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

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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, & Scery, 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 [RRBs]) to a dyad (i.e., social-communication impairments and RRBs), and the addition of atypical sensory behavior as a RRB 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 Niikerk 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,
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, Breweaes, 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, Desprès, 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, Mukactova-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.