.1). Group comparisons revealed that, similarly to the whole group analyses, elderly with ASD reported more cognitive failures, had higher scores on visual memory immediate recall, and had lower scores on phonemic fluency, compared to COM participants. In contrast, older individuals with ASD had no longer reduced ToM scores compared to the COM group (Table 4.2). The impact of age was similar among groups on all investigated domains (Table 4.4), including visual memory, which is in contrast to the overall analyses.

Exploratory analyses

Subjective experience of cognitive failures was not associated with actual test performance in either the ASD or the COM group (all *p*s > .1, Spearman's rho ranged from -.11 to .16).

DISCUSSION

In the current study we investigated age-related differences in cognition across a large sample of individuals with ASD. While changes with age have largely been examined within the general population, alterations faced by adults with ASD when growing old have hardly received any attention. Albeit cross-sectional age-related cognitive decline might be similar or reduced in older adults with ASD, an earlier study indicated it might also be increased, suggesting that ASD and aging can be two factors that jeopardize each other (Geurts & Vissers, 2012). However, in the present study, we did not find any evidence for this alarming hypothesis, as we observed similar or reduced age-related differences across the adult lifespan in ASD. Hence, for some cognitive domains having an ASD diagnosis might be a protective factor to typically observed age-related decrease in functioning.

Young individuals with ASD demonstrate relatively intact abilities in visual and verbal memory and difficulties in generativity (Boucher et al., 2012; Hill, 2004). As expected, similar strengths and weaknesses were observed from young to late adulthood (Boucher et al., 2012; Bowler, Limoges, & Mottron, 2009; Bramham et al., 2009; Geurts & Vissers, 2012; Rumsey & Hamburger, 1988), with adults with ASD even outperforming their non-ASD counterparts on visual memory. This latest finding would fit with the idea of individuals with ASD having enhanced visual functioning (Samson, Mottron, Soulieres, & Zeffiro, 2012). Also ToM, a major difficulty in childhood and adolescence, was impaired when considering the whole age range (Chung et al., 2014). ToM deficits were, however, no longer observed in older adults with ASD

Table 4.2 Group means, standard deviations, and statistics of the CFQ and of each neuropsychological test for both the whole group and a subset of participants over 50 years.

			All				50+			
Domain	Measure	Dependent variable	ASD	COM	*F*	η_p^2	ASD	COM	*F*	η_p^2
General cognition	CFQ	CFQ total score	46.0 (15.3)	29.1 (10.6)	96.47**	.29	47.2 (13.1)	30.3 (11.1)	54.30**	.33
Visual memory[a]	WMS-III	Immediate recall score	90.6 (11.4)	87.5 (11.7)	4.17*/**	.02	88.53(10.4)	82.0 (12.3)	9.30**	.08
		Delayed recall score	77.1 (20.0)	79.8 (21.8)	0.01	.00	71.7 (20.3)	66.8 (24.6)	1.35	.01
		Recognition score	45.0 (2.6)	45.3 (2.5)	0.56	.00	44.8 (2.4)	44.2 (2.4)	1.88	.02
Verbal memory[b]	RAVLT	Immediate recall score	47.9 (11.1)	49.2 (10.3)	0.94	.00	45.5 (9.9)	44.3 (10.3)	0.54	.00
		Delayed recall score	10.4 (3.4)	10.4 (3.1)	0.00	.00	9.9 (3.0)	8.9 (3.1)	3.41	.03
		Recognition score	29.2 (1.3)	29.1 (1.4)	0.17	.00	29.1 (1.2)	28.5 (1.9)	3.17	.03
Generativity and semantic memory[c]	DAT	Nr of correct words	39.9 (11.2)	43.4 (10.9)	5.82*/**	.02	38.3 (10.7)	43.0 (11.3)	5.12*/**	.04
	GIT	Nr of correct words	44.3 (11.2)	47.7 (10.2)	6.12*/**	.03	42.2 (10.6)	46.8 (11.4)	4.48*	.04
Theory of mind	Faux Pas	Faux pas score	27.1 (4.9)	29.4 (6.2)	10.27**	.04	26.7 (4.9)	27.8 (6.0)	1.02	.01

Note. ASD = autism spectrum disorder; COM = comparison group; CFQ = Cognitive Failure Questionnaire; WMS-III = Wechsler Memory Scale 3rd edition; RAVLT = Rey Auditory Verbal Learning Task; DAT = Dutch version of the Controlled Word Association Task; GIT = Groninger Intelligentie Test.

[a] MANOVA overall test for all participants: $F(3, 232) = 4.41$, $p = .005$, $\eta_p^2 = .05$. While removing the outliers did not change the results of WMS delayed recall and recognition, it altered the results of immediate recall, $F(1, 231) = 7.32$, $p = .007$, $\eta_p^2 = .03$. The scores of the ASD and COM group were now significantly different. Removing the outliers on the other variables did not change the pattern of findings. MANOVA overall test for subset 50+: $F(3, 109) = 3.76$, $p = .01$, $\eta_p^2 = .09$.

[b] MANOVA overall test for all participants: $F(3, 232) = 1.43$, $p = .24$, $\eta_p^2 = .02$. MANOVA overall test for subset 50+: $F(3, 111) = 2.47$, $p = .07$, $\eta_p^2 = .06$.

[c] MANOVA overall test for all participants: $F(2, 233) = 3.98$, $p = .02$, $\eta_p^2 = .03$. Removing outliers strengthened the effects, $F(2, 231) = 5.54$, $p = .004$, $\eta_p^2 = .05$. MANOVA overall test for subset 50+: $F(2, 110) = 3.22$, $p = .04$, $\eta_p^2 = .06$. Removing outliers strengthened the effect of phonemic fluency, $F(1, 109) = 4.18$, $p = .02$, $\eta_p^2 = .07$. The scores of the ASD and COM group were now significantly different.

*$p < .05$. **$p < .01$

Table 4.3 Standardized beta coefficients and p values of the regression models with Age, Group, and Age×Group as factors for all 236 participants.

	WMS-III						RAVLT											
	IR[a]		DR[b]		REC[c]		IR[d]		DR[e]		REC[f]		DAT[g]		GIT[h]		FP[i]	
	β	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*
Age	-.48	<.001***	-.47	<.001***	-.49	<.001***	-.46	<.001***	-.42	<.001***	-.37	<.001***	-.05	.58	-.06	.47	-.26	.003**
Group	.13	.03*	.01	.92	-.05	.42	-.06	.29	.00	.99	.03	.68	-.16	.02*	-.16	.01*	-.21	.001**
Age×Group	.21	.01*	.09	.30	.23	.007**	.14	.09	.16	.07	.18	.04*	-.03	.74	-.13	.15	.13	.15

Note. WMS-III = Wechsler Memory Scale 3rd edition; RAVLT = Rey Auditory Verbal Learning Task; IR = immediate recall; DR = delayed recall; REC = recognition; DAT = Dutch version of the Controlled Word Association Task; GIT = Groninger Intelligentie Test; FP = Faux Pas. Removing the outliers strengthened the already found effects, but did not change the pattern of findings.

[a] R^2 = .15, $F(3, 232)$ = 13.88, p < .001. [b] R^2 = .17, $F(3, 232)$ = 15.56, p < .001. [c] R^2 = .14, $F(3, 232)$ = 12.18, p < .001. [d] R^2 = .15, $F(3, 232)$ = 13.14, p < .001. [e] R^2 = .11, $F(3, 232)$ = 9.73, p < .001. [f] R^2 = .08, $F(3, 232)$ = 6.58, p < .001. [g] R^2 = .03, $F(3, 232)$ = 2.36, p = .07. [h] R^2 = .06, $F(3, 232)$ = 4.73, p = .003. [i] R^2 = .08, $F(3, 229)$ = 6.69, p < .001.

*p < .05. **p < .01. ***p < .001

Table 4.4 Standardized beta coefficients and p values of the regression models with Age, Group, and Age×Group as factors for the subset of 50+ participants (n = 113).

	WMS-III						RAVLT											
	IR[a]		DR[b]		REC[c]		IR[d]		DR[e]		REC[f]		DAT[g]		GIT[h]		FP[i]	
	β	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*
Age	-.34	.007**	-.26	.04*	-.38	.003**	-.41	.002**	-.34	.009**	-.20	.129	-.20	.12	-.22	.08	-.22	.10
Group	.27	.003**	.09	.30	.11	.21	.04	.63	.16	.08	.16	.09	-.24	.009**	-.245	.007**	-.10	.28
Age×Group	.13	.28	-.07	.58	.08	.54	.16	.21	.12	.35	.10	.45	-.07	.59	-.11	.40	.05	.69

Note. WMS-III = Wechsler Memory Scale 3rd edition; RAVLT = Rey Auditory Verbal Learning Task; IR = immediate recall; DR = delayed recall; REC = recognition; DAT = Dutch version of the Controlled Word Association Task; GIT = Groninger Intelligentie Test; FP = Faux Pas. Removing the outliers did not change the pattern of findings.

[a] R^2 = .15, $F(3, 109)$ = 6.27, p < .001. [b] R^2 = .11, $F(3, 109)$ = 4.47, p = .005. [c] R^2 = .13, $F(3, 109)$ = 5.20, p = .002. [d] R^2 = .11, $F(3, 109)$ = 4.30, p = .007. [e] R^2 = .10, $F(3, 109)$ = 4.09, p = .009. [f] R^2 = .05, $F(3, 109)$ = 1.90, p = .134. [g] R^2 = .09, $F(3, 109)$ = 3.60, p = .016. [h] R^2 = .10, $F(3, 109)$ = 4.16, p = .008. [i] R^2 = .08, $F(3, 108)$ = 1.65, p = .182.

*p < .05. **p < .01

(50+) compared to the older adults without ASD. This result was neither explained by ToM enhancement nor by reduced age-related deterioration in ASD, as predicted. Although age seemed to have a smaller impact in ASD, the difference with non-ASD was too small to detect a differential age-related pattern. Nevertheless, we hypothesize that individuals with ASD continue to be actively involved in trying to understand social situations and other people's thoughts as they know it is difficult for them, leading to similar performance in old age compared to typically aging adults.

While performance declined with increasing age on verbal memory, generativity was not negatively affected by age. This pattern was similar in the two groups (i.e., parallel pattern). Large studies among typically developing adults generally report age-related deterioration on phonemic and semantic fluency (Tombaugh, Kozak, & Rees, 1999), but age effects might be masked in individuals with high verbal intelligence or high educational level (Bolla, Lindgren, Bonaccorsy, & Bleecker, 1990; Tombaugh et al., 1999). Finally, we found a differential pattern for visual memory: Adults without ASD showed an age-related decrease in performance, whereas adults with ASD did not. Hence, the impact of age was reduced in ASD. A similar effect was reported in a recent study on relational memory processes, in which the role of age seemed to be less pronounced in adults with ASD (age range 20-61 years) on object order recognition (Ring et al., 2015). Furthermore, another recent study suggested that individuals with ASD, in contrast to for example individuals developing dementia, have hyperplastic brains that protect them against cognitive decline (Oberman & Pascual-Leone, 2014). Indeed, based on a database analysis of Harvard Clinical and Translational Science Center records, individuals with ASD seem to suffer less frequently from Alzheimer's dementia than a general or schizophrenia population (Oberman & Pascual-Leone, 2014). Although an intriguing finding, it can result from a report bias. Moreover, having a hyperplastic brain may explain general reduced age-related deterioration in ASD, but does not clarify why this advantage would only be restricted to visual memory.

Alongside observed difficulties in some domains, adults with ASD subjectively experienced many cognitive daily challenges, with a large amount of individuals reporting clinically significant failures (<2SD below normative mean), as revealed by additional exploratory analyses (see Supplementary material Chapter 4, Table S.4.1). Despite these findings, only a few participants performed within the clinical range during testing. Moreover, there is no concordance between subjective cognitive complaints and objective test performance. Hence, even though cognitive performance difficulties in ASD may be clinically insignificant, this discordance warrants further research.

Some may argue that our study suffers from some limitations affecting the interpretation of our findings. First, as the current study was cross-sectional in nature, rather than longitudinal, we cannot yet draw conclusions on how changes in cognition actually develop over time among individuals with ASD. Therefore, conclusions about cross-sectional age-related decline should be interpreted with caution. Second, it can be argued that our sample was intellectually high-functioning with relatively mild ASD characteristics. Most participants were diagnosed in adulthood, which has been associated with relatively mild symptomatology and sufficient cognitive abilities to compensate for ASD-related difficulties (Heijnen-Kohl & van Alphen, 2009). Nevertheless, all ASD participants already had a formal, clinical diagnosis and before an ASD diagnosis is given, individuals go through thorough assessment by a multidisciplinary team during which developmental history is commonly assessed. Moreover, the majority of participants met ADOS criteria for ASD. Exploratory analyses on only those individuals who exceeded the ADOS threshold, yielded similar results and did not alter the interpretation of our major findings (see Table S.4.2 and S.4.3, Supplementary material Chapter 4). The inclusion of intellectually normal-to-high-functioning individuals was of importance to test whether age-related patterns were comparable to typical developing adults. However, many individuals with ASD have an intellectual disability (Matson & Shoemaker, 2009) and our results may not apply to them. Third, the majority of our ASD participants suffered from a comorbid psychiatric condition, such as depression or anxiety. Although inclusion of those individuals increases the representativeness of the sample, it also may have influenced our findings. Yet, recently, it was shown that comorbidity was not correlated with neuropsychological performance in ASD males (Wilson et al., 2014). Fourth, although we included a large age range, some age-related differences or changes become apparent only in very old age. As a result, further research including even older individuals may provide more knowledge on the effect of age in ASD. Fifth, we did not replicate some findings of our earlier study (Geurts & Vissers, 2012). Nevertheless, post-hoc correction for multiple comparisons of the results previously obtained with exploratory regression analyses did reveal similar age-related patterns as found in the current 50+ group. This discrepancy underlines the importance of confirmatory replication studies.

Conclusions

Age-related deterioration in cognitive functioning is characteristic of typical aging. In the current cross-sectional study, we demonstrated that this pattern is parallel or less pronounced in individuals with ASD. We did not find evidence for the hypothesis that age-related differences in cognition are increased in ASD. Cognitive strengths and weaknesses occurring in adulthood are still present in old age, although ToM impairments seem to be less apparent in late adulthood.

Taken together, the findings of this cross-sectional study suggest that ASD may indeed be a safeguard for age-related cognitive decline, but also reveal the crucial role of replication studies. Moreover, the subjectively experienced daily challenges and poor quality of life of older adults with ASD (van Heijst & Geurts, 2014) highlight the importance of research into older adulthood in ASD and the need for more knowledge in order to provide better social and environmental support to improve the life of individuals with ASD across the lifespan. The investigation of cognitive aging in ASD is a completely new and exciting area of research and our study represents a logical initial step providing unique insights into this direction. However, as longitudinal and cross-sectional studies do not always reveal the same age-related patterns (Nyberg et al., 2012), follow-up studies are needed to determine the applicability of these findings on the long term.

SUPPLEMENTARY MATERIAL CHAPTER 4

Inter-rater concordance

Figures reproduced by 62 participants (26.3%; 31 ASD, 31 COM) during the Visual Reproduction subtest of the WMS-III (Wechsler, 1997b) were scored by a second rater. Discrepancies were resolved through discussion between raters. Mean concordance rates were 93.2% and 92.3% for immediate and delayed recall respectively.

Responses of all 236 participants (118 ASD, 118 COM) given on the Faux Pas test (Stone et al., 1998) were coded by two raters. Discrepancies were again resolved through discussion. Overall concordance rate was 97.5%.

Inter-individual differences

As large inter-individual differences in cognitive challenges among individuals with ASD are observed (Gonzalez-Gadea et al., 2013; Towgood et al., 2009), we not only compared groups, but also evaluated the performance of each participant against a normative sample to determine the clinical relevance of potential problems.

For this purpose, raw scores of the dependent variables of visual memory, verbal memory, generativity and semantic memory, theory of mind, and Cognitive Failures Questionnaire (CFQ) (D. E. Broadbent et al., 1982), were converted to z-scores (ie, mean of 0 and standard deviation of 1) based on performance of the COM group. The performance of each participant was compared with this normative sample (Table C.1). A standard deviation of 2 was used to determine whether individuals performed at a sub-normal (<2SD) or supra-normal level (>2SD).

The groups did not differ in the amount of participants scoring below or above 2SD from the mean in none of the comparisons (all *p*s>.06, Fisher's Exact Test, two-tailed), except for CFQ ($p<.001$), with 40.7% of the ASD group scoring above the 98th percentile. In the ASD group, 12 participants were impaired (<2SD) on one domain, six on two domains, two on three domains, and three on four domains. In the COM group, 13 participants were impaired (<2SD) on one domain, four on two domains, two on three domains, and one on four domains. In the ASD group, three participants supra-normally performed (>2SD) on one domain, and one participant on two domains. In the COM group, seven participants supra-normally performed (>2SD) on one domain. The number of participants showing sub-normal or supra-normal performance on one or more domains did not differ between groups (Fisher's Exact Test, two-tailed: $p=.94$ and $p=.36$, respectively).

Table S.4.1 Percentages of ASD and COM participants scoring 2SD below or above the normative mean.

Domain	Measure	Dependent variable	All				50+			
			ASD		COM		ASD		COM	
			% <2SD	% >2SD	% <2SD	% >2SD	% <2SD	% >2SD	% <2SD	% >2SD
Visual memory	WMS-III	Immediate recall score	2.5	0	4.2	0	1.8	0	3.6	0
		Delayed recall score	2.5	0	5.9	0	1.8	0	3.6	0
		Recognition score	6.8	0	5.1	0	3.5	0	7.1	0
Verbal memory	RAVLT	Immediate recall score	5.9	0.8	1.7	2.5	0	3.5	1.8	3.6
		Delayed recall score	6.8	0	2.5	0	1.8	7.0	1.8	3.6
		Recognition score	2.5	0	5.1	0	0	0	3.6	0
Generativity and semantic memory	DAT	Nr of correct words	3.4	1.7	2.5	1.7	5.3	1.8	3.6	0
	GIT	Nr of correct words	5.1	1.7	1.7	1.7	5.3	0	0	1.8
Theory of mind	Faux Pas	Faux pas score	2.5	0	2.5	0	3.5	0	1.8	0
General cognition	CFQ	CFQ total score	0	40.7	0.8	2.5	0	35.1	1.8	1.8

Note. ASD = autism spectrum disorder; COM = comparison group; WMS-III = Wechsler Memory Scale 3rd edition; RAVLT = Rey Auditory Verbal Learning Task; DAT = Dutch version of the Controlled Word Association Task; GIT = Groninger Intelligentie Test. Scores were converted to z-scores based on means and standard deviations of the COM group.

Table S.4.2 Group means, standard deviations, and statistics of the CFQ and of each neuropsychological test for the whole group with exclusion of ASD participants that did not meet ADOS criteria (n = 30).

			All (without ADOS)			
Domain	**Measure**	**Dependent variable**	**ASD**	**COM**	***F***	η_p^2
General cognition	CFQ	CFQ total score	45.4 (16.2)	29.1 (10.6)	76.0**	.27
Visual memory[a]	WMS-III	Immediate recall score	90.3 (11.7)	87.5 (11.7)	2.92	.01
		Delayed recall score	76.0 (20.0)	79.8 (21.8)	0.07	.00
		Recognition score	44.9 (2.6)	45.3 (2.5)	1.22	.01
Verbal memory[b]	RAVLT	Immediate recall score	48.0 (11.3)	49.2 (10.3)	0.70	.00
		Delayed recall score	10.5 (3.5)	10.4 (3.1)	0.01	.00
		Recognition score	29.1 (1.3)	29.1 (1.4)	0.08	.00
Generativity and semantic	DAT	Nr of correct words	39.4 (10.3)	43.4 (10.9)	6.80**	.03
memory[c]	GIT	Nr of correct words	44.2 (10.8)	47.7 (10.2)	5.54*	.03
Theory of mind	Faux Pas	Faux pas score	26.4 (4.9)	29.4 (6.2)	13.41**	.06

Note. ADOS = Autism Diagnostic Observation Schedule; ASD = autism spectrum disorder; COM = comparison group; CFQ = Cognitive Failure Questionnaire; WMS-III = Wechsler Memory Scale 3rd edition; RAVLT = Rey Auditory Verbal Learning Task; DAT = Dutch version of the Controlled Word Association Task; GIT = Groninger Intelligentie Test.

[a]MANOVA overall test for all participants: $F(3, 202) = 4.49$, $p = .004$, $\eta_p^2 = .06$.

[b]MANOVA overall test for all participants: $F(3, 202) = 1.19$, $p = .31$, $\eta_p^2 = .02$.

[c]MANOVA overall test for all participants: $F(2, 203) = 4.22$, $p = .02$, $\eta_p^2 = .04$.

*$p < .05$. **$p < .01$.

Table S.4.3 Standardized beta coefficients and *p* values of the regression models with Age, Group, and Age×Group as factors for all participants with exclusion of ASD participants that did not exceed the ADOS threshold (n = 30).

	WMS-III						**RAVLT**											
	IR[a]		**DR**[b]		**REC**[c]		**IR**[d]		**DR**[e]		**REC**[f]		**DAT**[g]		**GIT**[h]		**FP**[i]	
	β	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*	*β*	*p*
Age	-.48	<.001***	-.47	<.001***	-.49	<.001***	-.46	<.001***	-.42	<.001***	-.37	<.001***	-.05	.57	-.07	.46	-.26	.004**
Group	.11	.09	-.04	.57	-.08	.19	-.07	.29	.00	.99	.01	.85	-.18	.009**	-.18	.01*	-.25	<.001**
Age×Group	.20	.02*	.07	.42	.22	.009**	.16	.07	.19	.03*	.15	.10	.00	.96	-.14	.12	.13	.15

Note. ASD = autism spectrum disorder; ADOS = Autism Diagnostic Observation Schedule; WMS-III = Wechsler Memory Scale 3rd edition; RAVLT = Rey Auditory Verbal Learning Task; IR = immediate recall; DR = delayed recall; REC = recognition; DAT = Dutch version of the Controlled Word Association Task; GIT = Groninger Intelligentie Test; FP = Faux Pas. Removing the outliers strengthened the already found effects, but did not change the pattern of findings.

