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DOI
10.1016/j.neubiorev.2016.09.003

Publication date
2016

Document Version
Final published version

Published in
Neuroscience and Biobehavioral Reviews

License
Article 25fa Dutch Copyright Act

Citation for published version (APA):
changing ASD-ADHD symptom co-occurrence across the lifespan with adolescence as crucial time window: Illustrating the need to go beyond childhood

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Abstract

Literature on the co-occurrence between Autism Spectrum Disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) is strongly biased by a focus on childhood age. A review of the adolescent and adult literature was made on core and related symptoms of ADHD and ASD. In addition, an empirical approach was used including 17,173 ASD-ADHD symptom ratings from participants aged 0 to 84 years. Results indicate that ASD/ADHD constellations peak during adolescence and are lower in early childhood and old age. We hypothesize that on the border of the expected transition to independent adulthood, ASD and ADHD co-occur most because social adaptation and EF skills matter most. Lower correlations in childhood and older age may be due to more diffuse symptoms reflecting respectively still differentiating and de-differentiating EF functions. We plea for a strong research focus in adolescence which may –after early childhood– be a second crucial time window for catching-up pattern explaining more optimal outcomes. We discuss obstacles and opportunities of a full lifespan approach into old age.

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1. Background and aim

Autism spectrum disorder (ASD) and Attention-Deficit/Hyperactivity Disorder (ADHD) frequently co-occur. In clinical practice, we daily struggle deciding if one, or the other, or both disorders, best describe the child’s problems (e.g., Costello et al., 2011; Grzdziński et al., 2016; Miodovnik et al., 2015). In part, this co-occurrence may be due to common etiological mechanisms (Doherty and Owen, 2014; Johnson et al., 2015; Rommelse et al., 2010, 2011; Rommelse and Hartman, 2016; Ronald and Hoekstra, 2011). A large body of literature has convincingly shown that many similarities are present in genetic factors, functional and structural brain characteristics, and cognitive profiles. However, these studies included predominantly children (∼6–11 year olds). Despite everyone’s awareness of change in the mechanisms underlying the development of an individual until elderly age in typical development, studies on neurodevelopmental disorders like ADHD and ASD have remained strongly focused on childhood (see Fig. 1). Age of onset for ASD and ADHD is nearly always in childhood (Mohr Jensen and Steinhausen, 2015; but see Moffitt et al., 2015), and a research focus on etiology rather than course is one likely reason for this bias. Another related reason is that it is easier to recruit children during the school age years at which point in time they are referred to outpatient clinics than later on. Such studies are mostly cross-sectional, due to the costs involved in longitudinal follow-up. Yet, the necessary step forward to further our understanding the co-occurrence of ADHD and ASD is to document how behavior relevant for ADHD and ASD changes over the lifespan. Co-occurrence need not only to originate from shared etiological factors involved in the onset but also from factors that determine the course of both disorders. These are often not the same (e.g., Pingault et al., 2015). The extent to which these are shared between ADHD and ASD may change over the lifespan. As a first aim, the present paper provides a review of the lifespan literature, focusing on ADHD and ASD core symptoms as well related (social) behaviors including executive function which have been shown impaired in both disorders, and how these patterns of development relate to normative development. Given that several recent reviews and meta-analyses have extensively documented on the co-occurrence of ADHD and ASD in the (early) childhood years (∼0–11 years; Doherty and Owen, 2014; Johnson et al., 2015; Rommelse et al., 2010, 2011; Ronald and Hoekstra, 2011), we only briefly refer to this childhood literature and will focus this paper on the much less studied and therefore much more fragmented findings beyond childhood instead. This implies a shift from etiology to course of both disorders. As a second aim, the present paper will empirically illustrate the association between ASD and ADHD symptoms over the life-course (0–84 years), by combining multiple samples with dimensional measures of ASD and ADHD. Our work will illustrate the need for a lifespan-approach in studying ASD-ADHD co-occurrence, reveal the major obstacles that need to be overcome when moving our research beyond childhood years, but also substantiate what can already be done in the short-term to advance our knowledge.