[a]R^2 = .16, $F(3, 202) = 12.89$, $p < .001$. [b]R^2 = .18, $F(3, 202) = 14.82$, $p < .001$. [c]R^2 = .16, $F(3, 202) = 12.31$, $p < .001$. [d]R^2 = .15, $F(3, 202) = 11.82$, $p < .001$. [e]R^2 = .11, $F(3, 202) = 8.47$, $p < .001$. [f]R^2 = .09, $F(3, 202) = 6.45$, $p < .001$. [g]R^2 = .04, $F(3, 202) = 2.42$, $p = .07$. [h]R^2 = .06, $F(3, 202) = 4.46$, $p = .005$. [i]R^2 = .10, $F(3, 199) = 7.57$, $p < .001$.

*$p < .05$. **$p < .01$. ***$p < .001$.

Chapter 5

Atypical working memory decline across the adult lifespan in autism spectrum disorder?

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ABSTRACT

Whereas working memory (WM) performance in typical development increases across childhood and adolescence, and decreases during adulthood, WM development seems to be delayed in young individuals with autism spectrum disorder (ASD). How WM changes when individuals with ASD grow old is largely unknown. We bridge this gap with a cross-sectional study comparing age-related patterns in WM performance (*n*-back task: three load levels) among a large sample of individuals with and without ASD (N = 275) over the entire adult lifespan (19–79 years) as well as inter-individual differences therein. Results demonstrated that, despite longer RTs, adults with ASD showed similar WM performance to adults without ASD. Age-related differences appeared to be different among adults with and without ASD as adults without ASD showed an age-related decline in WM performance, which was not so evident in adults with ASD. Moreover, only IQ scores reliably dissociated inter-individual differences in age-gradients, but no evidence was found for a role of basic demographics, comorbidities, and executive functions. These findings provide initial insights into how ASD modulates cognitive aging, but also underline the need for further WM research into late adulthood in ASD and for analyzing individual change trajectories in longitudinal studies.

Keywords: autism spectrum disorder (ASD), working memory, aging, regression trees, executive functions

INTRODUCTION

Autism Spectrum Disorder (ASD) is a heterogeneous neurodevelopmental disorder characterized by qualitative impairments in social interaction and communication, and restricted, repetitive behavior (American Psychiatric Association, 2013), and is associated with impairments in executive functions (EF) (Hill, 2004; Pennington & Ozonoff, 1996). EF is an umbrella term referring to various cognitive functions involved in control and coordination that are necessary for complex, goal-directed behavior. At the same time, EF deficits are observed during typical aging (e.g., Friedman et al., 2009; Salthouse & Miles, 2002; Verhaeghen & Cerella, 2002). While ASD is a lifelong condition, surprisingly little is known about alterations in cognitive functioning in individuals with ASD when they grow old. Hence, the current study addresses the question whether cross-sectional age-gradients in a core EF function, namely working memory (WM), deviate in ASD clients in comparison to a typically developing control sample.

WM is the ability to maintain and manipulate information online in the absence of actual sensory information in order to guide goal-directed behavior (e.g., Baddeley, 2003; Cowan, 2014). As such, it is important for daily life functioning. In typical development, WM performance increases throughout childhood into adolescence (Conklin, Luciana, Hooper, & Yarger, 2007; Gathercole, Pickering, Ambridge, & Wearing, 2004; Tamnes et al., 2013) and decreases during adulthood (Borella et al., 2008; Hasher & Zacks, 1988; Park et al., 2002; see Sander, Lindenberger, & Werkle-Bergner, 2012 for an overview). While those observations derive mainly from cross-sectional studies, longitudinal evidence suggests non-linear change-patterns with accelerated decline in older adulthood (Nyberg et al., 2012; for further elaborations, see Lindenberger, Von Oertzen, Ghisletta, & Hertzog, 2011; Raz & Lindenberger, 2011).

Although the developmental trajectory of WM in ASD is not well charted, there is preliminary evidence for it being deviant from typical development (see O'Hearn et al., 2008). Cross-sectional studies demonstrated that WM improved from childhood to adolescence in both ASD and typically developing individuals (Happé et al., 2006; Luna et al., 2007; but see Rosenthal et al., 2013), but that WM development from adolescence to young adulthood was delayed in ASD (i.e., maturity was reached at a later age) (Luna et al., 2007). A recent longitudinal study over a two-year period pointed out that WM development among children and adolescents might be arrested (Andersen et al., 2014). These findings suggest a delayed development of WM in individuals with ASD that protracts into young adulthood (O'Hearn et al., 2008). So far, the trajectory of WM development in middle adulthood is unknown. In late adulthood, an initial small cross-sectional study suggests comparable age-related decline in older individuals with

ASD compared to typically developing elderly, but WM abilities in those with ASD still seem to be reduced in old age (Geurts & Vissers, 2012).

Whether WM is indeed impaired in individuals with ASD is, however, still a topic of debate: Studies comparing individuals with and without ASD of the same age on a group level show inconsistent results (e.g., Koshino et al., 2008; Ozonoff & Strayer, 2001; Williams et al., 2005; see Barendse et al., 2013 for a review). WM impairments are mainly found when individuals with ASD are compared to typically developing individuals rather than to other pathological groups (Russo et al., 2007); when spatial WM rather than verbal WM is examined (Steele et al., 2007; Williams et al., 2005; but see Ozonoff & Strayer, 2001); and when there are increased demands on WM, for example when the complexity of the task is high or when item manipulation is required instead of maintenance only (Koshino et al., 2008; Steele et al., 2007; Williams et al., 2005).

Whereas WM is sensitive to age-related decline, considerable inter-individual differences exist between individuals of the same age (Eenshuistra et al., 2004; Vogel & Awh, 2008) that tend to increase with advancing adulthood (e.g., Nagel et al., 2008; Werkle-Bergner et al., 2012). Similarly, among individuals with ASD, individual differences may partially explain the inconsistent WM findings. For example, de Vries and Geurts (2014) found that a relatively small subgroup of children with ASD that demonstrated WM deficits accounted for the WM impairment found on a group level when comparing children with and without ASD. These findings underscore that both ASD and aging are characterized by broad heterogeneity.

Several factors have been proposed to drive age-related cognitive decline and WM performance, such as slowing speed of processing (Salthouse, 1996), worsening suppression of irrelevant information (i.e., interference control) (Hasher & Zacks, 1988) degrading sensory functioning (Baltes & Lindenberger, 1997), changes in global intelligence (Hockey & Geffen, 2004), social participation status (Lövdén, Ghisletta, & Lindenberger, 2005), depressive symptoms (Paterniti, Verdier-Taillefer, Dufouil, & Alperovitch, 2002), and Attention Deficit Hyper Activity disorder (ADHD) (Engelhardt, Nigg, Carr, & Ferreira, 2008). Some of these factors are also known to be critical in ASD. For example, comorbid conditions are common in ASD (Hofvander et al., 2009), individuals with ASD show interference control difficulties (Geurts et al., 2014) and response slowing (Travers et al., 2014), and societal participation, such as having a job and being satisfied with received environmental support, is generally low (Howlin et al., 2013; Magiati et al., 2014; van Heijst & Geurts, 2014). Given the substantial inter-individual differences in typical aging as well as in ASD, and the overlap in factors contributing to both conditions, the present study addresses the additional question whether differential age-related

patterns in WM performance could be observed in specific subgroups among adults with and without ASD.

In summary, the current cross-sectional study investigates WM in ASD over the entire adult lifespan (i.e., including middle and late adulthood) by means of an *n*-back task. In an *n*-back task, a continuous stream of stimuli is presented and the objective is to indicate whether the current stimulus matches a stimulus shown *n* trials previously. Stimuli used in the current study consisted of simple pictures (Severens, Lommel, Ratinckx, & Hartsuiker, 2005). An *n*-back task taps into core WM-processes such as maintenance of items in memory, updating of task relevant information, binding of items into a serial order, and resolution of proactive interference (Chatham et al., 2011). Hence, it is often used in cognitive neuroscience research to investigate WM (Jarrold & Towse, 2006; Smith & Jonides, 1997) by experimentally manipulating load parametrically (Jaeggi, Buschkuehl, Perrig, & Meier, 2010). The aims of the current study are threefold. First, we investigate WM performance across different load levels comparing adults with and without ASD. We hypothesize that, if there is WM impairment in ASD, this should become apparent in the cognitively more demanding condition (i.e., 2-back condition). Second, we study the effect of age on WM performance over the adult lifespan in ASD and non-ASD to examine developmental patterns. In typical development, age-related changes in WM performance are independent of modality (verbal or visuospatial) or span/non-span (Conklin et al., 2007; Park et al., 2002). Therefore, given that age-related differences of spatial WM span were found to be similar among older adults with and without ASD (Geurts & Vissers, 2012) before, we hypothesize similar age-related differences in WM performance across groups in our study as well (that is, a parallel pattern of age-gradients across groups). Third, we explore whether we can find predictors of inter-individual differences in age-related patterns of WM performance using regression trees.

METHODS

Participants

ASD group. Our sample consisted of 168 individuals with an ASD who were recruited through different mental health institutions across the Netherlands, and by means of advertisement on client organization websites. They were screened, based on self-reported information, for the following exclusion criteria: (1) no clinical ASD diagnosis according to Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) (American Psychiatric Association, 2000) criteria; (2) history of neurological disorders (e.g. epilepsy, stroke, cerebral contusion); (3) diagnosed with schizophrenia, or having experienced more than one psychosis. Based on these

criteria, 26 individuals were excluded, and the ASD diagnoses of the remaining 142 participants were verified by administering the Autism Diagnostic Observation Schedule module 4 (ADOS) (Lord et al., 2000) and the Autism-spectrum Quotient (AQ) (Baron-Cohen et al., 2001). If participants did not score above the cut-off of 7 on the ADOS, a score above the AQ cut-off of 26 was required (Woodbury-Smith et al., 2005). Of the 39 participants who did not meet the ADOS criterion, only five did also not meet the AQ criterion and were excluded from further analysis. Of the remaining 138 participants, two were excluded as their IQ, estimated with two subtests of the Wechsler Adult Intelligence Scale third edition (WAIS-III) (Wechsler, 1997a) was below 80; none of the participants was excluded based on a Mini Mental State Exam score below 26 (MMSE) (Folstein et al., 1975). Moreover, we excluded two participants due to a current alcohol- or drugs dependency and 14 participants due to having experienced more than one psychosis or not remembering how many psychoses were experienced during lifetime, revealed by administration of the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998), which were previously not indicated by self-report. Finally, we excluded one individual who could not be evaluated for screening due to non-compliance to answering MINI questions. The eligible ASD group consisted of 118 participants.

Comparison group. The comparison group (COM) consisted of 193 individuals without ASD who were recruited by means of advertisements on the university website and on social media, and within the social environment of the researchers. They were screened, based on self-reported information, for the following exclusion criteria: (1) clinical diagnosis of ASD or ADHD; (2) a history of neurological disorders; (3) diagnosed with schizophrenia, or having ever experienced a psychotic episode; (4) ASD or schizophrenia in close family members (i.e. parents, children, brothers and sisters). Fourteen individuals were excluded and the remaining 179 participants filled out the AQ. If participants scored above the suggested AQ cut-off for the general population of 32 or higher (Baron-Cohen et al., 2001) they were excluded. One participant did exceed the AQ cut-off and one participant had too many missing AQ responses (10.0%). Of the remaining 177 participants, two were excluded as their estimated IQ was below 80; none of the participants was excluded based on a MMSE score below 26. Finally, after administering the MINI, we excluded: (1) six participants due to a current alcohol- or drugs dependency; (2) two participants who could not be evaluated for screening due to non-compliance to answering questions. The eligible COM group consisted of 167 participants.

N-back data of six ASD participants were lost due to technical problems, two COM participants withdrew after the first session, and two participants (one ASD, one COM) did not complete the *n*-back task. Hence, 111 participants with ASD and 164 participants without ASD were included (see Figure 5.1 for an illustration of the inclusion process). The groups were

matched on age and estimated IQ. However, the proportion of females was larger in the COM group than in the ASD group. As expected, the ASD group demonstrated higher levels of ASD traits than the COM group (Table 5.1).

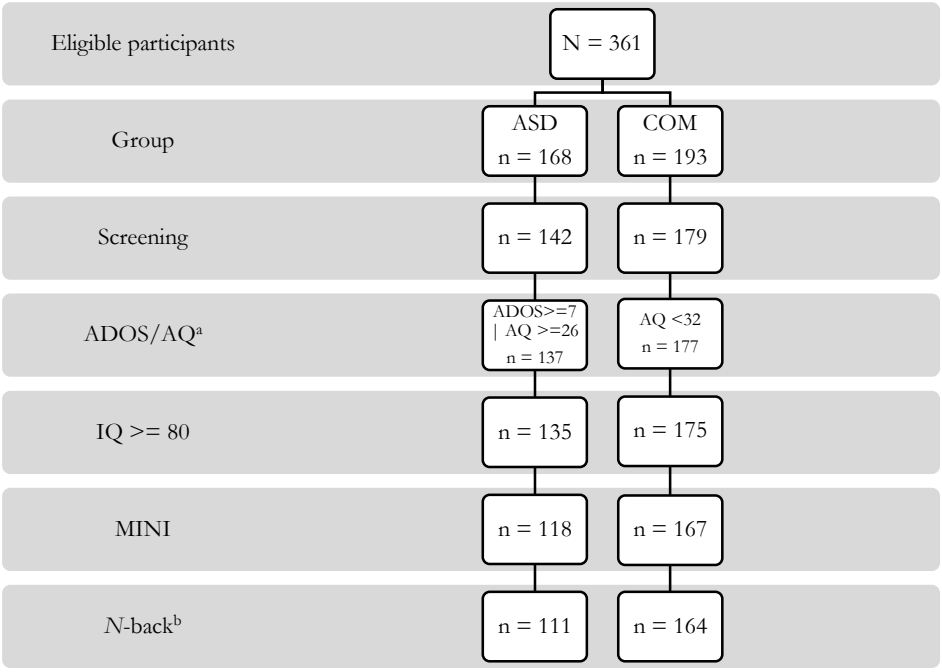

Figure 5.1 Diagram of the inclusion process.

Note. ASD=autism spectrum disorder, COM=comparison, ADOS=Autism Diagnostic Observation Schedule, AQ=Autism-spectrum Quotient, IQ=estimated intelligence quotient.

[a]Only five participants of those scoring below the ADOS cut-off (<7; n=35) did also score below the AQ cut-off (<26).

[b]*N*-back data of some participants could not be obtained. See methods section for details.

Materials

Instruments used for ASD assessment and screening are reported in the supplementary material of Chapter 5.

N-back. *N*-back stimuli were black and white drawings of simple objects (Severens et al., 2005). These stimuli were chosen to be comparable with a previous study of our research group among children with ASD (de Vries & Geurts, 2014). We employed an adapted version of their task. The task consisted of three different load levels representing increasing demand for WM: 0-back,

Table 5.1 Means (standard deviations), demographic and clinical scores of the ASD and COM group.

	Group		
	ASD (n=111)	COM (n=164)	Statistics
Gender	79 M/32 F	93 M/71 F	Fisher's test, p=.016, odds ratio=1.88
Education[a]	0/1/0/3/31/51/25	0/0/1/5/28/80/50	Fisher's test, p=.144
Diagnosis[b]	16/57/33/5	-	-
Age	47.5 (15.0)	46.0 (16.5)	F(1,273)=0.58, p=.448, η_p^2=.00
	range 20-79	range 19-77	
IQ	115.2 (16.9)	113.3 (16.7)	F(1,273)=0.87, p=.352, η_p^2=.00
	range 84-155	range 80-155	
MMSE	29.1 (1.0)	29.1 (1.0)	F(1,273)=0.16, p=.687, η_p^2=.00
	range 26-30	range 26-30	
AQ	33.4 (8.1)	12.2 (5.1)	F(1,272)[b]=703.61, p<.001, η_p^2=.72
	range 8-49	range 2-26	
ADOS	8.59 (3.11)	-	
	range 1-19		

Note. ASD=autism spectrum disorder; COM=comparison group; M=male; F=female; IQ=estimated intelligence quotient; MMSE=Mini Mental State Examination; AQ=Autism-spectrum Quotient; ADOS=Autism Diagnostic Observation Schedule.

[a]The numbers between slashes indicate the educational level based on the Verhage coding system (1964), ranging from 1 (primary education not finished) to 7 (university degree).

[b]The numbers between slashes indicate a diagnosis of Autism/Asperger Syndrome/Pervasive Developmental Disorder Not Otherwise Specified/ASD.

[c]One ASD participant did not complete the AQ (but met the ADOS criterion and, hence, was included).

[d]Of the final sample, 27 participants scored below the ADOS cut-off (<7). Excluding these participants from the analyses did not alter the pattern of results.

1-back, and 2-back. In the 0-back condition, serving as a baseline, participants had to respond 'yes' when a car was depicted and 'no' for every other image. In the 1-back condition, participants had to respond 'yes' when the picture shown was identical to the previous picture and 'no' when it was not. In the 2-back condition, participants had to respond 'yes' when the picture shown matched the picture two trials before and 'no' when it did not match.

Stimuli were presented on a computer screen each for 1000 ms and were afterwards replaced by a black mask for 750 ms or until response was given. During this time window, participants were instructed to respond by giving either a 'yes' or a 'no' response by pressing the corresponding button. The next stimulus was presented after a fixed 250 ms intertrial interval. To ensure the task was properly understood, we gave extensive task instructions for each load

level. First, the task was orally explained and instructions were displayed on screen. Second, a paper-version practice block (15 trials) was administered in order to give participants time to familiarize themselves with the task and allow the experimenter to give additional instructions as needed. Third, participants performed a computerized practice block (24 trials). Moreover, task instructions were repeated before each experimental block. The task consisted of four experimental blocks per load level (24 trials each). Blocks consistently switched between load levels, i.e. 0-back was followed by 1-back, which was followed by 2-back, which was followed by 0-back, etcetera. Stimuli were presented in a pseudo-randomized order. To rule out the effect of interfering response mapping memory processes, two cues were provided: a 'yes' card was presented in accordance of the associated 'yes' key, and a 'no' card in accordance of the associated 'no' key. Participants were instructed to respond as fast and as accurately as possible. The task yielded two dependent variables: accuracy (proportion of correct responses), and mean reaction time (RT) on correct responses.

Predictor variables. To explore whether we could predict age-related differences in WM performance, we selected a series of potential predictor variables based on (1) a known relationship with WM decline in typical aging; and (2) being critical in individuals with ASD. Therefore, we included, in addition to demographic and clinical variables (estimated IQ, diagnosis [ASD, no ASD], gender, education, AQ traits) measures of (a) processing speed (measured as mean RT on correct trials during a choice response task (Donders, 1869); see Supplementary material Chapter 5); (b) interference control (measured as mean RT difference between compatible and incompatible trials during a Simon task [i.e. Simon effect; (Simon, 1969)]; see Supplementary material Chapter 5); (c) comorbidity, by choosing the three most common comorbid conditions in ASD (Hofvander et al., 2009), that is depression, anxiety (measured with depression and anxiety subscales of the Symptom Checklist-90 [(Arrindell & Ettema, 2005; Derogatis, 1977)]), and ADHD (using the attention and hyperactivity, and inattention subscales of the ADHD list [(Kooij et al., 2004)]); (d) participation status, operationalized as satisfaction with and need for environmental support and professional employment (measured with the environmental subscale of the abbreviated World Health Organization Quality of Life questionnaire [(Herrman et al., 1998; Trompenaars, Masthoff, Van Heck, Hodiamont, & De Vries, 2005)]; professional employment was encoded according to the International Standard Classification of Occupations-08).

Procedure

Participants were informed about the study purposes and its procedure and written informed consent was obtained. Thereafter, participants filled out a series of questionnaires and were

tested in two sessions. In the first session, the ADOS (only ASD group), two subtests of the WAIS, MMSE and MINI were administered. In the second session, the *n*-back, choice response task, and Simon task, among seven other tasks, were administered in counterbalanced order. Not all administered questionnaires and tests are of relevance for the current study, so these will be discussed elsewhere (e.g., Lever & Geurts, 2015). Participants received compensation for their travel expenses; most COM participants also received a small amount of additional compensation (max. €20). The study was approved by the ethical review board of the Department of Psychology at the University of Amsterdam (2011-PN-1952); all procedures complied to relevant laws and institutional guidelines.

Statistical analyses

Prior to *n*-back analyses, we removed RT outliers. At an individual level, trials with RTs deviating more than 3 standard deviations from the mean and RTs faster than 100 milliseconds were removed. This procedure resulted in the exclusion of less than 3.1% of all trials in each group (i.e., the maximum percentage of removed outliers was 3.1% for the ASD group [M = 1.6%, SD = 0.5%] and 3.1% for the COM group [M = 1.6%, SD = 0.5%] and did not differ between groups, $F(1,273)=0.52$, $p=.472$).

At a group level, mean RTs were calculated over the remaining responses on correct trials. RTs were normally distributed and, therefore, not transformed. Accuracy was calculated as the proportion of correct responses (correct number of trials per total number); Arcsine-square-root transformation was applied to increase normality, but, to ease interpretation, accuracy rates are reported in raw score units.

To test whether the groups differed in their WM performance across load levels, we performed two mixed-design Analyses of Variance (ANOVAs) with repeated measures of load (0-back, 1-back, 2-back) as within-subject factor and group (ASD, COM) as between-subject factor. As the ASD and COM group differed in their male to female ratio ($p=.016$ by Fisher's Exact Test), and gender may influence WM performance in either ASD or aging (e.g., Lejbak, Crossley, & Vrbancic, 2011), gender (male, female) was added as a between-subject factor in the overall group analyses. Accuracy and RTs on correct trials constituted the dependent variables.

To investigate whether age-related differences in WM performance varied across groups, we composed a difference score by subtracting untransformed accuracy on the 0-back condition from untransformed accuracy on the 2-back condition[v]. Arcsine-square-root transformation was applied to the difference score to increase normality. The resulting

[v] This procedure was chosen to account for unspecific variance and to obtain the largest possible contrast in WM ability.

transformed difference score constituted the dependent variable for our regression analysis with (centered) age, group, and age×group interaction as predictors. As age-related WM decline might accelerate with increasing age, we explored whether there were differential effects of a quadratic component of age on WM in the ASD and COM group. To this end, we tested an additional model including a quadratic age term as main effect (age^2) and its interaction with group (age^2×group).

All group-level analyses were run both with and without outlier correction (i.e., data points more than three times the interquartile range above or below the first quartile). We report results with outlier correction and state results without outlier correction only if the pattern of results changed. To reduce the probability of Type I errors, alpha level was set at .01 for the group comparisons and the age-related regression analyses. Whenever the assumption of sphericity was violated, we used the Greenhouse-Geisser correction (but we report uncorrected degrees of freedom).

With Bayesian statistics, we explored the robustness of the group comparisons and age-related differences. Bayesian hypothesis testing allows assessing the strength of evidence for a hypothesis H_a over an alternative hypothesis H_b based on the observed data (Rouder, Speckman, Sun, Morey, & Iverson, 2009). Typically, hypothesis H_a is the hypothesis of interest (i.e., H_1) and H_b is the null hypothesis stating that there is no effect (i.e., H_0). We can calculate a Bayes factor to quantify the evidence in favor of the data supporting H_1 rather than H_0, which is denoted as BF_{10}. We can also use the Bayes factor to express evidence in favor of H_0, by using the relation $BF_{01} = 1/ BF_{10}$. For example, $BF_{10} = 5$ indicates that it is 5 times more likely that the data derived from H_1 than from H_0, whereas $BF_{10} = 1/5$ indicates that it is 5 times more likely that the data derived from H_0 than from H_1. A BF_{10} between 1 and 3 indicates anecdotal evidence, between 3 and 10 substantial evidence, between 10 and 30 strong evidence, between 30 and 100 very strong evidence, and above 100 extreme evidence in favor of H_1 (Jeffreys, 1961; Wagenmakers, Wetzels, Borsboom, & van der Maas, 2011). When $BF_{10} = 1$, there is no evidence in the data for either H_1 or H_0 and when $BF_{10} < 1$ there is evidence in favor of H_0.

To explore whether we could predict inter-individual differences in age-related trends, we used regression trees (also see Brandmaier, von Oertzen, McArdle, & Lindenberger, 2013; see Strobl, Malley, & Tutz, 2009 for an overview). Regression trees are a nonparametric regression approach based on model-based recursive partitioning: in a hierarchical fashion, predictors are selected that partition the sample best into homogeneous subgroups with different parameter estimates of an initially specified regression model. Membership to the resulting subgroups is determined by predictors in the form of a hierarchy of decisions forming a tree: Inner nodes of the tree represent decision nodes, terminal nodes (or leaves) represent regression

models. A tree is created by recursively selecting the predictor that best explains heterogeneity in the sample. In other words, at each level of growing a tree, the predictor that predicts maximal differences in the regression model is selected as a splitting variable. The exact splitting point is selected by maximizing the difference of the fit between the current node (i.e., parent node) and its two daughter nodes. The parent node is split into two daughter nodes if they represent better fit of the model to the data than the parent node. This process is repeated until a stopping criterion (e.g., a specified minimal number of observations or a specified threshold for the minimum improvement of a split's model fit) is met. The result is a tree with a set of leaves, each containing a subset of observations associated with different parameters of the initially specified regression models.

To build our regression tree, we (1) set up the initial regression model regressing the accuracy difference score on age as baseline model, and (2) determined potential predictors as candidates for the decision nodes in a tree. These candidates included a set of demographic variables (group, gender, education, profession, IQ, environmental support), comorbidities (depression, ADHD, anxiety, ASD), and EFs (interference control, processing speed). The tree was grown using the 'party' package (Hothorn, Hornik, & Zeileis, 2006) in R. We set our stopping criterion to a minimum number of cases per terminal node of 20 and used Bonferroni correction for multiple comparisons at each node of the tree.

The baseline model was specified as a linear regression model with arcsine-square-root accuracy difference score regressed on age. Thus, the tree was geared up for exploring subgroups with differential age-gradients in WM performance. While the regression tree was run with R 3.0.2 (R Core Team, 2012), the Bayes factors were calculated with JASP 0.7.0, an open source statistical package (Love, Selker, Verhagen et al., 2015a). The other analyses were run with SPSS 22.0 (IBM Corp., 2013).

RESULTS

Group differences

As expected, there was a main effect of load level on the proportion of correct responses. Post-hoc tests using Bonferroni correction revealed that accuracy decreased with increasing WM load. Accuracy was higher on 0-back (97.3%) than on 1-back (95.4%; $p<.001$) condition and higher on 1-back than on 2-back (88.9%; $p<.001$) condition. The main effects of group and gender were not significant. Also, none of the interactions were significant (see Table 5.2). These results showed that decline in performance due to increasing WM load was similar for individuals with and without ASD.

Analyses on RTs revealed the expected significant main effect of load level, indicating that RTs increased with increasing WM load. Post-hoc pairwise comparisons using Bonferroni correction showed that RTs on the 0-back condition (513 ms) were faster than responses on the 1-back condition (607 ms; $p<.001$), and that RTs on the 1-back condition were faster than RTs on the 2-back condition (712 ms; $p<.001$). There was a significant main effect of group. The ASD group showed higher RTs (629 ms) than the COM group (596 ms; $p=.002$). None of the interactions reached significance (see Table 5.2).

To quantify evidence in favor of the data supporting the null findings on accuracy, we ran Bayesian exploratory ANOVAs with arcsine transformed accuracy as dependent variable and group and gender as independent variables: $BF_{10} = 1/7.2$ for the 0-back (please note that $BF_{10} < 1$ and, thus, there is evidence in favor of H_0, indicating that it is 7.2 times more likely that the data derived from H_0 than from H_1), $BF_{10} = 1/1.4$ for the 1-back, and $BF_{10} = 1/1.3$ for the 2-back. This indicates that the data provides substantial evidence for H_0 (i.e., group does not have an effect) on the baseline condition and only anecdotal evidence for H_0 on the 1-back and 2-back condition.

Table 5.2 Statistics of the repeated measures ANOVAs with load as within-subject factor, and group and gender as between-subject factors, assessing WM accuracy and RTs of the ASD and COM group.

		Statistics		
Dependent variable	Factors	*F*	*p*	η_p^2
Correct responses	load	**350.49**	**<.001**	**.56**
	group	1.30	.256	.01
	gender	1.26	.264	.01
	group×gender	0.90	.345	.00
	load×group	2.70	.070	.01
	load×gender	0.90	.406	.00
	load×group×gender	0.28	.749	.00
RTs	load	**1154.49**	**<.001**	**.81**
	group	**10.07**	**.002**	**.04**
	gender	0.43	.514	.00
	group×gender	0.41	.522	.00
	load×group	1.94	.149	.01
	load×gender	0.33	.699	.00
	load×group×gender	0.49	.594	.00

Note. RTs=Reaction Times. Degrees of freedom are (2,542) for all within-group analyses, and (1,271) for all between-group analyses. Significant values ($p<.01$) are indicated in bold script.

Age effects

As gender did not have any influence on the results shown above, we excluded gender as a predictor from further regression analyses.[vi] The regression model investigating differences in accuracy over age explained 9% of the observed variance. There was a main effect of age, demonstrating that increasing age was associated with larger difference scores (Table 5.3). The main effect of group and the age×group interaction were non-significant at the corrected alpha level, which indicated that the groups did not significantly differ in their difference scores and that age had a similar impact on WM decline in the ASD and COM group, when a linear pattern was considered. However, adding age^2 and age^2×group improved the model ($F_{change}(2,269)=4.19$, $p_{change}=.016$) and changed our findings. The model explained 12% variance and both interaction terms were significant, indicating differential age-related patterns, linear and quadratic, across the ASD and COM group. Post hoc regression analyses per group indicated a linear pattern in the COM group ($F(1,162)=19.79$, $p<.001$, $R^2=.11$, $F_{change}(1,161)=2.62$, $p_{change}=.108$, $R_{change}^2=.01$), and a combined linear and quadratic pattern in the ASD group ($F(1,109)=2.94$, $p=.089$, $R^2=.03$, $F_{change}(1,108)=5.46$, $p_{change}=.021$, $R_{change}^2=.05$; also see Figure 5.2).[vii]

Table 5.3 Beta's and *p*-values for the regression models assessing the difference scores between 2- and 0-back for correct responses.

		Accuracy difference score	
	predictor	*β*	*p*
Model 1[a]	age	-.311	.000***
	group	-.121	.038*
	age×group	.082	.261
Model 2[b]	age	0.400	.383
	group	-0.296	.001**
	age×group	-1.232	.008**
	age^2	-0.730	.117
	age^2×group	1.365	.004**

[a] $F(3,271)=8.95$, $p<.001$, $R^2=.09$. [b] $F(5,269)=7.17$, $p<.001$, $R^2=.12$.

*$p<.05$. **$p<.01$. ***$p<.001$

[vi] However, we cross-checked whether gender indeed did not influence the results by running all regression analyses with gender and gender×group as additional predictors. In none of the analyses, gender or gender×group were significant predictors; the pattern of findings did not change.

[vii] We explored whether the ASD and COM group differed in their errors patterns and the impact of age. Analyses of the proportion of commission errors (i.e., erroneous responses) yielded similar results to those obtained with accuracy. Analyses of the proportion of omission errors (i.e. missed responses) revealed no group differences and no different impact of age between groups. Hence, participants with and without ASD demonstrated similar (age-related) error patterns across *n*-back WM performance.

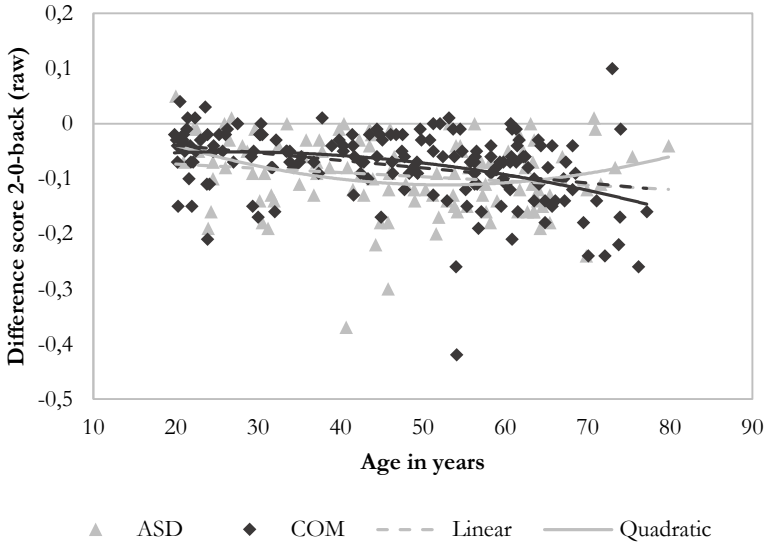

Figure 5.2 The impact of age (linear and quadratic) on the difference scores of correct trials in the ASD and COM group.

To assess the evidential strength for an interaction between age and group, we ran a Bayesian exploratory regression analysis with the difference score as dependent variable and group, age, and age×group as predictors. We tested the hypothesis that the interaction model was preferred (H_1) over the model with only main effects (H_0). This comparison resulted in a BF_{10} = 1/2.7, indicating anecdotal evidence against the hypothesis that group and (linear) age interact in accuracy difference score. When adding a quadratic term and its interaction with group to the regression analysis, both the interaction models were preferred to the model without the linear interaction term (BF_{10} = 6.8) or without the quadratic interaction term (BF_{10} = 11.6). Hence, the data provided substantial and strong evidence in favor of the hypothesis that group and age interact in the accuracy difference score when allowing for a non-linear pattern. We followed-up on this result by running also Bayesian regressions per group, as we did in the frequentist analyses above. In the ASD group, the combined linear and quadratic model (H_1) was preferred to the model with only linear age (H_0) (BF_{10} = 5.0). Nevertheless, comparing the combined model to the model without any age effects (i.e., the null model; H_0) yielded a BF_{10} = 2.2, indicating only anecdotal evidence for an age effect in the ASD group. In the COM group, the model with only linear age was preferred to the combined model (BF_{01} = 1/1.5) and the model with linear age was preferred to the null model (BF_{10} > 100), indicating extreme evidence for a (linear) age effect in the COM group.

Exploratory regression trees

Participants with missing values in one or more predictor variables were excluded from the regression tree analyses (remaining n=257; 105 ASD, 152 COM). Exploratory regression tree analyses yielded a tree with a single decision node suggesting that IQ is a predictor of differential age-gradients on the accuracy difference score (see Figure 5.3). The resulting two terminal nodes (IQ=94 constituted the splitting point, thus there was one leaf with participants with IQ≤94, and one leaf with participants with IQ>94) differed in their parameters of the initially specified model. Follow-up regression analysis with (centered) age, group (IQ≤94, IQ>94), and age×group as predictors, revealed a main effect of group. Participants with an IQ over 94 (n=227; 93 ASD, 134 COM) had smaller difference scores (p<.001) than participants with an IQ of 94 or lower (n=30; 12 ASD, 18 COM). Also the age×group interaction was significant (p=.035). Post-hoc tests showed that age impacted those with higher IQs (F(1,225)=28.83, R^2=.11, p<.001, β=0.34), but did not have an impact in those with lower IQs (F(1,28)=0.02, R^2=.00, p=.902, β=-0.02). In other words, participants with higher IQs showed overall better relative performance, but declined with increasing age. Participants with lower IQs performed poor overall, without any significant age-related differences. Individuals in the two terminal nodes did not differ in their mean age or gender ratio. None of the other predictors predicted age-related differences in WM performance after Bonferroni correction.

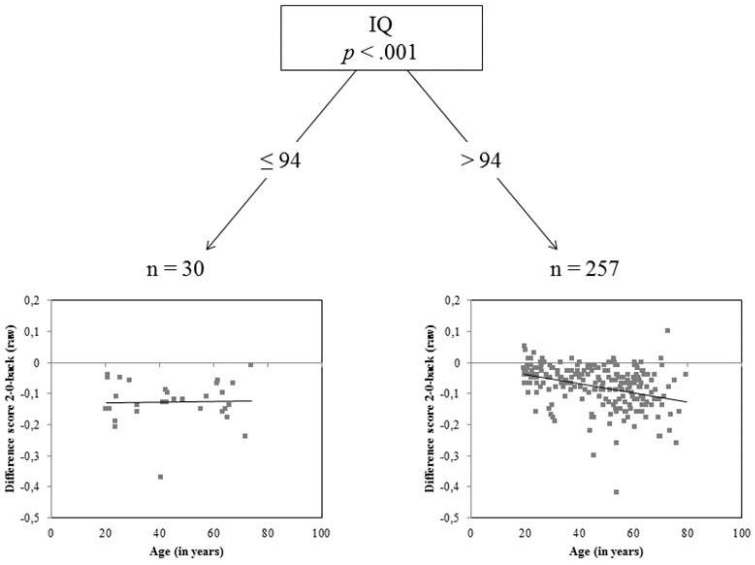

Figure 5.3 Visual representation of the regression tree with IQ as predictor.

DISCUSSION

In the current study, we investigated age-related patterns of cognitive functioning in ASD in one essential executive function, namely WM. EFs are known as a major challenge in ASD and deteriorate in typical aging. So far, the question whether age-related cognitive decline follows a different pattern in ASD has been highly under-investigated. The present cross-sectional findings suggest, despite longer RTs, similar WM performance, but a differential age-related WM pattern in ASD clients compared to individuals without ASD.

The *n*-back task results revealed the typical decrease in performance with increasing WM load (e.g., Smith & Jonides, 1997). *N*-back performance did not significantly differ between adults with and without ASD on neither load level, as revealed by both conventional frequentists and Bayesian analyses. There are three possible explanations for this unpredicted result. First, the version of our task may not have been as challenging for adults with ASD as we expected. Even though a 2-back task involves manipulation and updating of information (Chatham et al., 2011), a further increment of *n* might have been necessary to sufficiently challenge all individuals and to eventually detect subtle WM difficulties in ASD. Second, the used stimuli were simple pictures, but as they were easy to name, verbal WM might have been invoked. Adults with ASD perform generally well on *n*-back tasks using obvious verbal stimuli, such as letters, and our findings are in line with these studies (Koshino et al., 2005; Williams et al., 2005). Third, individuals with ASD present a heterogeneous group and also their WM performance reveals large inter-individual differences. Although the overall group may perform similarly to individuals without ASD, it does not preclude that a small subgroup of adults with ASD does have WM difficulties, as previously found in children (de Vries & Geurts, 2014).

Despite comparable WM accuracy rates, adults with ASD needed more time to respond. Although in previous studies using an *n*-back task no RT differences were found (e.g., Williams et al., 2005), diminished processing speed is often observed in individuals with ASD (Travers et al., 2014). Furthermore, response slowing in ASD occurred independent of WM load, and seems, hence, a general feature rather than specific for WM. Nonetheless, WM accuracy apparently comes with a speed penalty that is greater for individuals with than without ASD. Whether these longer RTs are a result of a different strategy, which favors accuracy over speed (speed-accuracy trade-off), or part of a differential processing style and unrelated to accuracy, should be tested in a future study in which speed/accuracy instructions are experimentally manipulated.

Consistent with previous cross-sectional studies in typical aging, WM performance gradually declines with increasing age in adults without ASD (see Sander et al., 2012). This age-

related pattern seemed, however, differentially expressed in individuals with ASD: The pattern was both linear and quadratic, with increasing age being associated with better performance, revealed by smaller difference scores. The difference score takes baseline performance (i.e., 0-back) into account and aims at filtering out unspecific variance. Smaller (compared to larger) difference scores indicated that increased load had a smaller detrimental effect on performance and, thus, designate better (relative) performance. Alternatively, one may argue that smaller differences scores are due to relatively poor baseline performance. We explored this possibility, but did not find any evidence in favor of this alternative. Individuals with ASD had similar baseline performance compared to those without ASD ($F(1,273)=.13$, $p=.723$, $\eta_p^2=.00$) and age had a comparable effect in both groups on baseline ($p=.400$, $\beta=-0.06$). Hence, adults with ASD had relatively good performance at increased load, rather than relatively poor performance at baseline, irrespective of age. More specifically, closer inspection of the age-related differences in WM performance among adults with ASD (Figure 5.2) revealed that especially the oldest individuals with ASD demonstrated relatively small difference scores and, thus, exhibited relativity good WM performance at increased load. Nevertheless, there are two reasons why this pattern should be interpreted with caution. First, the inverted U-shape, suggesting improvement in old age, seems to be mainly driven by the oldest adults. Fjell and colleagues (2010) warn against over-interpreting outcomes that are driven by extremes of the age-range as they could be misleading about the true shape of the distribution. Second, although the Bayesian explorations indicated that there is substantial and strong evidence for differential age-related patterns, there is only anecdotal evidence that the data support an age effect when allowing for a non-linear pattern in the ASD group. Hence, although the pattern could fit with the idea of ASD being a 'safeguard' for typical age-related decline in WM performance (Geurts & Vissers, 2012; Lever & Geurts, 2015; Oberman & Pascual-Leone, 2014), careful interpretation about the pattern among older adults with ASD is warranted and further research is needed.

In children with ASD, WM development from childhood to young adulthood seems to be delayed (see O'Hearn et al., 2008), and preliminary evidence suggests that WM difficulties persist into older adulthood (Geurts & Vissers, 2012). Our current results depart from these previous findings by demonstrating that WM development in middle and late adulthood does not necessarily continue to be deviant. There was no evidence for a WM deficit across adulthood in ASD, as measured by an *n*-back task, and no evidence for a pattern of increased age-related difficulties, which would result in an even larger difference between individuals with and without ASD in old age. Although speculative, this would suggest that some WM capacities, such as the ability of updating, matures after adolescence into adulthood, at a later stage than typically developing individuals (Andersen et al., 2014; Luna et al., 2007), and finally catch-up across

adulthood. Nevertheless, there are two important distinctions to be made with the previous study on WM in late adulthood. First, in contrast to us, Geurts and Vissers (2012) used a spatial span task. Span tasks and *n*-back tasks both rely on WM related functions, such as the online maintenance of information, but they might tap into different processes (Redick & Lindsey, 2013). While (simple or complex) span tasks involve the brief retention of stimuli (simple) and additional processing tests (complex), *n*-back tasks also involve the updating of information. Second, their task relied on spatial WM and individuals with ASD present more difficulties with spatial WM than with verbal WM (Steele et al., 2007; Williams et al., 2005). Whether our task taps into verbal or more visual WM processes remains a topic of debate. Hence, despite the fact that both studies found a parallel age-related pattern (when allowing for only linear age-related differences), it is unclear if the discrepancy on group comparisons is due to different WM modality or to different underlying WM processes. Therefore, whether deficient span performance protracts into late adulthood in ASD whereas non-span performance does not, or spatial WM difficulties protract into late adulthood, whereas verbal WM capacities do not, remains a question to be answered – ideally with longitudinal designs (e.g., Lindenberger et al., 2011; Raz & Lindenberger, 2011).

With regression trees, we explored whether we could distinguish subgroups of participants with different age-gradients indicating increased or reduced differences in WM performance with age. This exploratory method revealed that IQ constitutes a predictor of separate subgroups with different WM performances and/or differential age effects. Participants with lower IQs (IQ≤94) performed worse than participants with higher IQs (IQ>94); the former did not show age-related WM decline, while the performance of the latter participants decreased with increasing age. An explanation for these non-intuitive results can be found in the data distribution, rather than in a floor effect, which one might expect: Visual exploration revealed that those with lower IQs show large heterogeneity, with participants of approximately the same ages ranging widely in difference scores. Hence, this could be a non-systematic relationship rather than the absence of linear age-related change (see Thomas et al., 2009). With regard to the exact splitting point, Brandmaier and colleagues (Brandmaier, von Oertzen, McArdle, & Lindenberger, 2014) warned against the reification of splits of continuous variables; the reported IQ cutoff of 94 is of course subject to sampling error and, rather than reifying two distinct groups, we recommend to interpret it is as a change point estimate, which might approximate a smooth underlying function.

Strengths, limitations, and future directions

Given the large inter-individual differences among individuals with ASD on the one hand (e.g., Towgood et al., 2009) and among older adults on the other (e.g., Werkle-Bergner et al., 2012), it seems crucial to study individual age-related processes over time (e.g., Lindenberger et al., 2011; Raz & Lindenberger, 2011). Even though this large cross-sectional study represents a significant initial attempt in the understanding of aging processes involved in individuals with ASD and provides, therefore, unique insights, it does not take into account how an individual ages. Therefore, longitudinal studies will be an important next step to examine the nature of age-related changes in WM performance among individuals with ASD.

The aim of our study was to understand age-related differences in adults with and without ASD. Arguably, to investigate typical aging, samples should involve individuals with normal-to-high intelligence. One could claim that, therefore, our sample was not representative of the general ASD population, which includes also individuals with intellectual disabilities (American Psychiatric Association, 2013). In fact, our results may not apply to individuals with ASD and co-occurring intellectual disability. However, in contrast to many studies, other psychiatric comorbid conditions did not constitute an exclusion criterion. This is crucial, as a large proportion of individuals with ASD suffer from at least one comorbid condition (Hofvander et al., 2009). Although comorbidities, such as depression or ADHD, may influence WM performance (Engelhardt et al., 2008; Paterniti et al., 2002), this is unlikely in our study, given our main findings and the fact that these conditions did not constitute predictors in the regression trees. Instead of compromising our findings, we believe it represents a strength of our study by augmenting the validity of our findings.

Although our ASD participants had a prior ASD diagnosis based on extensive diagnostic assessment in which, generally, developmental history is inquired, not all diagnoses could be verified by the ADOS (Lord et al., 2000), which is a recurrent problem when administering the ADOS to intellectually able adults with ASD (see Bastiaansen et al., 2011). To make sure that those who did not met ADOS criteria did not influence our findings, we reran the group comparison and age-related regression analyses without those individuals. The pattern of results did not change. Furthermore, we did not administer the ADOS to the comparison group and cannot, thus, ensure that none of these participants had an undiagnosed ASD. Nevertheless, we inquired about ASD in participants themselves and in close family members and screened for ASD traits with the AQ. Therefore, the presence of ASD in the comparison group seems unlikely.

Conclusions

In sum, the present study provides unique cross-sectional evidence about age-related differences in WM performance among a large group of adults with and without ASD. Individuals with ASD, despite longer RTs, showed comparable WM performance across adulthood. The age-related gradual decline observed in typical individuals was differentially expressed in ASD when allowing for a non-linear pattern. Albeit old age in ASD seemed to be associated with better WM performance, we argued that this finding should be interpreted with caution. Furthermore, additional exploratory Bayesian analyses suggested that age-related differences in WM performance among adults with ASD were barely worth mentioning. These findings provide initial insights into how ASD modulates cognitive aging, but also underlie the need for further WM research into late adulthood in ASD and for analyzing individual change trajectories in longitudinal studies.

SUPPLEMENTARY MATERIAL CHAPTER 5

ASD assessment and screening

Diagnostic instruments. The Dutch version of the Autism Diagnostic Observation Schedule module 4 (de Bildt & de Jonge, 2008; Lord et al., 2000) was used to assess the presence of autism spectrum disorder (ASD) symptoms. It is a standardized, semi-structured observation instrument and consists of a variety of structured activities and questions to elicit social behavior. Observed behavior is rated on 31 items within the domains of communication, reciprocal social interaction, imagination and restricted and repetitive behavior. A subset of items is used to generate the diagnostic algorithm. We used a total score of 7 or higher on the combined social-communication domain as a threshold for the classification of ASD (Bastiaansen et al., 2011).

To further confirm the presence of ASD symptoms in the ASD group and, conversely, to ensure the comparison (COM) group did not contain individuals with distinct ASD traits, the Dutch version of the Autism-spectrum Quotient (AQ) (Baron-Cohen et al., 2001; Hoekstra et al., 2008) was administered. The AQ is a self-report screening questionnaire developed for individuals without intellectual disabilities, consisting of 50 items that assess five different domains: social skill, attention switching, attention to detail, communication, and imagination. Participants have to indicate to which extent they agree with each item on a four-point Likert scale, ranging from (1) "completely agree" to (4) "completely disagree". Total scores can vary between 0 and 50, with higher scores indicating more pronounced autism traits. The AQ is a valid and reliable instrument (Baron-Cohen et al., 2001; Hoekstra et al., 2008) showing good specificity and sensitivity (Woodbury-Smith et al., 2005).

Cognitive functioning. Intellectual functioning as measured by intelligence quotient (IQ) was estimated with two subtests of the Dutch Wechsler Adult Intelligence Scale third edition (Uterwijk, 2000; Wechsler, 1997a): Vocabulary and Matrix Reasoning. Both subtests have high correlations with full scale IQ (Wechsler, 1997a) and provide in combination a reliable estimate of full scale IQ (e.g., Ringe, Saine, Lacritz, Hynan, & Cullum, 2002). Estimated scores can vary between 45 and 155, but in the current study only participants with an IQ above 80 were included.

The Mini Mental State Exam score (MMSE) (Folstein et al., 1975; Kok & Verhey, 2002; Molloy et al., 1991) is a valid, reliable (Folstein et al., 1975) and widely used instrument for the screening of cognitive impairment in elderly individuals. The MMSE consists of 11 questions assessing basic aspects of cognitive functioning, including orientation in time and space, immediate and delayed recall, calculus and language. A score over 25 is considered within the range of normal cognitive functioning.

Comorbidity. The presence or absence of alcohol dependence, substance dependence, and psychoses was assessed with the Mini International Neuropsychiatric Interview Plus (MINI-Plus) (Sheehan et al., 1998; van Vliet et al., 2000). The MINI(-Plus) is standardized diagnostic psychiatric interview that explores several psychiatric disorders according to DSM criteria. For each disorder, two to four screenings questions were used. The diagnosis was rejected when the answers were negative. When the answers were positive, additional questions were used to further investigate the diagnostic criteria. The MINI is a valid and reliable instrument (Lecrubier et al., 1997; Sheehan et al., 1997).

Simon task and choice reaction time task

Simon task

Participants performed a standard visual Simon task, adapted from Broeders and colleagues (in prep), which was presented at a 15.6 inch laptop screen. A fixation cross (0.90 centimeters) was presented at the center of the screen for a variable inter-trial interval ranging from 1250 to 1750 milliseconds. Next, a circle appeared on either the right or the left side (4.23 centimeters) of fixation until response was made for a maximum of 1500 milliseconds. The circle had a diameter of 2.11 centimeters and was either green or blue. Each color was associated with a left or right response key. When the color of the circle was presented on the same side as the associated response button (e.g., the green circle that required a left response appeared on the left side of the fixation cross), the trial was considered compatible. When the color of the circle was presented on the non-associated side (e.g., the green circle that required a left response appeared on the right side of the fixation cross), the trial was considered incompatible. Four experimental blocks of 60 trials each were preceded by two practice blocks during which participants could familiarize with the task. The first practice block consisted of 30 only compatible trials. The second practice block consisted of a mixture of 60 compatible and incompatible trials. As participants had difficulties to memorize the color-response association, two colored cues were provided in concordance with the color-response mapping. Color and response side were counterbalanced across trials resulting in an equal probability of compatible and incompatible trials. Hence, each participant was presented with 120 compatible and 120 incompatible trials. Also, the color-response mappings were counterbalanced across participants (i.e. half of the participants associated the green circle with the left response button and the blue circle with the right response button; the other half associated the blue circle with the left response button and the green circle with the right response button). Mean difference in reaction time between compatible and incompatible trials constituted the dependent variable.

Choice reaction time (CRT) task

Participants performed a simple CRT task which was an adapted version of the employed Simon task. A fixation cross (0.90 centimeters) was presented at the center of the screen for a variable inter-trial interval ranging from 1250 to 1750 milliseconds. Next, a circle appeared in the middle of the screen, on fixation, until response was made for a maximum of 1000 milliseconds. The circle had a diameter of 2.11 centimeters and was either green or blue. Each color was associated with a left or right response key. Color-response associations were counterbalanced; two colored cues were again provided to facilitate color-response mapping. One experimental block of 60 trials was preceded by a short practice block of 20 trials. Mean reaction time on correct responses constituted the dependent variable.

Chapter 6

Reactive and proactive interference control in adults with autism spectrum disorder across the lifespan

Lever, A. G., Ridderinkhof, K. R., Marsman, M., & Geurts, H. M. (2016). Reactive and proactive interference control in adults with autism spectrum disorder across the lifespan. *Manuscript under review.*

ABSTRACT

As a large heterogeneity is observed across studies on interference control in autism spectrum disorder (ASD), research may benefit from the use of a cognitive framework that models specific processes underlying reactive and proactive control of interference. We administered a Simon conflict task in two independent adult samples and applied distributional analyses to examine temporal dynamics of interference control in ASD. Along comparable interference effects in both reactive and proactive control, young adult males (n=23, 18-36 years) diagnosed with ASD made as many fast errors on conflict trials as neurotypical controls (n=19) and showed similar suppression on slow responses (Study 1). However, over the adult lifespan (19-79 years), individuals with ASD (n=118) made fewer fast errors on conflict trials, and had overall slower and more accurate responses than controls (n=160) (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. Our findings suggest that it is fruitful to distinguish different processes involved in interference control and contribute to an increased understanding of interference control mechanisms in adults with ASD.

Keywords: autism spectrum disorder, response inhibition, aging, reactive and proactive interference control, conflict adaptation

INTRODUCTION

Autism spectrum disorder (ASD) is a heterogeneous, neurodevelopmental disorder that is thought to last a lifetime (American Psychiatric Association, 2000; American Psychiatric Association, 2013). Core symptoms of ASD include qualitative impairments in social communication and social interaction, and restricted, repetitive patterns of behavior, interests, or activities. ASD is also associated with difficulties in cognitive control (Solomon et al., 2008). Cognitive control refers to those processes that allow for monitoring and regulating goal-directed behavior in order to flexibly adapt behavior to environmental requirements (Botvinick et al., 2001). Inhibition is such a cognitive control process. It refers to the mechanism or set of processes that result in the containment of prepotent behavioral responses when such responses are reflex-like, premature, inappropriate or incorrect (Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). A lack of inhibitory control is thought to underlie some of the core symptoms observed in ASD (Lopez et al., 2005). A recent meta-analysis indicated that individuals with ASD were moderately impaired on inhibitory control, but substantial heterogeneity across studies was observed (Geurts et al., 2014). The use of rather crude measures, such as mean reaction time, common in the ASD cognitive control literature, was suggested to be one of the major reasons for this heterogeneity. Therefore, more fine grained models of specific aspects of cognitive control are needed to better understand the stages in which difficulties are or are not encountered by individuals with ASD. In this study, we will use the theoretical framework of the dual-route model (Kornblum et al., 1990) and its extension, the activation-suppression hypothesis (Ridderinkhof, 2002), to test whether individuals with ASD have difficulties in the underlying mechanisms of interference control.

Interference control, or resistance to distractor interference, is a specific aspect of the multifaceted nature of inhibition (Friedman & Miyake, 2004; Nigg, 2000). It refers to the ability to suppress irrelevant information and is often measured with conflict tasks, such as the Eriksen flanker task (Eriksen & Eriksen, 1974) or the Simon task (Simon, 1969). In these tasks, a conflict is induced between two types of responses: an automatically activated response, which is driven by a task-irrelevant stimulus feature (e.g., spatial location in the Simon task), and a deliberate response, which is driven by a task-relevant stimulus feature (e.g., color in the Simon task). The source triggering interference may vary across conflict tasks. For example, the Eriksen flanker task elicits interference at the both level of stimulus and response dimension, while interference in the Simon task is induced by only response conflict (Egner, 2007; van den Wildenberg et al., 2010).

Interference control in ASD

The existing literature on interference control in ASD is rather inconsistent, with some studies demonstrating impairments among individuals with ASD (Adams & Jarrold, 2012; Christ et al., 2007; Christ et al., 2011; Henderson et al., 2006), and others showing no differences between individuals with ASD and typically developing controls (Geurts et al., 2008; Larson et al., 2012; Schmitz et al., 2006; Solomon et al., 2008; Solomon et al., 2009). The adherence of findings in a recent meta-analysis point to the idea of interference difficulties in ASD (Geurts et al., 2014). However, the question whether or not individuals with ASD present interference control difficulties is based on the assumption that interference control is a coherent, unified process, while we know from the cognitive control literature that it is not (Ridderinkhof, Forstmann, Wylie, Burle, & van den Wildenberg, 2011). According to Geurts et al. (2014), more elaborate models of cognitive control should, therefore, be applied in order to attempt to disentangle which underlying processes contribute to an overall decrease in performance (see also Solomon et al., 2008; Solomon et al., 2009; Solomon et al., 2014, for such an application). In this study, we will entertain one such more elaborate model, a variety of dual-process models, and the specific techniques associated with each component process, as detailed below.

Proactive and reactive control

Dual-process models provide an account to explain interference control in conflict tasks (De Jong, Liang, & Lauber, 1994; Kornblum et al., 1990; Ridderinkhof, van der Molen, & Bashore, 1995) by assuming that stimulus information is processed along two separate pathways: a direct reflex-like route and a more deliberate route. While along the first route, information is rapidly and semi-automatically processed and directly activates a response, the second route involves deliberate decision processes and takes more time to build up. In case of the Simon task, the spatial location of the stimulus, although irrelevant, directly activates the corresponding spatial response via the direct reflex-like route. The relevant stimulus feature (e.g., color) is processed along the deliberate route to correctly translate the stimulus-response mapping based on task instructions. On congruent trials, the irrelevant stimulus feature (i.e., spatial location), activating the direct route, and relevant stimulus feature (i.e., color), activating the deliberate route, converge at the level of response activation, leading to fast and accurate responses. On incongruent trials, the irrelevant and relevant stimulus features do not correspond and cause interference, leading to slower and less accurate responses.

Although the mean interference or congruency or Simon effect (i.e., the difference in reaction time and accuracy between congruent and incongruent trials) is a useful measure to reflect the additional time and demands required to solve interference, it does not capture the

temporal dynamics of information processing that are involved in conflict situations (see van den Wildenberg et al., 2010). The activation-suppression hypothesis provides an explicit account to explain these temporal aspects. According to this hypothesis, the activation of the response associated with the irrelevant stimulus feature via the direct route can be selectively inhibited by the deliberate route, but this process needs time to build up and is, therefore, only efficient after some time (Ridderinkhof, 2002). Several predictions follow from these assumptions. First, fast responses on incongruent trials do not benefit from the selective inhibition process as there is not enough time to build it up, resulting in a large number of fast errors. Second, as slow responses on incongruent trials do have this advantage, these are associated with more accurate responses. Third, even though congruent trials have faster and more accurate responses than incongruent trials, these responses become slower and more error-prone when intervals are longer, due to the activation of the suppression process that tends to inhibit the correct response. Congruent trials will, thus, benefit from faster responses, whereas their facilitation is reduced on slower responses. In contrast, incongruent trials are facilitated on slower responses. As a result, the interference effect is more affected by selective response inhibition on slow trials than on fast trials (van den Wildenberg et al., 2010).

These predictions can be examined with a related analytical technique that, thus, allows to study the temporal dynamics underlying the manifestation of fast, impulsive errors and its subsequent build-up of selective response suppression (Ridderinkhof, 2002). We focus on two types of these distributional analyses: conditional accuracy functions (CAFs) and delta plots. CAFs provide a way to study automatic response capture by plotting accuracy data as a function of the entire RT distribution. Typically, CAFs reveal a high number of errors on fast RTs on incongruent trails, indicating strong automatic response capture in conflicting situations. Delta plots provide a graphical representation of response suppression by plotting RT differences between congruent and incongruent trials (i.e., the Simon effect) as a function of the entire RT distribution. Typically, delta plots reveal a reduction of the Simon effect on slower RTs, eventually even becoming negative, indicating efficient response suppression as an act of top-down control.

The function of detecting and solving interference after the occurrence of a conflict situation within the same trial, including the mechanisms of selective response suppression, is often designated as within-trial or *reactive* control. It relies upon the transient activation of the lateral prefrontal cortex, in combination with a more extensive network of other brain regions (Braver, 2012; Ridderinkhof et al., 2011). After such a conflict situation, one can also decide to adjust behavioral settings before the next trial in order to anticipate and prevent interference before it occurs. This mechanism is called between-trial or *proactive* control and involves the use

of goal-relevant information to bias attention, perception, and action systems. It relies upon sustained activation of the lateral prefrontal cortex (Braver, 2012). As a result of this proactive control mechanism, interference effects on RT and accuracy are typically reduced when current trials are preceded by conflict (i.e., incongruent) trials. More specifically, when a congruent trial is followed by another congruent trial, responses are typically fast and accurate, whereas when a congruent trial is followed by an incongruent trial, responses are slower and error prone due to a low level of control. After an incongruent trial, however, control is enhanced, resulting in a smaller difference in RTs or errors between current congruent or incongruent trials, and, hence, a smaller interference effect. This effect is called the Gratton effect (Gratton, Coles, & Donchin, 1992), conflict adjustment effect (Botvinick et al., 2001), or congruency sequence effect (CSE) (Egner, 2007). We will refer to the CSE effect since this is a theory-neutral, operational term.

Reactive and proactive control in ASD

Although reactive and proactive control, as described above, have been investigated among clinical groups, such as Attention Deficit Hyperactivity Disorder (ADHD) (Ridderinkhof, Scheres, Oosterlaan, & Sergeant, 2005), mild cognitive impairment (Wylie, Ridderinkhof, Eckerle, & Manning, 2007), and Parkinson's disease (e.g., Wylie, Ridderinkhof, Bashore, & van den Wildenberg, 2010), only a handful of studies examined these mechanisms among individuals with ASD. For example, Solomon and colleagues (2014) investigated the neural substrates underlying reactive and proactive control. Given that adolescents with ASD recruited brain regions associated with reactive control – anterior cingulate cortex and ventrolateral prefrontal cortex – rather than with proactive control – lateral prefrontal cortex – during a prepotent response task, they concluded that individuals with ASD prefer to rely on reactive rather than proactive control (Solomon et al., 2014). Nevertheless, at a behavior level, the authors only used a measure of reactive control and it is thus unclear whether these individuals with ASD showed intact or deficient congruency sequence effects. In an adapted version of the Eriksen flanker task, children and adolescents with ASD did not seem to show behaviorally deviant conflict monitoring and adaptation effects (i.e., CSE), even though the neural processes underlying the detection and resolution of conflict were altered (Larson et al., 2012). Similar CSEs among individuals with and without ASD were also found when using social-emotional stimuli to induce conflict (Worsham, Gray, Larson, & South, 2015). Yet, despite these interesting findings, studies on temporal dynamics of interference control processes among individuals with ASD are lacking.

Present study

In sum, in the current paper, we rely on the above-described accounts in order to have a conceptual and more fine-grained model of cognitive control that may capture and explain the ASD-related heterogeneity observed in interference control. We present two studies in which we investigate reactive and proactive control and the temporal dynamics of interference control processes among individuals with ASD. Automatic response capture and deliberate response suppression during reactive control are compared between individuals with and without ASD. In the first study, we examine these underlying cognitive control mechanisms in a group of adults between 18 and 36 years old. Based on previous findings, we expect to observe deviant interference control during reactive control processes (Geurts et al., 2014), but an intact CSE (Larson et al., 2012; Worsham et al., 2015). In absence of literature on response capture and selective response suppression in ASD, we do not have a specific prediction on this regard. In the second study, we aim to validate the results of Study 1 in an independent sample composed of adults between 20 and 79 years in which we additionally examine the effect of age on interference control in ASD.

STUDY 1

METHODS STUDY 1

Participants

Twenty-four males aged 18-36 years with a clinical ASD diagnosis according to DSM-IV-TR criteria (American Psychiatric Association, 2000) determined by a multidisciplinary team, were recruited through the Dr. Leo Kannerhuis, a specialized autism clinic in the Netherlands, and by advertisements on the website of the Dutch Autism Association. Twenty age-matched males without an ASD were recruited among acquaintances of Dr. Leo Kannerhuis employees and formed the comparison group (COM). All non-ASD participants scored below 26 on the Autism-spectrum Quotient (AQ) (Baron-Cohen et al., 2001). Individuals with an estimated IQ below 80 were excluded, which resulted in the exclusion of one COM participant. Due to a stress reaction, one ASD participant was not able to finalize the Simon task and was, therefore, excluded from further analyses.

As these adults participated in a study assessing autonomic and endocrine activity (Smeekens, Didden, & Verhoeven, 2013), the following exclusion criteria were also applied: cardiac disease and complaints, respiratory problems, liver- and/or kidney failure, use of beta-

blockers or antidepressant medication. The final sample consisted of 23 adults with ASD and 19 adults without ASD (Table 6.1).

Table 6.1 Means (standard deviations), demographic and clinical scores of the ASD and COM group (Study 1).

	Group		
	ASD (n=23)	COM (n=19)	Statistics
Education[a]	18/5/0	1/12/6	Fisher's test, $p<.001$
Diagnosis[b]	4/5/12/2	-	-
Age	23.3 (4.7)	26.0 (4.8)	$t(1,40)=-1.88$, $p=.067$, $\eta_p^2=.08$
	range 18-36	range 18-35	
IQ	108.9 (13.6)	117.8 (13.7)	$t(1,40)=-2.10$, $p=.042$, $\eta_p^2=.10$
	range 83-137	range 86-149	
AQ	24.4 (7.8)	8.5 (4.5)	$t(1,40)=7.90$, $p<.001$, $\eta_p^2=.61$
	range 13-38	range 2-17	

Note. ASD=autism spectrum disorder group; COM=comparison group; IQ=estimated intelligence quotient; AQ=Autism-spectrum Quotient.

[a] The numbers between slashes indicate the educational level based on the Verhage coding system (1964): junior general secondary or vocation education/senior general secondary education or vocation colleges/university education.

[b] The numbers between slashes indicate a diagnosis of Autism/Asperger Syndrome/Pervasive Developmental Disorder Not Otherwise Specified/ASD.

Measures

Simon task

Participants performed a visual Simon task (Broeders et al., in prep). A square fixation point of 0.30 centimeters was presented at the center of the screen for a variable intertrial interval ranging from 1750 to 2250 milliseconds. Next, a circle appeared on either the left or the right side of fixation (2.09 centimeters) until a response was made or the maximum time of 1500 milliseconds was exceeded. The circle had a diameter of 1.27 centimeters and was either green or blue. Two response keys were associated with the colors. The green circle required a left-hand response; the blue circle required a right-hand response. When the color of the circle was presented on the same side as the associated response button (e.g., the green circle requiring a left response appeared on the left side of the fixation point), the trial was considered congruent. When the color of the circle was presented on the non-associated side (e.g., the green circle requiring a left response appeared on the right side of the fixation point), the trial was considered incongruent.

Participants were instructed to respond as fast and accurate as possible. Each participant completed a practice block of 12 trials to learn the color-response association. Next, four experimental blocks of 60 trials each were presented. Color and response side were randomly varied across trials; congruent (n = 120) and incongruent (n = 120) trials were randomly assigned.

Cognitive functioning

Cognitive functioning (estimated IQ) was assessed with two subtests of the Wechsler Adult Intelligence Scale third edition (WAIS-III) (Wechsler, 1997a): Vocabulary and Block Design. Both subtests have very good internal consistency (*a*=.91/.89) and good test-retest reliability (*r*=.91/.88). In combination, Vocabulary and Block Design are highly correlated with full scale IQ (e.g., Ringe et al., 2002).

Diagnostic measures

All participating adults with ASD already had a diagnosis within the autism spectrum diagnosed by a multidisciplinary team including a psychologist and a psychiatrist according to DSM-IV criteria. Yet, the Dutch version of the AQ (Baron-Cohen et al., 2001; Hoekstra et al., 2008) was administered to assess the presence of autistic traits. The AQ is a self-report questionnaire consisting of 50 statements that encompass five areas: social skills, attention switching, attention to detail, communication, and imagination. Participants indicate on a four point Likert-scale whether to 'definitely agree', 'slightly agree', 'slightly disagree', or 'definitely disagree' with the statements. Each statement is scored zero or one point based on a "definitely agree/slightly agree" or "definitely disagree/slightly disagree" response. This results in a score ranging from 0 to 50. The Dutch version of the AQ shows satisfactory internal consistency (*a*=.71/.81) and test-retest reliability (*r*=.78) (Hoekstra et al., 2008).

Procedure

After written informed consent was obtained, the abbreviated version of the WAIS-III and the Simon task were administered among several other tasks described elsewhere (Smeekens et al., 2013). Within three days after completing the experimental session, participants filled out some questionnaires online, including the AQ. The study was approved by the local ethical review board of the Faculty of Social Sciences of the Radboud University Nijmegen, the Netherlands (ECG 0601011), and complied with all relevant laws and institutional guidelines.

Statistical analyses

First, extreme reaction time (RT) values (>3SD), either excessively slow or fast, were removed from the data of each participant. This conservative trim procedure resulted in the elimination of less than 2.6% of trials per subject (ASD: M = 1.3%, SD = 0.7%; COM: M = 1.2%, SD = 0.6%). Second, fast (<100ms) responses were also removed from the data, resulting in the elimination of 0.9% of trials per participant (ASD: M = 0.04%, SD = 0.2%; COM: M = 0.02%, SD = 0.1%). Third, mean RT and mean accuracy (i.e., mean percentage of correct responses) were calculated for each participant. As RTs and accuracy data were not normally distributed, RTs were log transformed and arcsine-square-root transformation was applied to accuracy to obtain normality.

To investigate reactive control of interference, two mixed design Analyses of Variance (ANOVAs)[viii] were computed with Congruency (congruent, incongruent) as within-subject factor and Group (ASD, COM) as between-subject factor and log transformed RT and arcsine-square-root transformed accuracy as dependent variables. The strength of automatic response capture was examined by means of conditional accuracy functions (CAFs). In a CAF, accuracy rates are plotted as a function of the entire RT distribution. Therefore, RTs of congruent and incongruent trials are rank-ordered and divided into five approximately equal-sized segments, called bins. Next, accuracy rates are calculated for each bin, resulting in five accuracy values for congruent trials and five accuracy values for incongruent trials. These values are plotted against the mean RT for each bin. The accuracy values within the first, and fastest, bin are considered a measure of strength of automatic response capture. These accuracy values of the ASD and COM group are compared by means of a paired sample t-test. The proficiency of suppression was examined with delta plots. Delta plots show the Simon effect as a function of the entire RT distribution. Also for this measure, RTs are rank-ordered and divided into five bins, but now for correct responses only. Mean RTs are calculated for both congruency levels in each bin. Next, the Simon effect is calculated for each bin, resulting in five Simon effect values. These are plotted against the mean RT for each bin. The delta slope of the slowest segment, that is the difference between the Simon effect of the fourth and the fifth bin, is considered a measure of proficiency of suppression. These slopes of the ASD and COM group are compared with a paired sample t-test.

To investigate proactive control of interference, two mixed design ANOVAs were computed with Congruency (congruent, incongruent), Group (ASD, COM) and trial sequence

[viii] The groups differed on their mean IQs. However, as IQ was not correlated with the Simon effect, RTs, or accuracy on (in)congruent trials (all rs < .2, all ps > .16), IQ was not considered as covariate in the analyses.

(preceding trial congruent [PTC], preceding trial incongruent [PTI]) as experimental factors and log transformed RT and arcsine-square-root transformed accuracy as dependent variables.

Next to conventional *p*-values, we used Bayes factors (Jeffreys, 1935; Jeffreys, 1961; Kass & Raftery, 1995) to quantify evidence for a hypothesis H_a against an alternative hypothesis H_b, based on the observed data. Typically, H_a is the hypothesis of interest (denoted here as H_1) and H_b the null-hypothesis stating that there is no effect (denoted here as H_0). We indicate the Bayes factor expressing evidence for H_1 over H_0 as BF_{10}, which can also be used to quantify evidence in favor of the null-hypothesis H_0 by using the relation $BF_{01} = 1/ BF_{10}$. For instance, when $BF_{10} = 3$, it is three times more likely that the data derived from H_1 than from H_0, and when $BF_{10} = 1/3$, it is three times more likely that the data derived from H_0 than from H_1. To aid the interpretation of Bayes factors, Wagenmakers, Wetzels, Borsboom, & van der Maas (2011) suggested to use the following scale: "anecdotal evidence" in favor of H_1 when $1 < BF_{10} \leq 3$, "substantial evidence" when $3 < BF_{10} \leq 10$, "strong evidence" when $10 < BF_{10} \leq 30$, "very strong evidence" when $30 < BF_{10} \leq 100$, and "extreme evidence" when $BF_{10} > 100$. Note that $BF_{10} = 1$ indicates that there is no evidence for or against H_1 (meaning that it is equally likely that the data derived from H_1 or H_0), and that a $BF_{10} < 1$ indicates evidence in favor of H_0.

We computed Bayes factors for the t-tests and ANOVA models described above. In the Bayesian t-tests, we compare the (null) hypothesis that the groups do not differ with the (alternative) hypothesis that the groups differ by comparing a model with the main effect of group to the null model. In the Bayesian mixed design ANOVAs, we compare the most complex model that includes the effect we are interested in with the model that excludes this effect. For example, by determining the evidential strength for an interaction between group and congruency, we compare a model with the main effects of group and congruency to a model with the main effects of group and congruency and the interaction term. This procedure yields a Bayes factor that indicates to which extent which model is preferred and, thus, indicates the evidence in favor of or against the hypothesis that group and congruency interact.

Bayes factors were computed using the freely available statistical software program JASP (Love, Selker, Verhagen et al., 2015b; Love et al., submitted), which can be downloaded from https://jasp-stats.org/. All other analyses were run with SPSS 22.0 (IBM Corp., 2013). There were no outliers (i.e., data points more than three times the interquartile range above or below the first quartile) on reactive control, whereas there was one outlier in the ASD group in the proactive control analyses. As removing this outlier did not change the pattern of findings, we reported the results including this outlier.

RESULTS STUDY 1

On reactive control (Table 6.2), as predicted, there was a pronounced effect of congruency on both RT and accuracy: Congruent trials were associated with faster RTs ($BF_{10} > 100$) and more accurate responses ($BF_{10} = 69.07$) than incongruent trials. This congruency effect did not interact with group (RT: $BF_{10} = 1/2.47$; accuracy: $BF_{10} = 1/3.31$), nor was there a main effect of group on accuracy ($BF_{10} = 1/3.03$). For RT, there was a slight preference against a main effect of group, although the amount of evidence was very small and, therefore, inconclusive ($BF_{10} = 1/1.39$) (Figure 6.1). Hence, the two groups presented a comparable Simon effect (i.e., the difference between congruent and incongruent trials: $RT_{incongruent} - RT_{congruent}$, $accuracy_{congruent} - accuracy_{incongruent}$).

Accuracy rates of the fastest responses on incongruent trials did not differ between groups ($t(1,40) = 0.50$, $p = .620$, $\eta_p^2 = .01$, $BF_{10} = 1/2.98$) indicating that the strength of response capture was similarly expressed across the ASD and COM group (Figure 6.2a). Likewise, there was no effect of group on the delta slope of the slowest responses ($t(1,40) = 1.72$, $p = .094$, $\eta_p^2 = .07$), indicating that the strength of response suppression was comparable between the ASD and COM group (Figure 6.2b). Nevertheless, evidence was rather inconclusive as the Bayes factor in favor of the null hypothesis was close to one ($BF_{10} = 1/1.03$).

On proactive control, as predicted, we found that responses were faster ($BF_{10} > 100$) and more accurate ($BF_{10} > 100$) when congruent trials were preceded by congruent trials rather than when preceded by incongruent trials, and when incongruent trials were preceded by incongruent trials rather than when preceded by congruent trials (Table 6.3, Figure 6.3). In other words, the Simon effect was larger after congruent trials than after incongruent trials. This effect did not differ between groups (RT: $BF_{10} = 1/3.83$; accuracy: $BF_{10} = 1/2.87$). Hence, proactive control is similarly enhanced after a conflict situation in individuals with and without ASD.

Table 6.2. Statistics of group comparisons on reactive control (Study 1).

	RTs			Accuracy		
Factors	*F*	*p*	η_p^2	*F*	*p*	η_p^2
congruency	**121.88**	**<.001**	**.75**	**13.65**	**.001**	**.25**
group	1.36	.251	.03	0.02	.891	.00
group×congruency	0.22	.641	.01	0.03	.859	.00

Note. RTs=Reaction Times. Degrees of freedom are (1, 40) for all group analyses. Significant values ($p<.05$) are indicated in bold script.

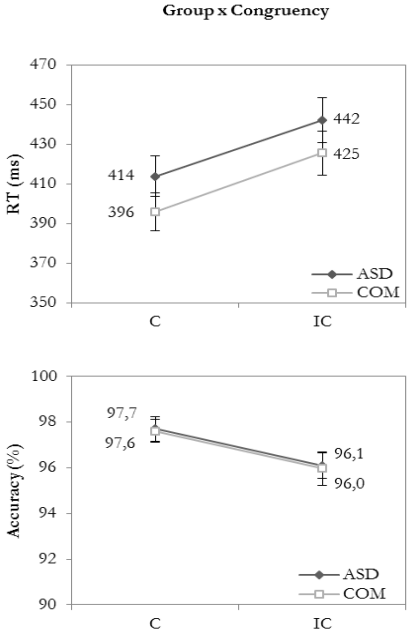

Figure 6.1 Mean reactions times (RTs) and accuracy rates for congruent and incongruent trials per group (Study 1).

Note. ASD = autism spectrum disorder group; COM = comparison group; C = congruent; IC = incongruent. Error bars present standard errors.

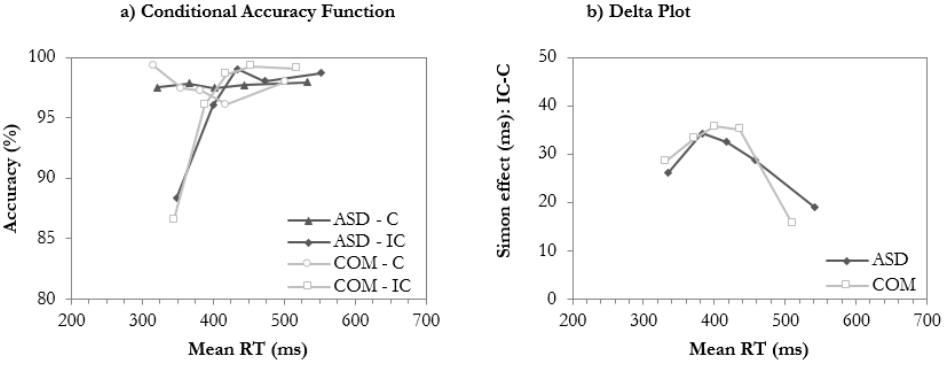

Figure 6.2 (a) Conditional accuracy functions and **(b)** delta plots per group (Study 1).

Note. ASD = autism spectrum disorder group; COM = comparison group; C = congruent; IC = incongruent.

Table 6.3 Statistics of the group comparison on proactive control (Study 1).

	RTs			Accuracy		
Factors	*F*	*p*	η_p^2	*F*	*p*	η_p^2
congruency	**128.88**	**<.001**	**.76**	**9.37**	**.004**	**.19**
trial sequence	**7.48**	**.009**	**.16**	**4.57**	**.039**	**.10**
group	1.33	.256	.03	0.00	.973	.00
congruency×trial sequence	**152.57**	**<.001**	**.79**	**74.45**	**<.001**	**.65**
group×congruency	0.12	.727	.00	0.35	.559	.01
group×trial sequence	0.05	.826	.00	0.55	.465	.01
group×congruency×trial sequence	0.13	.717	.00	0.00	.995	.00

Note. RTs=Reaction Times. Degrees of freedom are (1, 40) for all analyses. Significant values (p<.05) are indicated in bold script.

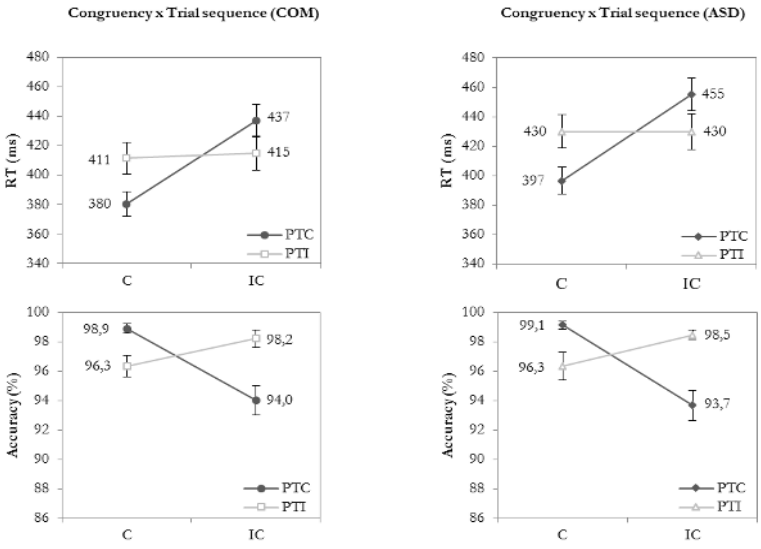

Figure 6.3 The congruency sequence effect per group (Study 1).

Note. ASD = autism spectrum disorder group; COM = comparison group; C = congruent; IC = incongruent; PTC = previous trial congruent; PTI = previous trial incongruent. Error bars present standard errors.

DISCUSSION STUDY 1

In line with earlier clinical studies (Ridderinkhof et al., 2005; Wylie et al., 2007; Wylie et al., 2010), we applied distributional techniques, designed to test the activation-suppression hypothesis (Ridderinkhof, 2002), and examined CSEs to study the underlying mechanisms of interference control in ASD. With regard to reactive control, Study 1 demonstrated that the congruency effect elicited by conflict and the number of fast errors on incongruent trials was comparable among young adults with and without ASD. Fast responses on incongruent trials are prone to errors as they activate a direct reflex-like route that leads to the activation of the incorrect response and are considered a measure of automatic response capture (Ridderinkhof, 2002). Furthermore, the deliberate suppression of responses by means of the deliberate route, revealed by a reduction of the Simon effect on slow responses (van den Wildenberg et al., 2010), was similar in individuals with ASD and controls.

Study 1 also indicated that the proactive mechanism adopted to detect and adjust behavior in reaction to conflict situations seems to be intact in individuals with ASD. As in typically developing adults (Botvinick et al., 2001; Egner, 2007; Gratton et al., 1992), we observed a reduced interference effect after incongruent trials compared to congruent trials, indicating enhanced cognitive control after conflict. This behavioral result is in line with previous studies in ASD (Larson et al., 2012; Worsham et al., 2015).

Hence, we demonstrated in Study 1 similar reactive and proactive interference control abilities in young adults with ASD compared to those without ASD. Despite that the exploratory Bayesian analyses show support for these frequentist results as they indicate some evidence against H_1 (i.e., a group effect), the amount of evidence ranges from small ($BF_{10} \leq 1/3.83$) to no evidence at all ($BF_{10} \leq 1/1.03$). In addition, there are some potential methodological caveats suggesting that we need to be careful in making strong claims based on this single study.

First, although the task we used has proven its validity in a sample of Parkinson disease patients (e.g., Broeders et al., in prep), it was not yet administered to individuals with ASD. The interstimulus interval of the Simon task had a rather long duration and the colored circles appeared close to the fixation point. Adults with ASD are sensitive to event presentation rate, showing similar performances on slow or medium event rate, but decreased performance on fast event rates (Raymaekers, van der Meere, & Roeyers, 2004). Moreover, Adams and Jarrold (2012) showed that increasing size of the target and increasing distance between distractors in a Flanker task reduced the interference effect in typically developing controls, but not in children with ASD. Also in the Simon task, increasing the distance between fixation and the stimulus (i.e., a larger eccentricity) reduced the Simon effect (Hommel, 1993). If individuals with ASD are less

sensitive to distractor salience, than they should demonstrate a larger interference effect compared to controls when distractor salience is large. These observations suggest that diminishing the interstimulus interval and increasing the stimulus-fixation distance should facilitate finding an effect between individuals with and without ASD when difficulties in interference control indeed exists in ASD. Therefore, we changed these parameters of the Simon task in a second study.

Second, only 12 practice trials were administered before starting the test session. This small number may suffice to acquaint the participants with the global properties of the task, but perhaps not to train them to attain asymptote reaction times, in particular when responding to incongruent stimuli.

Third, the low number of self-reported ASD traits caught our attention. It may indicate that the ASD participants presented mild symptoms, which could be a potential argument for absent interference control deficits, but it also may illustrate poor introspection (see Frith, 2004). As these AQ scores did not deviate from those previously reported by participants with the same mean age (Bishop & Seltzer, 2012; Ketelaars et al., 2008; Kurita, Koyama, & Osada, 2005), it seems plausible that young adults tend to report low ASD traits. Furthermore, although the sample consisted of individuals who were diagnosed with ASD by a specialized mental health institution, their diagnoses were not independently verified by the researchers with a standardized diagnostic instrument to assess the quality and quantity of current ASD symptomatology. Therefore, in the second study, we administered one of the most commonly used instruments in ASD research: the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000) to assess the current presence of ASD symptoms to validate the clinical diagnosis as determined by ASD experts.

Finally, despite the observation that age does not seem to be a relevant moderator in interference control among individuals with ASD (Geurts et al., 2014), only a few studies took adults with ASD into account and it is, thus, unclear whether the absence of age-related effects protracts into adulthood. Typically developing adults experience age-related decline in several cognitive domains (e.g., Friedman et al., 2009; Verhaeghen & Cerella, 2002). Although aging is not systematically associated with impairments in interference control (Nieuwenhuis et al., 2002; Wild-Wall, Falkenstein, & Hohnsbein, 2008) and proactive control of interference seems to be spared (Puccioni & Vallesi, 2012; Yano, 2011), older adults generally show a larger Simon effect compared to younger adults (see Proctor, Pick, Vu, & Anderson, 2005, for an overview; Van der Lubbe & Verleger, 2002; Pick & Proctor, 1999; Kawai, Kubo-Kawai, Kubo, Terazawa, & Masataka, 2012). Whether automatic response capture and deliberate response suppression are sensitive to age-related differences is yet unknown. Hence, we set out to examine the role of age

in interference control processes among individuals with and without ASD across adulthood in a new experiment, extending the age range of the sample to the adult lifespan.

In sum, to determine whether we can corroborate our null findings in an independent ASD sample, we conducted Study 2 with an adapted visual Simon task in a larger sample with an extended age range to investigate also age-related differences in underlying processes of interference control across adulthood in ASD.

STUDY 2

METHODS STUDY 2

Participants

Individuals between 19 and 79 years with a diagnosis within the autism spectrum according to DSM-IV criteria (American Psychiatric Association, 2000) were diagnosed by a multidisciplinary team including a psychologist or psychiatrist and were recruited through several mental health institutions across the Netherlands and by advertisements on client organization websites. Of the 168 individuals, 45 were excluded due to (1) the absence of a clinical ASD diagnosis, (2) the current or former presence of neurological problems (e.g., epilepsy, stroke, cerebral contusion), schizophrenia or psychoses, (3) a current alcohol- or drugs dependency, or (4) an estimated IQ below 80. ADOS module 4 (Lord et al., 2000) and AQ (Baron-Cohen et al., 2001) were administered to verify the participants' clinical diagnosis. Participants who scored above the ADOS threshold (≥7) or AQ (≥26) threshold were included in the current study. Of the 39 participants who did not meet the ADOS criterion, only five did also not meet the AQ criterion and were excluded from further analysis. This resulted in an eligible ASD sample of 118 participants, of whom all completed the Simon task (for a description of the sample, see also Lever & Geurts, 2015; Lever et al., 2015).

Individuals without ASD were recruited by means of advertisements on the university website and on social media, and within the social network of the researchers. Of the 193 individuals, 36 were excluded due to (1) the presence of ASD or schizophrenia in close relatives, (2) a diagnosis of ADHD, (3) the current or former presence of neurological problems (e.g. epilepsy, stroke, cerebral contusion), schizophrenia or a psychosis, comorbid psychoses or a history of schizophrenia, (3) a current alcohol- or drugs dependency, or (4) an estimated IQ below 80. COM participants with an incomplete AQ (≥10% missing values, n=1) or an AQ score above the threshold proposed for the general population (≥32, n=1; Woodbury-Schmidt

Table 6.4 Means (standard deviations), demographic and clinical scores of the ASD and COM group (Study 2).

	Group		
	ASD (n=118)	COM (n=160)	Statistics
Gender	83 M/35 F	91 M/69 F	Fisher's test, p=.024, odds ratio=1.79
Education[a]	0/1/0/3/35/53/26	0/0/1/5/25/79/50	Fisher's test, p=.032
Diagnosis[b]	18/60/35/5	-	-
Age	47.6 (14.9)	46.1 (16.5)	F(1, 276)=0.66, p=.419, η_p^2=.00
	range 20-79	range 19-77	
IQ	114.8 (16.9)	114.0 (16.5)	F(1, 276)=0.16, p=.695, η_p^2=.00
	range 84-155	range 80-155	
MMSE	29.1 (1.0)	29.2 (1.0)	F(1, 276)=0.56, p=.457, η_p^2=.00
	range 26-30	range 26-30	
AQ	33.8 (8.3)	12.1 (5.2)	F(1, 275)[c]=708.90, p<.001, η_p^2=.72
	range 8-49	range 2-26	
ADOS[d]	8.6 (3.1)	-	
	range 1-19		

Note. ASD=autism spectrum disorder group; COM=comparison group; M=male; F=female; IQ=estimated intelligence quotient; MMSE=Mini Mental State Examination; AQ=Autism-spectrum Quotient; ADOS=Autism Diagnostic Observation Schedule.

[a] The numbers between slashes indicate the educational level based on the Verhage coding system (1964), ranging from 1 (primary education not finished) to 7 (university degree).

[b] The numbers between slashes indicate a diagnosis of Autism/Asperger Syndrome/Pervasive Developmental Disorder Not Otherwise Specified/ASD.

[c] One ASD participant did not complete the AQ (but met the ADOS criterion and, hence, was included).

[d] Of the final sample, 27 participants scored below the ADOS cut-off (<7). Excluding these participants from the analyses did not alter the pattern of results.

et al., 2005) were also excluded. This resulted in an eligible COM sample of 167 participants, of whom 160 completed the Simon task.

ASD and COM participants were matched on age and estimated IQ. However, the proportion of females was larger in the COM group than in the ASD group (see Table 6.4).

Measures

Simon task

Participants performed a modified visual Simon task compared to Study 1. A fixation cross (0.90 centimeters) was presented at the center of the screen for a variable intertrial interval ranging

from 1250 to 1750 milliseconds. Next, a circle (diameter 2.11 centimeters) appeared on either the right or the left side (4.23 centimeters) of fixation. As in Study 1, the circle was displayed until response was made for a maximum of 1500 milliseconds and was either green or blue. Also, each color was associated with a left or right response key and participants were instructed to respond as fast and accurate as possible. Four experimental blocks were preceded by two practice blocks, instead of one short practice block in Study 1, during which participants could familiarize with the task. The first practice block consisted of 30 only congruent trials. The second practice block consisted of a mixture of 60 congruent and incongruent trials. As participants had difficulties to memorize the color-response association, two colored cues were provided in concordance with the color-response mapping. Color and response side were again counterbalanced across trials resulting in an equal probability of congruent (n = 120) and incongruent trials (n = 120). In addition, the color-response mappings were counterbalanced across participants (i.e., half of the participants associated the green circle with the left response button and the blue circle with the right response button; the other half associated the blue circle with the left response button and the green circle with the right response button).

Cognitive functioning

Cognitive functioning (estimated IQ) was assessed with two subtests of the WAIS-III (Wechsler, 1997a): Vocabulary and Matrix Reasoning, instead of Block Design in Study 1. Both subtests have very good international consistency (a=.91/.91) and good test-retest reliability (r=.91/.78). In combination, Vocabulary and Matrix Reasoning are highly correlated with full scale IQ (e.g., Ringe et al., 2002).

Diagnostic measures

The Dutch version of the ADOS Module 4 (de Bildt & de Jonge, 2008; Lord et al., 2000) was administered to assess the presence of ASD symptoms. The ADOS is a standardized semi-structured instrument designed for the assessment of ASD. Social interaction, communication, and play are elicited by means of 10-15 small conversations and activities. A client's behavior is observed and scored according to 31 criteria. A subset of criteria is used to compute the "original" diagnostic algorithm. We used a threshold of 7 for the classification of ASD. The ADOS was administered and scored by a trained and certified psychologist. Module 4 has moderate sensitivity (0.61), good specificity (0.82), and good predictive value (0.81) when administered to high-functioning adults (Bastiaansen et al., 2011).

As in Study 1, the Dutch version of the AQ (Baron-Cohen et al., 2001; Hoekstra et al., 2008) was administered to assess the presence of autistic traits.

Procedure

After written informed consent was obtained, participants underwent an extensive screening during which the ADOS (only ASD participants) and the abbreviated version of the WAIS-III were administered. A few weeks later, the participants returned for an experimental session, including the Simon task. As the current study is part of larger project on aging in ASD, more tasks and questionnaires were administered, but these are described elsewhere (e.g., Lever & Geurts, 2015; Lever et al., 2015). The order of tasks in the experimental session was counterbalanced across participants. Travel expenses were refunded up to 20 euros. The study was approved by the local ethical review board of the Department of Psychology of the University of Amsterdam, the Netherlands (2011-PN-1952), and complied with all relevant laws and institutional guidelines.

Statistical analyses

Study 2 used the same procedure to analyze the data as described in Study 1, but gender was added as a between-subject factor as the ASD and COM group differed on their gender ratio. In addition, to investigate the effect of age on reactive and proactive control, centered age was added as a covariate to the mixed design ANOVAs and the interaction between centered age and group was inspected. Furthermore, we computed step-wise regressions with centered age in the first step, and group, group-by-centered age, and gender in the second step as predictors on accuracy of the first bin and on the slowest segment of the delta slope to examine the effect of age on automatic response capture and suppression, respectively. In addition to the previously mentioned Bayesian analyses, we ran Bayesian (mixed design) ANCOVAs with centered age as covariate and Bayesian regressions to assess the evidential strength for the data supporting the hypothesis of a differential age-related effect in the two groups on reactive and proactive control by comparing two models, as described in the Methods section of Study 1.

Applying the conservative trim procedure to remove extreme RT values (>3SD) resulted in the elimination of less than 2.6% trials per subject (ASD: M = 1.2%, SD = 0.6%; COM: M = 1.1%, SD = 0.5%). Removing fast (<100ms) responses resulted in the elimination of less than 4.7% of trials per participant (ASD: M = 0.05%, SD = 0.2%; COM: M = 0.1%, SD = 0.5%). RTs were again log transformed and arcsine-square-root transformation was applied to accuracy to increase normality.

Again, Bayes factors were computed with JASP (Love et al., 2015b; Love et al., submitted), whereas all other analyses were run with SPSS 22.0 (IBM Corp., 2013). As removing one outlier (i.e., data points more than three times the interquartile range above or below the first quartile) in the COM group for the reactive control analyses and six outliers (5 COM, 1

ASD) for the proactive control analyses did not change the pattern of results, we reported the results including these outliers.

RESULTS STUDY 2

On reactive control (Table 6.5), as expected, there was again a marked effect of congruency on both RT and accuracy: Congruent trials were associated with faster RTs ($BF_{10} > 100$) and more accurate responses ($BF_{10} > 100$) than incongruent trials. Adults with ASD showed longer RTs ($BF_{10} = 19.89$) and were more accurate ($BF_{10} = 15.89$) than adults without ASD. These longer and more accurate responses were independent of trial type (i.e., congruent/incongruent trials; RT: $BF_{10} = 1/1.73$; accuracy: $BF_{10} = 1/2.74$) and longer RTs were not affected by gender (main effect: $BF_{10} = 1/1.66$, interaction: $BF_{10} = 1/7.12$). Nevertheless, females were more accurate than males ($BF_{10} = 1.98$), and accuracy was differently influenced by gender in the two groups ($BF_{10} = 2.03$). Follow-up analyses revealed that the accuracy congruency effect (i.e., Simon effect) was similarly expressed in females with and without ASD ($F(1, 102) = 1.15$, $p = .285$, $\eta_p^2 = .01$, $BF_{10} = 1/2.92$) whereas males without ASD demonstrated a larger Simon effect than males with ASD ($F(1, 172) = 6.37$, $p = .013$, $\eta_p^2 = .04$, $BF_{10} = 3.06$) (Figure 6.4).

Table 6.5 Statistics of the group comparisons on reactive control (Study 2).

	RTs			Accuracy		
Factors	*F*	*p*	η_p^2	*F*	*p*	η_p^2
congruency	**828.18**	**<.001**	**.75**	**272.33**	**<.001**	**.50**
group	**8.02**	**.005**	**.03**	**7.03**	**.009**	**.03**
gender	0.42	.517	.00	**4.04**	**.046**	**.02**
group×gender	0.67	.412	.00	1.60	.207	.01
group×congruency	1.62	.205	.01	0.41	.524	.00
gender×congruency	3.14	.078	.01	**5.51**	**.020**	**.02**
group×gender×congruency	0.32	.575	.00	**5.56**	**.019**	**.02**

Note. RTs=Reaction Times. Degrees of freedom are (1, 276) for all group analyses. Significant values ($p<.05$) are indicated in bold script.

In contrast to Study 1, accuracy rates of the fastest responses on incongruent trials differed between groups ($F(1, 274) = 4.10$, $p = .044$, $\eta_p^2 = .02$, $BF_{10} = 3.69$). The COM group demonstrated more fast errors, indicating stronger response capture, than the ASD group (Figure 6.5a-c). There was no main effect of gender ($F(1, 274) = 0.02$, $p = .904$, $\eta_p^2 = .00$, BF_{10}

= 1/7.11) nor an interaction effect ($F(1, 274) = 2.82$, $p = .095$, $\eta_p^2 = .01$), even though the Bayes factor of this interaction effect indicates that evidence is inconclusive ($BF_{10} = 1/1.35$). The gradient of the delta slope of the slowest responses was comparable across groups ($F(1, 274) = 1.52$, $p = .219$, $\eta_p^2 = .01$, $BF_{10} = 1/5.07$), indicating similar response suppression (Figure 6.5d-f). Gender did not seem to influence this result (main effect: $F(1, 274) = 3.24$, $p = .073$, $\eta_p^2 = .01$, $BF_{10} = 1.23$ [i.e., is inconclusive]; interaction: $F(1, 274) = 1.63$, $p = .203$, $\eta_p^2 = .01$, $BF_{10} = 1/2.51$).

On proactive control, as in Study 1, responses were faster ($BF_{10} > 100$) and more accurate ($BF_{10} > 100$) when congruent trials were preceded by congruent trials rather than when preceded by incongruent trials, and when incongruent trials were preceded by incongruent trials rather than when preceded by congruent trials (Table 6.6). In other words, the Simon effect was larger after congruent trials than after incongruent trials. Although this effect was again similar across groups on RTs ($BF_{10} = 1/4.85$), it was more pronounced in the COM group on accuracy ($BF_{10} = 1/1.39$) (Figure 6.6). Hence, albeit individuals without ASD might more strongly release control after a non-conflict situation when accuracy is considered, the Bayes factor shows that the evidence for this effect is anecdotal at best. Yet, cognitive control is enhanced after a conflict situation in both groups, revealed by a reduction of the Simon effect after incongruent trials.

Role of age

When examining the effect of age on reactive control, increasing age was associated with longer RTs ($F(1, 273) = 73.33$, $p < .001$, $\eta_p^2 = .21$, $BF_{10} > 100$), and higher accuracy rates ($F(1, 273) = 14.59$, $p < .001$, $\eta_p^2 = .05$, $BF_{10} > 100$). Whereas RTs were longer overall, independently of whether congruent or incongruent trials were presented (i.e., the RT Simon effect was not affected by age) ($F(1, 273) = 0.17$, $p = .680$, $\eta_p^2 = .00$, $BF_{10} = 1/23.26$), age interacted with congruency on accuracy ($F(1, 273) = 5.11$, $p = .025$, $\eta_p^2 = .02$), although there is little evidence for (or against) this effect ($BF_{10} = 1.03$). The association between increasing age and higher accuracy rates was significant on incongruent trials (B = .002, SE = .001, $t(1, 273) = 2.62$, $p = .009$) but not on congruent trials (B = .000, SE = .001, $t(1, 273) = 0.92$, $p = .359$) (i.e., the accuracy Simon effect became smaller with increasing age). Nevertheless, the role of age on reactive control did not differ across groups (RT: $F(1, 273) = 2.47$, $p = .117$, $\eta_p^2 = .01$, $BF_{10} = 1/9.66$; accuracy: $F(1, 273) = 1.09$, $p = .298$, $\eta_p^2 = .00$, $BF_{10} = 1/3.11$).

Although increasing age was related to a lower percentage of fast errors ($F(1, 276) = 5.04$, $p = .026$, $\beta = 0.13$, $R^2 = .02$, $BF_{10} = 1.43$), it was not when the whole model was considered ($p = .262$, $\beta = 0.08$, $BF_{10} = 1/2.03$), suggesting the effect of age to be small (Figure 6.7a). Also the Bayesian analysis provide little evidence for or against an age effect. However, increasing age yielded a steeper downward slope of the delta plot at longer RTs (Figure 6.7b) ($F(1, 276) = 6.28$,

p = .013, β = -0.15, R^2 = .02, BF_{10} = 2.55), which was even more pronounced when the whole model was considered (p = .007, β = -0.20, BF_{10} = 8.01). Hence, the strength of response capture is likely to be constant across the adult lifespan, whereas the efficiency of response suppression was increased in older adults. Both effects did not differ across groups (respectively, $t(273)$ = 0.97, p = .333, BF_{10} = 1/2.49, and $t(273)$ = 0.86, p = .391, BF_{10} = 1/2.78).

Age also affected the efficiency of proactive control (Figure 6.8). Older adults demonstrated a larger Simon effect after congruent trials than after incongruent trials compared to younger adults on RT ($F(1, 273)$ = 9.24, p = .003, η_p^2 = .03, BF_{10} = 8.73), but not on accuracy ($F(1, 273)$ = 0.96, p = .328, η_p^2 = .00, BF_{10} = 1/4.46). The role of age was similar in the two groups on both RT ($F(1, 273)$ = 2.83, p = .094, η_p^2 = .01, BF_{10} = 1/4.15) and accuracy ($F(1, 273)$ = 1.07, p = .302, η_p^2 = .00, BF_{10} = 1/2.64).

Table 6.6 Statistics of the group comparisons on proactive control (Study 2).

	RTs			Accuracy		
Factors	*F*	*p*	η_p^2	*F*	*p*	η_p^2
congruency	**838.85**	**<.001**	**.75**	**258.92**	**<.001**	**.49**
trial sequence	**41.75**	**<.001**	**.13**	**26.76**	**<.001**	**.09**
group	**8.10**	**.005**	**.03**	**6.21**	**.013**	**.02**
gender	0.43	.513	.00	**4.61**	**.033**	**.02**
group×gender	0.73	.394	.00	2.48	.116	.01
congruency×trial sequence	**1178.13**	**<.001**	**.81**	**499.23**	**<.001**	**.65**
group×congruency	1.57	.211	.01	0.53	.469	.00
gender×congruency	3.32	.069	.01	2.60	.108	.01
group×trial sequence	0.37	.546	.00	0.05	.821	.00
gender×trial sequence	0.01	.918	.00	3.44	.065	.01
group×gender×congruency	0.43	.510	.00	**4.16**	**.042**	**.02**
group×gender×trial sequence	0.34	.561	.00	0.23	.632	.00
group×congruency×trial sequence	1.23	.268	.00	**4.51**	**.035**	**.02**
gender×congruency×trial sequence	0.78	.377	.00	0.06	.814	.00
group×gender×congruency×trial sequence	1.13	.289	.00	0.53	.469	.00

Note. RTs=Reaction Times. Degrees of freedom are (1, 274) for all analyses. Significant values (p<.05) are indicated in bold script.

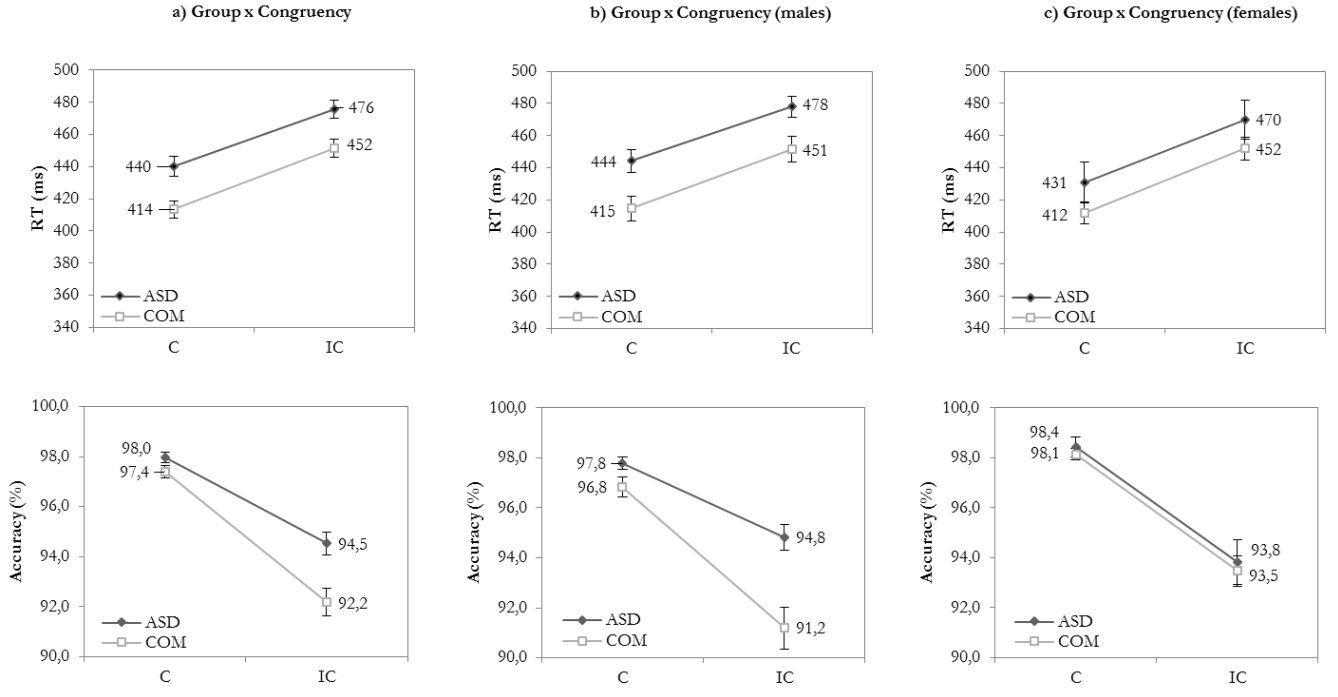

Figure 6.4 Mean reactions times (RTs) and accuracy rates for congruent and incongruent trials per group: **(a)** overall, **(b)** only males, and **(c)** only females (Study 2).

Note. ASD = autism spectrum disorder group; COM = comparison group; C = congruent; IC = incongruent. Error bars present standard errors.

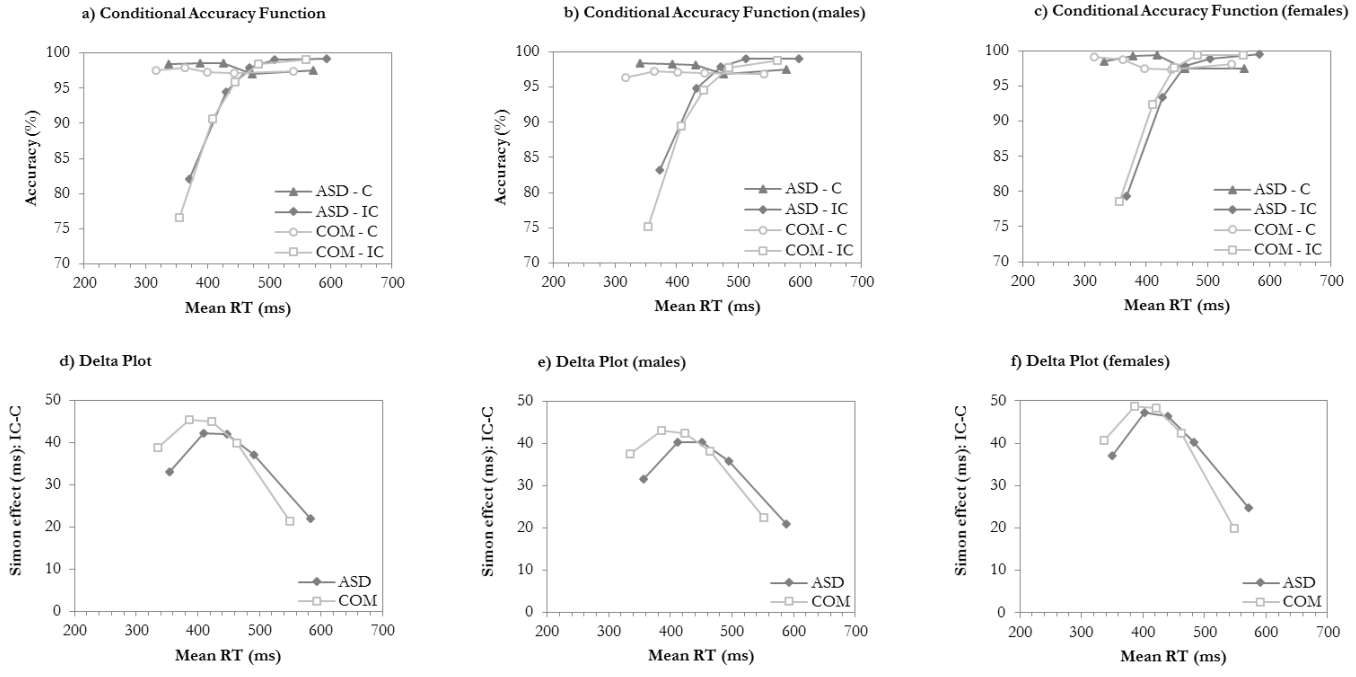

Figure 6.5 Conditional accuracy functions **(a)** overall, **(b)** only males, and **(c)** only females and delta plots **(d)** overall, **(e)** only males, and **(f)** only females per group (Study 2).

Note. ASD = autism spectrum disorder group; COM = comparison group; C = congruent; IC = incongruent.

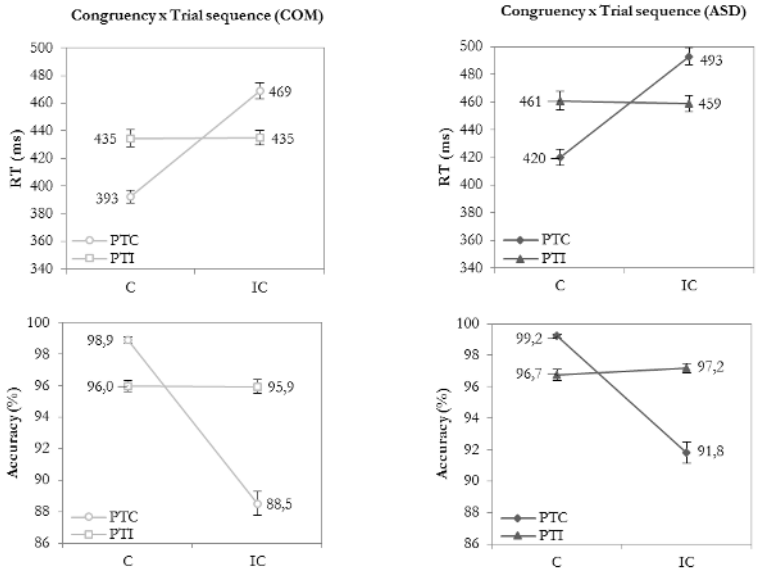

Figure 6.6 The congruency sequence effect per group (Study 2).

Note. ASD = autism spectrum disorder group; COM = comparison group; C = congruent; IC = incongruent; PTC = previous trial congruent; PTI = previous trial incongruent. Error bars present standard errors.

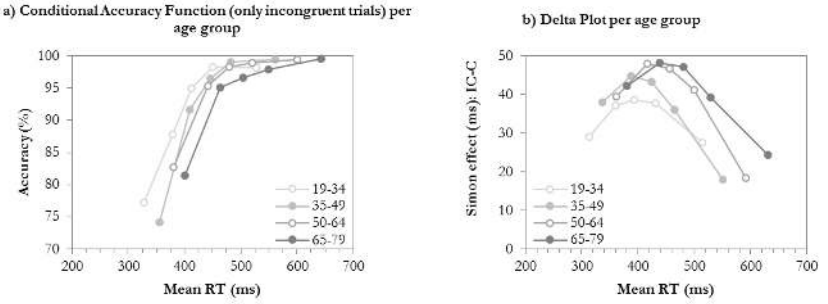

Figure 6.7 Exploratory **(a)** conditional accuracy functions for only incongruent trials and **(b)** delta plots per age group in years (Study 2).

Note. ASD = autism spectrum disorder group; COM = comparison group; C = congruent; IC = incongruent.

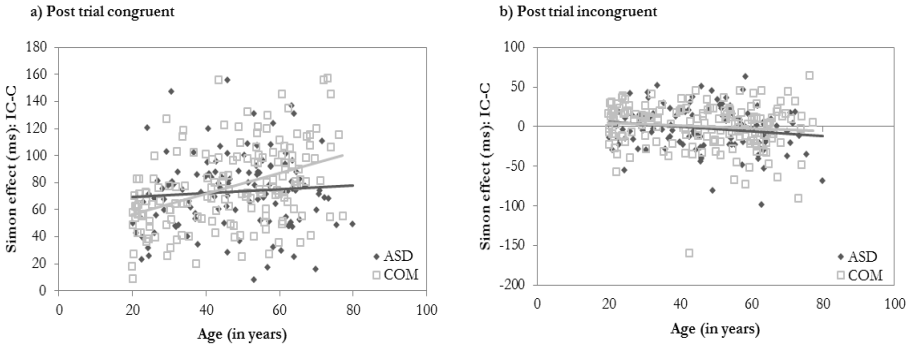

Figure 6.8 The (linear) effect of age plotted against the mean Simon effect for **(a)** post congruent trials and **(b)** post incongruent trials per group (the darkest line indicates the ASD group).
Note. ASD = autism spectrum disorder group; COM = comparison group.

Exploratory analyses

Given the somewhat contrasting findings between Study 1 and 2, we explored whether a subgroup with the same gender and age characteristics as in Study 1 would demonstrate a similar pattern as found in Study 1. Therefore, we selected only male participants between 19 and 36 years of age (ASD: n = 22; COM: n = 32) and reran all analyses. We replicated all results of Study 1. The Bayes factors were also comparable to those entailed in Study 1, ranging from BF_{10} = 1/3.97 (RT interaction reactive control) to BF_{10} = 1.86 (delta slope).

DISCUSSION STUDY 2

Despite slower RTs, adults with ASD showed more accurate responses compared to age- and IQ-matched controls and were not differently affected by interference from incongruent trials. Automatic response capture was reduced in adults with ASD, whereas deliberate response suppression was similar across groups. Exploratory Bayesian analyses supported these frequentist results and provided substantial to strong evidence in favor of or against the group-related hypotheses. Furthermore, females were more accurate than males, but this was mainly explained by the performance of the males without ASD who showed larger interference effects than males with ASD. Females with and without ASD performed similarly. Bayesian evidential strength for these results were, however, only anecdotal.

The proactive control mechanism of detecting and adjusting responses to previous trials, which results in a reduced interference effect on RT after conflict trials (Botvinick et al., 2001; Egner, 2007; Gratton et al., 1992), was also in Study 2 similar between adults with and

without ASD (Larson et al., 2012; Worsham et al., 2015). This indicates that both groups enhanced control after incompatible trials. Even though controls were more sensitive to interference after congruent trials, suggesting that they more strongly released control when a previous trial was a non-conflict trial, exploratory Bayesian analyses indicated no group effect. Hence, this latest finding should be interpreted with caution.

Slower and more accurate responses, and reduced response capture fit well together and converge to the idea of a more cautious response strategy among adults with ASD. Although the task instructions were to respond as fast and accurate as possible, individuals with ASD reported that they preferred to be accurate rather than fast, despite several attempts of the researchers to emphasize the importance of speed. Hence, adults with ASD seem to adopt a conservative response criterion.

Increasing age was associated with slower and more accurate responses as well, but we did not find evidence for a larger RT Simon effect in older adults. In regular Simon tasks, age-related differences have previously been reported to be absent (see Proctor, Miles, & Baroni, 2011; Vu & Proctor, 2008; Proctor et al., 2005), although in tasks that used spatial features for both the relevant and irrelevant stimulus dimensions, age changes have been reported (Castel, Balota, Hutchison, Logan, & Yap, 2007; Kawai et al., 2012; Pick & Proctor, 1999; Van der Lubbe & Verleger, 2002). This would suggest that older adults present problems suppressing irrelevant information (i.e., stimulus location) when the relevant stimulus dimension also contains spatial information, such as an arrow (Proctor et al., 2011).

Although age-related RT prolongation did not result in significantly fewer fast errors on incongruent trials, deliberate suppression on the slowest RTs was enhanced in older adults. These findings suggests that a more conservative approach is adopted with increasing age during reactive control. However, on proactive control, while age did not influence the RT Simon effect after incongruent trials (see also Puccioni & Vallesi, 2012; Yano, 2011), it did after congruent trials. Increasing age was related to greater interference when the congruent trial was followed by an incongruent trial. Yet, the CSE remains intact across adulthood (Puccioni & Vallesi, 2012; Yano, 2011).

GENERAL DISCUSSION

The aim of the current studies was to investigate the temporal dynamics underlying reactive and proactive interference control processes among adults with ASD. In the first study, we examined these processes in young adults by using a visual Simon task. In the second study, we tried to validate the findings in an independent sample and, moreover, examined to role of age.

Study 1 demonstrated that young adults with ASD present comparable interference control performance compared to young adults without ASD as measured with a Simon task. The findings of Study 1 and 2 converge, despite changing task parameters, when considering only young adults (18-36 years). Young adults with and without ASD performed similarly on reactive and proactive control, and on the underlying reactive control processes of response capture and response suppression. When considering large part of the adult lifespan (19-79 years) in Study 2, our results provide a partially different perspective. On reactive control, adults with ASD were slower but more accurate, and had reduced response capture but similar response suppression. On proactive control, as in Study 1, there were no differences between groups.

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. Slowing of RTs has been previously reported for individuals with ASD (Travers et al., 2014), but increased accuracy also suggests a shift in the balance between speed and accuracy. Typical aging is associated with diminished processing speed as well (e.g., Salthouse, 1996) and older adults take more time in making decisions and avoiding errors, whereas younger adults decide more quickly and find making errors more acceptable (Rabbitt, 1979; Salthouse, 1979; Smith & Brewer, 1995). Indeed, older adults adjust their behavior in order to minimize the number of errors against the cost of speed (Starns & Ratcliff, 2010). Older adults might also be less able to *estimate* the time or *control* the time of their responses and, therefore, provide slower responses (Rabbitt, 1979). A similar suggestion has been proposed for individuals with ASD (Falter, Noreika, Wearden, & Bailey, 2012). Hence, it seem that there are some similarities between the behavior of individuals with ASD and typically developing older adults (see Bowler, 2007, for the aging analogy in ASD).

The current results appear inconsistent with those entailed by a meta-analysis indicating that individuals with ASD present interference control difficulties (Geurts et al., 2014). Although in the meta-analysis no evidence for age affecting effect sizes was found, this might be due to the inclusion of only a few adult studies. The number of included adult studies may not have been sufficient to detect age-related differences. In addition, the type of task used might have affected the results. While the Simon task taps into processes related to response interference, the Eriksen flanker task also involves perceptual interference (Egner, 2007; van den Wildenberg et al., 2010). As our results suggest that response interference is not impaired among adults with ASD, the possibility that perceptual interference is affected in ASD should be evaluated. Indeed, individuals with ASD seem to demonstrate perceptual enhancement (e.g., Lever & Geurts, 2015; Mottron, Dawson, Soulieres, Hubert, & Burack, 2006; but see Van der Hallen et al., 2015) and it has been suggested that, therefore, they get more easily distracted (Adams & Jarrold, 2012).

Several limitations should be mentioned. First, we only included individuals with a normal-to-high intelligence. Whether our results generalize to the entire autism spectrum, including those individuals with an intellectual disability, remains unknown. Second, the cross-sectional nature of our study provides initial insights into age-related differences in interference control across adulthood in ASD, but does not allow to investigate changes over time (Raz & Lindenberger, 2011). Third, despite the suggestion of a more conservative response bias in ASD, there was an insufficient number of trials to examine speed-accuracy trade-off by means of, for example, diffusion models (Ratcliff & McKoon, 2008).

In sum, we used a cognitive framework to investigate interference control among adults with ASD, which provided the opportunity to not only examine overall measures but also underlying mechanisms involved in interference control processes. Across the adult lifespan, our findings do not support the idea of behaviorally impaired reactive and proactive interference control processes in ASD. Given our findings, it seems premature to conclude that the application of this cognitive dual-process model leads to an explanation for the observed heterogeneity among ASD studies on interference control (Geurts et al., 2014) and further research is, therefore, warranted. However, it does suggest that the framework is useful to disentangle different processes involved in interference control and it may contribute to an increased understanding of interference control among individuals with ASD.

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_{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, believes, 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 meta-cognitive 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, is 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, Thielscher, 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 Niekerk 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.

Dutch summary (Nederlandse samenvatting)

Autisme en veroudering:
Symptomatologie, bijkomende psychopathologie
en cognitief functioneren gedurende de levensloop

ACHTERGROND

Autismespectrumstoornissen (ASS) worden omschreven als heterogene, neurobiologische ontwikkelingsstoornissen die gekenmerkt worden door kwalitatieve beperkingen in sociale communicatie en sociale interactie en beperkte, repetitieve patronen van gedrag, interesses of activiteiten (American Psychiatric Association, 2000; American Psychiatric Association, 2013; Volkmar et al., 2004). ASS komt bij ongeveer 1% van de bevolking voor, ongeacht leeftijd (Brugha et al., 2011). Kenmerkende symptomen zijn afwijkend oogcontact, moeite met het aangaan en onderhouden van relaties, gefixeerde interesses en sensorische hypo- of hypergevoeligheid. Hoewel ASS in eerste instantie als een kindstoornis werd beschouwd (Kanner, 1943; Kanner, 1944) en onderzoek zich dus voornamelijk op kinderen heeft gericht (Mukaetova-Ladinska et al., 2012), wordt nu wel onderkend dat ASS ook gedurende de volwassenheid blijft bestaan (Gillberg & Steffenburg, 1987; Kanner, 1971; Rumsey et al., 1985). Omdat ASS voor het eerst in de jaren `40 werd beschreven (Asperger, 1944; Kanner, 1943) en het dus een relatief recente diagnose is, is het niet verrassend dat er nog heel weinig onderzoek is gedaan naar ASS bij oudere volwassenen (Happé & Charlton, 2012; Perkins & Berkman, 2012; Piven & Rabins, 2011; Wright et al., 2013). Het is echter wel relevant om meer over ASS in de volwassenheid te weten te komen. Als mensen met ASS ouder worden, dan moeten ze omgaan met de veranderingen die optreden als onderdeel van het verouderingsproces, maar ook met de moeilijkheden die geassocieerd worden met ASS. Daarnaast komen er steeds meer ouderen als gevolg van de vergrijzing. Dit betekent dat er mogelijk ook steeds meer ouderen met ASS zullen zijn die ondersteuning behoeven. Tot slot worden er steeds vaker ASS diagnoses pas in de volwassenheid gesteld, mede door verruiming en verandering van de diagnostische criteria en toegenomen kennis en bewustzijn van ASS. Dit proefschrift heeft dan ook als algemeen doel om meer kennis te vergaren over welke kenmerken wanneer gedurende de gehele volwassenheid op de voorgrond staan zodat behandeling en hulp hier op afgestemd kunnen worden.

Omdat er zo weinig bekend is over ASS gedurende de volwassen levensloop, hebben we ervoor gekozen om drie basale domeinen beter in kaart te brengen. Ten eerste hebben we ASS symptomen onderzocht. De diagnose ASS wordt gesteld op basis van gedragskenmerken en we wilden graag weten of en hoe deze kenmerken gedurende de levensloop veranderen (**Hoofdstuk 2**). Ten tweede hebben we bijkomende psychopathologie bestudeerd. Omdat mensen met ASS veel bijkomende psychische problemen ervaren, wilden we graag weten of deze problemen consequent gedurende de levensloop aanwezig zijn (**Hoofdstuk 3**). Tot slot hebben we onderzocht of volwassenen met ASS vergelijkbare leeftijd gerelateerde veranderingen in cognitief functioneren laten zien als volwassenen zonder ASS. We hebben ons hierbij gericht op

meerdere cognitieve domeinen, zoals geheugen en *theory of mind* (ToM; sociaal snapvermogen) (**Hoofdstuk 4**), werkgeheugen (**Hoofdstuk 5**) en interferentie controle (**Hoofdstuk 6**).

METHODE

De bevindingen van dit onderzoek (met uitzondering van Studie 1 beschreven in Hoofdstuk 6) zijn afkomstig van één grote groep volwassenen met een diagnose binnen het autisme spectrum (n_{max} = 241) en een vergelijkingsgroep van volwassenen zonder ASS (n_{max} = 199). Alle volwassenen waren tussen 19 en 79 jaar oud en hadden een geschat IQ van tenminste 80. De ASS groep is geworven via verschillende GGZ-instellingen en door middel van advertenties op de websites van cliëntorganisaties. De ASS diagnose was voor aanvang en onafhankelijk van dit project vastgesteld. Aanvullende diagnostische informatie kwam via een ASS vragenlijst (n = 237) en een diagnostisch observatie instrument (n = 142). De vergelijkingsgroep is benaderd via advertenties op de website van de universiteit en op *social media* en door middel van de sociale omgeving van de onderzoekers.

Gegevens voor dit onderzoek zijn tussen maart 2012 en juli 2014 verzameld door middel van psychologisch onderzoek bestaande uit vragenlijsten, interviews, en neuropsychologische en experimentele cognitieve tests. De grootte van de deelnemersgroep beschreven in elk hoofdstuk varieert als gevolg van het gebruikte instrument en het onderzoekdoel.

SYMPTOMATOLOGIE

In **Hoofdstuk 2** onderzochten we leeftijd gerelateerde verschillen in ASS symptomen. Door middel van vragenlijsten verkregen we informatie over ASS kenmerken, waaronder empathie en sensorische gevoeligheid (N_{max} = 435). Empathie is het inlevingsvermogen of de vaardigheid om de gedachten en gevoelens van anderen te begrijpen en bestaat uit zowel een cognitief als een affectief aspect (Davis, 1983). Sensorische gevoeligheid refereert zowel naar overgevoeligheid als ondergevoeligheid voor sensorische prikkels. Omdat een betekenisvolle bekende een belangrijk rol speelt bij ASS diagnostiek (National Institute for Health and Clinical Excellence, 2012), bijvoorbeeld voor het verschaffen van informatie over de ontwikkelingsgeschiedenis, en omdat er wel eens wordt getwijfeld aan de capaciteit van mensen met ASS om betrouwbare zelf-rapportage te geven (Frith, 2004; Johnson et al., 2009; Kievit & Geurts, 2011; maar zie De la Marche et al., 2015), hebben we zelf-rapportage vergeleken met rapportage door een bekende (bijvoorbeeld een partner, ouder of vriend; zogeheten proxy-rapportage).

In tegenstelling tot longitudinale onderzoeken bij jongere volwassenen die lieten zien dat de ernst van ASS symptomen over het algemeen afneemt met het ouder worden (bijv. Howlin et al., 2013; Piven et al., 1996; Woodman et al., 2015), vonden wij een piek in de middelbare volwassenheid wat betreft ASS kenmerken en sensorische gevoeligheid. Jongere en oudere volwassenen met ASS rapporteerden minder van deze symptomen dan volwassenen in de middelbare leeftijd. De perceptie van empathie werd niet beïnvloed door leeftijd.

Volwassenen met ASS rapporteerden meer ASS kenmerken en prikkelgevoeligheid en gaven aan minder te fantaseren en minder geneigd te zijn om het perspectief van een ander in te nemen dan controles. Tegelijkertijd maakten zij zich evenveel zorgen om anderen en voelden zij zich ongemakkelijker bij de emoties van anderen. Vrouwen met ASS rapporteerden meer ASS kenmerken en prikkelgevoeligheid dan mannen, terwijl dit bij controles juist andersom was. Deze bevindingen komen overeen met eerder onderzoek (Baron-Cohen et al., 2001; Crane et al., 2009; Minshew & Hobson, 2008; Rogers et al., 2007; zie Lai et al., 2011; Ruzich et al., 2015, voor een overzicht).

Tot slot vonden we dat de rapportages van mensen zelf en van hun betekenisvolle bekenden afweken. Proxies van mensen met ASS rapporteerden bijvoorbeeld meer sociale en minder sensorische symptomen en gaven geen verschillen in leeftijd en geslacht aan. De discrepantie tussen zelf- en proxyrapportage was echter zowel bij de mensen met ASS als bij de mensen zonder ASS aanwezig. Het lijkt daarom niet toepasselijk om te stellen dat er sprake is van verminderd zelfinzicht bij volwassenen met ASS. Er kan sprake zijn van een informanten bias (Hirschfeld, 1993; John & Robins, 1993; Leising et al., 2010), maar het kan ook zijn dat beide informanten verschillende ASS kenmerken herkennen en ervaren (Carlson et al., 2013).

Deze bevindingen zijn ook vanuit klinisch oogpunt relevant. Ten eerste suggereren de leeftijd gerelateerde verschillen in ASS symptomen dat het zinvol is om cliënten regelmatig gedurende de volwassen levensloop naar hun beleving van symptomen te vragen. Dit is dus niet alleen belangrijk als onderdeel van de diagnostiek, maar ook tijdens latere fases in het begeleidingstraject. Ten tweede geven deze resultaten aan dat mensen met ASS van middelbare leeftijd extra goed in de gaten gehouden zouden moeten worden omdat zij mogelijk extra steun en zorg nodig hebben. Ten derde is het belangrijk dat clinici rekening houden met man/vrouw verschillen bij het gebruik van zelfrapportage bij volwassenen met ASS zonder intellectuele beperking. Tot slot kunnen de verschillen in beleving tussen cliënten en hun betekenisvolle personen aanknopingspunten bieden voor het begrijpen van de ervaren problematiek (zie National Institute for Health and Clinical Excellence, 2012; Trimbos, 2013).

BIJKOMENDE PSYCHOPATHOLOGIE

Het doel in **Hoofdstuk 3** was het in kaart brengen van psychiatrische klachten en stoornissen bij volwassenen met ASS en het vergelijken van jonge, middelbare en oudere volwassenen hierin. Daarnaast zijn risicofactoren voor de meest voorkomende klachten en stoornissen onderzocht. Met behulp van vragenlijsten en een neuropsychiatrisch interview (N_{max} = 344) vonden we dat 79% van de volwassenen met ASS ooit in hun leven heeft voldaan aan de criteria voor een psychiatrische diagnose. Meest voorkomend waren stemmingsstoornissen (57%) en angststoornissen (54%). Deze percentages komen overeen met de bevindingen van eerdere studies bij jongere volwassenen (Hofvander et al., 2009; Lugnegård et al., 2011; Roy et al., 2015). Daarnaast bleken mensen met ASS gedurende de volwassenheid veel psychologische klachten te ervaren (zie ook van Heijst & Geurts, 2014). De ernst van deze klachten was echter vergelijkbaar met de klachten ervaren door een grote vergelijkingsgroep van poliklinische psychiatrische patiënten.

Een tweede bevinding was dat oudere volwassenen (55-80 jaar) minder vaak voldeden aan de criteria voor een psychiatrische diagnose dan jongere volwassenen. Hoewel dit aansluit bij de resultaten van grote cohort studies in de algemene populatie (Bijl et al., 1998; Kessler et al., 2005) en die van een eerdere studie bij volwassenen met ASS met een intellectuele beperking (Totsika et al., 2010), is het niet overeenkomstig met de enige andere studie gedaan bij oudere volwassenen met ASS zonder intellectuele beperking (Roy et al., 2015). We hebben dit verschil toegewezen aan de kleine groep en de definitie van "oudere volwassene" (40-62 jaar) in de eerdere studie. Psychische stoornissen zoals depressie komen met name bij volwassenen van middelbare leeftijd meer voor (Bijl et al., 1998; Kessler et al., 2005). Aangezien de volwassenen in de Roy studie (2015) veelal van middelbare leeftijd waren terwijl onze oudere groep bestond uit volwassenen van 55-80 jaar, lijkt de discrepantie hieraan toe te schrijven. We vonden ook dat depressie het meest voorkwam bij volwassenen met ASS van middelbare leeftijd en dat sociale fobie minder prevalent was bij ouderen met ASS.

Van de potentiele risicofactoren die we hebben meegenomen in onze analyses (zelf gerapporteerde en geobserveerde ernst van ASS, geslacht, sociaal economische status [opleiding en werk], woonsituatie, geschat IQ en algemeen cognitief functioneren) bleken ernst van ASS symptomen geassocieerd met depressieve en angstklachten. Daarnaast hingen zelf gerapporteerde ASS kenmerken samen met de aanwezigheid van angststoornissen gedurende de levensloop en, na de jongvolwassenheid, was vrouw-zijn een risicofactor voor stemmingsstoornissen.

In de middelbare volwassenheid zien we dus niet alleen een piek in ASS symptomen, maar ook in depressie. Dit suggereert dat het belangrijk is om deze volwassenen goed te monitoren en te zoeken naar adequate steun en zorg om hun situatie te verlichten en hun welbevinden te verbeteren.

COGNITIEF FUNCTIONEREN

Veroudering wordt geassocieerd met een achteruitgang in cognitief functioneren. Mensen krijgen bijvoorbeeld meer moeite met het onthouden van nieuwe informatie, met het actief houden van informatie, of met het bedenken van woorden en nieuwe oplossingen (generativiteit) (Borella et al., 2008; Friedman et al., 2009; Goh et al., 2012; Hasher & Zacks, 1988; Hultsch, 1998; Nyberg et al., 2012; Park et al., 2002; Park & Reuter-Lorenz, 2009; Salthouse, 1996; Salthouse, 2009; Verhaeghen & Cerella, 2002). Sommige van deze cognitieve problemen zijn ook aanwezig bij kinderen, adolescenten en jongvolwassenen met ASS (Boucher et al., 2012; Geurts et al., 2014; O'Hearn et al., 2008; Russell, 1997). Gezien deze overeenkomst tussen typische veroudering en ASS is het de vraag wat er gebeurt als mensen met ASS ouder worden.

In Hoofdstuk 4, 5 en 6 stond de vraag centraal of volwassenen met ASS een ander leeftijd gerelateerd patroon van veroudering laten zien vergeleken met controles. We hebben dit onderzocht door middel van een uitgebreide neuropsychologische testbatterij (Hoofdstuk 4) en experimentele testen (Hoofdstuk 5 en 6). Gebaseerd op de bevindingen van de allereerste groepsstudie bij ouderen met ASS waarbij cognitie is onderzocht (Geurts & Vissers, 2012), hebben we drie mogelijke hypotheses opgesteld. Ten eerste zouden volwassenen met ASS een vergelijkbaar verouderingspatroon kunnen laten zien (parallel). Ten tweede zou er sprake kunnen zijn van een verslechterend of versneld verouderingspatroon bij ASS (*double jeopardy*) waarbij leeftijd gerelateerd verschillen tussen volwassenen met en zonder ASS steeds groter worden. ASS en veroudering zouden dan twee factoren zijn die elkaar versterken. Ten derde zou er een verminderend verouderingspatroon verwacht kunnen worden bij ASS (*safeguard*), bijvoorbeeld doordat mensen met ASS compensatiemechanismen hebben ontwikkeld.

Geheugen, generativiteit en theory of mind

In **Hoofdstuk 4** vonden we op geen enkel domein evidentie voor een versneld verouderingspatroon (N_{max} = 236). Het patroon was parallel (verbaal geheugen, generativiteit, en ToM) of verminderd (visueel geheugen) in volwassenen met ASS vergeleken met controles. Deze bevindingen komen grotendeels overeen met eerder onderzoek (Geurts & Vissers, 2012).

Daarnaast toonden we aan dat cognitieve sterktes en zwaktes in de volwassenheid grotendeels blijven bestaan. Volwassenen met ASS vergeleken met controles, presteerden vergelijkbaar op verbaal geheugen, beter op de visueel geheugen, en minder goed op generativiteit en ToM. Een interessante bevinding was dat ToM problemen die vaak gevonden worden bij ASS (Boucher, 2012; Yirmiya et al., 1998; maar zie Scheeren et al., 2013), verdwenen bij oudere volwassenen met ASS. Ondanks dat slechts een paar mensen met ASS klinisch afwijkende prestaties lieten zien, werden er zeer veel cognitieve klachten gerapporteerd door volwassenen met ASS. Er was nauwelijks samenhang tussen prestaties op testen en de subjectief ervaren klachten. Het kan zo zijn dat mensen met ASS het nodig achten om veel klachten te rapporteren opdat zij adequate hulp krijgen, maar dit lijkt niet waarschijnlijk omdat proxies zelfs nog meer moeilijkheden rapporteren als het om symptomatologie gaat dan de mensen met ASS zelf (Hoofdstuk 2). Het kan echter ook te maken hebben met een focus op details of met het versterkt ervaren van bepaalde gevoelens, gedachtes of situaties. In combinatie met het moeilijk vinden om eigen klachten in perspectief te plaatsen, kunnen wellicht kleine cognitieve foutjes geïnterpreteerd worden als daadwerkelijke moeilijkheden in plaats van iets dat door meerdere personen wordt ervaren of passend is bij een bepaalde levensfase. Verder kunnen persoonlijkheidskenmerken, bijkomende psychologische problemen of gezondheidsproblemen een rol spelen. Tot slot kan het zijn dat neuropsychologische testen dagelijkse problemen niet oppikken.

Naast het onderzoeken van cognitieve functies door middel van neuropsychologische tests die in de klinische praktijk veel worden gebruikt, hebben we twee executieve functies specifieker onderzocht door middel van experimentele tests. Hierdoor kunnen onderliggende processen en eventuele problemen hierin beter in kaart worden gebracht. Executieve functies zijn cognitieve functies die gebruikt worden voor het controleren, coördineren en uitvoeren van doelgericht gedrag, zoals werkgeheugen (Hoofdstuk 5) en interferentiecontrole (Hoofdstuk 6). Deze twee domeinen worden beide geassocieerd met de temporele integratie van informatie (Fuster, 2002).

Werkgeheugen

Ook in **Hoofdstuk 5** vonden we geen bewijs voor een versneld verouderingsproces van werkgeheugen (N = 275). Werkgeheugen is het vermogen om informatie tijdelijk vast te houden en te bewerken voor het uitvoeren van doelgericht gedrag. Controles lieten een geleidelijke achteruitgang zien in werkgeheugen, terwijl ouderen met ASS zelfs iets beter leken te worden. Hoewel passend bij een *safeguard* patroon, moet dit resultaat echter zeer voorzichtig geïnterpreteerd worden. Door middel van Bayesian analyses waarmee we de evidentie voor een

bepaalde hypothese ten opzichte van een andere hypothese konden toetsen, lieten we namelijk zien dat evidentie voor een leeftijdseffect bij volwassenen met ASS heel erg klein is.

Daarnaast vonden we dat volwassenen met ASS niet slechter presteerden op een werkgeheugen taak dan volwassenen zonder ASS. Wel hadden mensen met ASS meer tijd nodig om tot een vergelijkbare prestatie te komen. Deze bevindingen waren tegenstrijdig met onze verwachtingen, maar kunnen verklaard worden doordat de taak niet moeilijk genoeg was, doordat verbaal werkgeheugen een belangrijkere rol speelde dan verwacht, of door individuele verschillen. Hoewel kinderen met ASS werkgeheugenproblemen lieten zien op een vergelijkbare taak, waren slechts een paar kinderen verantwoordelijk voor dit groepsverschil (de Vries & Geurts, 2014). Het kan dus zijn dat werkgeheugenproblemen voorkomen bij een kleine groep volwassenen, maar dit zou in toekomstig onderzoek verder onderzocht moeten worden.

Tot slot hebben we onderzocht of we leeftijd gerelateerde verschillen in werkgeheugen konden voorspellen aan de hand van een aantal factoren die samenhangen met achteruitgang van werkgeheugen bij typische veroudering en die een rol spelen bij ASS, zoals ASS ernst, geslacht, psychopathologie, opleiding, geschat IQ, en verwerkingssnelheid. Alleen IQ bleek een voorspeller, maar dit resultaat moet voorzichtig geïnterpreteerd worden gezien de grote heterogeniteit van de groep met een lager IQ.

Interferentiecontrole

In **Hoofdstuk 6** hebben we interferentiecontrole bestudeerd in twee onafhankelijke volwassen steekproeven (Studie 1: N = 42; Studie 2: N = 278). Interferentiecontrole is het vermogen om irrelevante informatie te negeren. Door middel van distributieanalyses konden we de temporele dynamiek bekijken die ten grondslag ligt aan interferentiecontrole processen, zoals reactieve controle (het vermogen om een conflict tussen een automatische respons en een intentionele respons die tot het gewenste gedrag leidt te detecteren en op te lossen) en proactieve controle (het vermogen om te anticiperen op een conflict). Ten eerste vonden we ook hier geen bewijs voor een versnelde achteruitgang bij ASS. Op zowel reactieve als proactieve controle lieten volwassenen met en zonder ASS hetzelfde patroon zien (parallel). Ten tweede zagen we een vergelijkbare reactieve en proactieve controle bij volwassenen met en zonder ASS. Desondanks was er een belangrijk verschil tussen jonge mannen (Studie 1) en middelbare en oudere mannen en vrouwen (Studie 2). Over de volwassen levensloop waren mensen met ASS trager, maakten ze minder fouten en waren ze minder gevoelig voor snelle foutieve responsen als gevolg van een conflict dan controles. Dit verschil kwam niet naar voren bij jonge mannen met ASS. Deze bevindingen doen vermoeden dat middelbare en oudere volwassenen met ASS een voorzichtiger responsstrategie hanteren die nog niet geobserveerd wordt bij jongvolwassenen.

CONCLUSIE

De resultaten beschreven in dit proefschrift zijn gebaseerd op de eerste grote cross-sectionele cohort studie bij volwassenen met een leeftijd tot 80 jaar. Onze bevindingen kunnen worden samengevat in vier hoofdconclusies. Een eerste belangrijke conclusie is dat we geen bewijs hebben gevonden voor een versneld verouderingspatroon bij deze specifieke groep van volwassenen met ASS. Hoewel cognitief functioneren op verschillende domeinen achteruitgaat bij mensen met ASS, is dit vergelijkbaar met de leeftijd gerelateerde verschillen die we zien bij volwassenen zonder ASS. Er zijn zelfs domeinen waarbij volwassenen met ASS een mindere sterke achteruitgang laten zien. Mogelijk kan dit voor mensen met ASS een geruststelling zijn.

Een tweede belangrijke bevinding is dat cognitieve problemen die op de voorgrond kunnen staan bij kinderen en adolescenten met ASS, zoals (werk)geheugenproblemen en problemen met het onderdrukken van afleidende informatie, niet meer aanwezig lijken te zijn in de volwassenheid. Moeilijkheden met het genereren van nieuwe oplossingen blijven echter wel bestaan. Interessant genoeg wijzen onze resultaten er op dat verschillen ToM tussen ouderen met en zonder ASS verdwijnen. Eventuele cognitieve problemen lijken echter gering bij deze groep volwassenen en zijn slechts bij een klein aantal mensen als klinisch afwijkend te beschouwen. De geobserveerde sterktes in cognitief functioneren bieden een bruikbaar aanknopingspunt voor interventies voor volwassenen en ouderen met ASS.

Ondanks dat cognitieve problemen niet op de voorgrond lijken te staan, ervaren volwassenen met ASS enorm veel klachten en een laag welbevinden (resultaten niet gerapporteerd in proefschrift). Ze rapporteren ernstige ASS symptomatologie en psychologische klachten en psychische stoornissen komen veelvuldig voor. Aansluitend bij deze derde conclusie, is dat de perceptie van ASS kenmerken en depressie het hoogst is bij volwassenen op middelbare leeftijd. Dit geeft aan dat het belangrijk is om in de klinische praktijk regelmatig te vragen naar de beleving van symptomen en psychische klachten en rekening te houden met de kwetsbaarheid van deze mensen.

Tot slot kunnen we concluderen dat er belangrijke verschillen zijn tussen subjectieve beleving en objectieve maten en tussen persoonlijke beleving en de beleving van een betekenisvolle informant (zoals een partner, ouder of vriend). Terwijl de eerste discrepantie aanleiding geeft om uit te zoeken waar de verschillen vandaan komen, laat de tweede discrepantie zien dat het belangrijk is om meerdere bronnen te betrekken bij de diagnostiek (zie ook Trimbos, 2013).

Hoewel individuele veranderingen in symptomatologie, bijkomende psychopathologie en cognitief functioneren niet konden worden onderzocht in dit proefschrift, is een longitudinaal

design de volgende stap waaraan we werken. Desondanks geven de huidige bevindingen relevante inzichten voor ASS in de klinische praktijk en in de maatschappij. ASS is een ontwikkelingsstoornis waarbij veel veranderingen optreden gedurende de levensloop en die een levenslange impact heeft. Dit suggereert dat adequate interventies en ondersteuning om de persoonlijke last van volwassenen met ASS te verminderen noodzakelijk zijn.

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List of abbreviations

ADHD	Attention deficit hyperactivity disorder
ADOS	Autism diagnostic observation schedule
AN(C)OVA	Analysis of (co)variance
AQ	Autism-spectrum quotient
ASD	Autism spectrum disorder
BF	Bayes factor
CAF	Conditional accuracy function
CFQ	Cognitive failures questionnaire
CI	Confidence interval
COM	Comparison group
COWAT	Controlled oral word association test
CSE	Congruency sequence effect
DSM	Diagnostic and statistical manual of mental disorders
EF	Executive functions
GAD	Generalized anxiety disorder
GIT	Groninger intelligentie test
ICC	Intra-class correlation coefficient
ICD	International classification of diseases and related health problems
ID	Intellectual disability
IQ	Intelligence quotient
IRI	Interpersonal reactivity index
ISCO	International standard classification of occupations
MAN(C)OVA	Multivariate analysis of (co)variance
MINI	Mini international neuropsychiatric interview
MMSE	Mini mental state examination
OCD	Obsessive compulsive disorder
PDD-NOS	Pervasive developmental disorder not otherwise specified
PDyD	Premenstrual dysphoric disorder
PTC	Preceding trial congruent
PTI	Preceding trial incongruent
PTSS	Post-traumatic stress disorder
RAVLT	Rey auditory verbal learning task

RRBI	Restricted, repetitive behaviors and interests
RT	Reaction time
SCID	Structured clinical interview for DSM-IV
SCL-90-R	Symptom checklist 90 revised
SSQ	Sensory sensitivity questionnaire
ToM	Theory of mind
WAIS	Wechsler adult intelligence scale
WHO	World health organization
WM	Working memory
WMS	Wechsler memory scale

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Curriculum Vitae, publications, and author contributions

Curriculum Vitae

Anne Geeke Lever was born in Apeldoorn, the Netherlands, in 1985. After graduating from secondary school (Staring College, Lochem), she travelled to Italy to do voluntary work in an elderly home. This experience contributed to her decision to study neuropsychology at the University of Turin, where she obtained her bachelor's degree cum laude in 2008. As part of her two year interdisciplinary master in mind sciences, she went to England for a research internship in experimental psychology at the University of Birmingham. She participated in a project on interpersonal memory based guidance of attention supervised by prof. Glyn W. Humphreys and became co-author on a peer-reviewed publication of this project. This work also constituted the basis for her master thesis, written under supervision of prof. Maurizio Tirassa. She graduated cum laude in 2011 at the University of Turin. Later that year she started her PhD project entitled "Aging in Autism: Symptomatology, co-occurring psychopathology, and cognitive functioning across the adult lifespan" under supervision of prof. dr. Hilde M. Geurts and prof. dr. K. Richard Ridderinkhof at the University of Amsterdam, the Netherlands. To further increase her knowledge on aging, she became a visiting student at the Lifespan Psychology department of the Max Planck Institute for Human Development in Berlin, Germany. Currently, she holds a part-time position as an assistant professor in clinical neuropsychology at the University of Amsterdam and as a postdoc at the VU medical center.

International peer-reviewed publications

Lever, A.G. & Geurts, H.M. (2016). *Quality of life in autism spectrum disorders from young to late adulthood.* Manuscript in preparation.

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Lever, A.G., Ridderinkhof, K.R., Marsman, M., & Geurts, H.M. (2016). *Reactive and proactive interference control in adults with autism spectrum disorder across the lifespan.* Manuscript under review.

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Other publications

Geurts, H.M., & **Lever, A.G.** (2016). The clinical neuropsychology of ASD. In: B. Barahona Correa and R.J. van der Gaag (Eds). *Autism spectrum disorders in adults.* Springer.

Geurts, H.M., Koolschijn, P.C.M.C., & **Lever, A.G.** (2014). Veroudering bij mensen met autisme: Versnelde achteruitgang? *Sterk! In Autisme. Autisme Centraal*, *1*, 3-7.

Lever, A.G, & Geurts, H.M. (2013). Een nieuw instrument voor sensorische gevoeligheid. *Wetenschappelijk Tijdschrift Autisme*, *2*, 68-73.

Oral presentations

Lever, A.G., & Geurts, H.M. (2016, May). *ASD-Related and Psychiatric Symptomatology Across the Adult Lifespan.* Meeting of International Society for Autism Research (IMFAR), Baltimore, United States.

Lever, A.G., Werkle-Bergner, M., Brandmaier, A.M., Ridderinkhof, K.R., & Geurts, H.M. (2015, December). *Working memory across the adult lifespan: Do individuals with and without autism show differential age-related decline?* Meeting of Dutch Society for Psychonomics (NVP), Egmond aan Zee, the Netherlands.

Lever, A.G. (2015, December). Aging in Autism: A lifespan perspective on symptomatology, comorbidity, and cognitive functioning. Talk at the Brown Bag Meeting, Brain & Cognition, Department of Lifespan Psychology, University of Amsterdam, the Netherlands.

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Lever, A.G., & Geurts, H.M. (2015, April). *Do Cognitive Challenges of Adults with Autism Persist, Abate or Increase into Old Age?* Meeting of Aging & Cognition, Dortmund, Germany.

Lever, A.G. (2014, September). Aging in Autism. Talk at the Max Planck Institute for Human Development, Department of Lifespan Psychology, Berlin, Germany.

Geurts, H.M. & **Lever, A.G.** (2014, May). *Self-reports of ASD symptomatology, cognition, & quality of life in adults (19 to 79 years) with ASD and without intellectual disabilities.* International Society for Autism Research (IMFAR), Atlanta, United States.

Refereed poster presentations

Lever, A.G., & Geurts, H.M. (2016, March). *Lifelong lasting? Self- and other-reported ASD symptoms across adulthood.* National Autism Meeting, Rotterdam, the Netherlands.

Lever, A.G., & Geurts, H.M. (2016, March). *Psychiatric co-occurring symptoms and disorders in young, middle-aged, and older adults with autism spectrum disorder.* National Autism Meeting, Rotterdam, the Netherlands.

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Author contributions

Chapter 2

Lever, A.G. & Geurts, H.M. (2016). *Lifelong lasting? Self- and other-reported ASD symptoms across adulthood*. Manuscript submitted.

AGL participated in the design and the execution and coordination of the study, performed measurements and the statistical analysis and interpretation of the data, and wrote the manuscript; HMG supervised the study, participated in the design, the set-up of the statistical plan and interpretation of the data, and reviewed the manuscript.

Chapter 3

Lever, A.G. & Geurts, H.M. (2016). Psychiatric co-occurring symptoms and disorders among young, middle-aged, and older adults with autism spectrum disorder. *Journal of Autism and Developmental Disorders*. Advanced online publication, doi:10.1007/s10803-016-2722-8.

AGL participated in the design and the execution and coordination of the study, performed measurements and the statistical analysis and interpretation of the data, and wrote the manuscript; HMG supervised the study, participated in the design, the set-up of the statistical plan and interpretation of the data, and reviewed the manuscript.

Chapter 4

Lever, A.G. & Geurts, H.M. (2015). Age-related differences in cognition across the adult lifespan in autism spectrum disorder. *Autism Research*. Advanced online publication, doi:10.1002/aur.1545.

AGL participated in the design and the execution and coordination of the study, performed measurements and the statistical analysis and interpretation of the data, and wrote the manuscript; HMG supervised the study, participated in the design, the set-up of the statistical plan and interpretation of the data, and reviewed the manuscript.

Chapter 5

Lever, A.G., Werkle-Bergner, M., Brandmaier, A.M., Ridderinkhof, K.R., & Geurts, H.M. (2015). Atypical working memory decline across the adult lifespan in autism spectrum disorder? *Journal of Abnormal Psychology, 124(4),* 1014-1026.

AGL participated in the design and the execution and coordination of the study, performed measurements and the statistical analysis and interpretation of the data, and wrote the manuscript; MWB participated in the set-up of the statistical plan and interpretation of the data, provided conceptual contributions to and reviewed the manuscript; AMB participated in the set-up of the statistical plan and interpretation of the data, helped with the data analyses, and reviewed the manuscript; KRR participated in the set-up of the statistical plan and interpretation of the data, and reviewed the manuscript; HMG supervised the study, participated in the design, the set-up of the statistical plan and interpretation of the data, and reviewed the manuscript.

Chapter 6

Lever, A.G., Ridderinkhof, K.R., Marsman, M., & Geurts, H.M. (2016). *Reactive and proactive interference control in adults with autism spectrum disorder across the lifespan*. Manuscript under review.

AGL participated in the design and the execution and coordination of the study, performed measurements and the statistical analysis and interpretation of the data, and wrote the manuscript; KRR supervised the study, participated in the set-up of the statistical plan and interpretation of the data, and reviewed the manuscript; MM provided conceptual contributions to and helped with the Bayesian data analyses; HMG supervised the study, participated in the design, the set-up of the statistical plan and interpretation of the data, and reviewed the manuscript.