2. Literature review

Electronic literature searches via PubMed were conducted for articles that were published in the English language (unlimited by date of publication). We searched for empirical studies with respondents beyond age 12. We used broad search terms in order not to miss out on relevant work, subsequently scrutinizing abstracts, and the full text, in selected papers that reported on findings relevant in relation to developmental aspect of core symptoms, related (social) behavior, and executive functioning. Both original
research articles as well as meta-analyses, systematic, and narrative reviews were included, and references in these papers were checked for additional relevant literature. We were particularly keen on finding studies with a developmental focus with multiple measures over time in order to capture possible longitudinal change. We confined ourselves to studies based on humans and filtered out those that were not described in English. Given that the information we were after is oftentimes “hidden” in papers (e.g., although not apparent from the title that a paper had a developmental focus, a correlation between age and symptoms could be provided), our research strategy was to employ a very lenient threshold at the level of inclusion based on the title, after which we made a more stringent selection of those paper that provided relevant developmental information. The following combination of keywords was employed: (“autism or ASD or ADHD) and (lifespan or “life course” or longitudinal or prospective or developmental) and (adolescents or adults or elderly) or (“attention problems” or impulsivity or hyperactivity) and (lifespan or “life course” or longitudinal or prospective or developmental) and (adolescents or adults or elderly) or (“executive functioning” or “cognitive control” or “effortful control” or “impulse control” or “attentional control” or “behavioral control”) and (lifespan or “life course” or longitudinal or prospective or developmental) and (adolescents or adults or elderly) or (“social development” or “theory of mind” or “social skills” or “social cognitive development”) and (lifespan or “life course” or longitudinal or prospective or developmental) and (adolescents or adults or elderly)). A detailed description of the different steps that were taken when searching the literature is provided in part 1 of the Supplementary file. Fig. 2 presents a PRISMA flow diagram depicting a summary of our selection procedure. In all, our search yielded 194 papers eligible which were studied carefully for inclusion in this review.

In what follows, the domains of core (and related) ADHD and ASD symptoms and executive functioning problems are covered, in this order. Each section starts with a brief discussion on the normal developmental pattern, followed by the findings for ADHD, then ASD and –if available– by findings directly related to both. All sections end with a summary.

2.1. Developmental change in core symptoms

2.1.1. Typical development

Major developments in activity, attention, regulation of behavior, social motivation and competence are in the (early) childhood years. Developmental progress in these functions and skills is typically different or lagging behind in children with ADHD and ASD given their (later onset of) core problems of inattention, hyperactivity, impulsivity, stereotypies, and social interest and understanding. Being on a different developmental path, individuals with ADHD and ASD will have less and different opportunities to practice attention, restraint, and reciprocity in social relations relative to typically developmental individuals. A lifespan understanding thereof thus requires an understanding of normative development. For example, particularly the development of attentional skills characterize childhood. This, in turn, has been strongly linked to the regulation of emotion and behavior offering additional insight into precursors or course modifiers of psychopathology including ASD and ADHD (Swingler et al., 2015). Likewise, theory of mind development, important for social understanding, shows a strong normative progress in early childhood years although development extends into adulthood (Andrews-Hanna et al., 2011;
Burnett et al., 2011; Lagattuta et al., 2015; Vetter et al., 2014). In adolescence, it is normative that attention and the regulation of behavior are put increasingly into practice in order to meet progressing demands at school. Self-initiated and prolonged study of diverging subjects and the planning and timely execution of homework are normatively rapidly developing skills (Karbach and Unger, 2014). Also in adolescence social skills are strongly put to the test and ‘exercised’ given the normative shift from parents to peers as the main social interaction partners (Véronneau et al., 2014). Individual differences in empathy at the start of adolescence as well as the increase in empathy over the adolescent years are predictive of social competencies two decades later, indicating the relevance of adolescence for social consequences in adulthood (Allemand et al., 2015). Starting young adulthood, normative behavior includes taking on more and more adult roles requiring EF and social Miller et al., 2008 skills including self-care, functioning at and maintaining work, finding and keeping a partner, and starting a family (Reale and Bonati, 2015). On the other end of the lifespan, with increasing age in late adulthood, attention skills, self-awareness, reciprocal social interaction, cognitive empathy, and theory of mind abilities undergo a differential rate of decline, with deteriorating cognitive empathy and theory of mind abilities partly driven by a decline in general cognitive abilities (e.g. processing speed, EF) (Bottiroli et al., 2016; Castelli et al., 2011; Moran et al., 2012; Palmer et al., 2014; Pardini and Nichelli, 2009; Phillips et al., 2011; Rakoczy et al., 2012). The Neuroimaging literature suggest that if older adults still perform as well as younger adults on social-cognitive tasks, they activate compensatory strategies (e.g., reactive versus pro-active cognitive control) (Castelli et al., 2010; De Sanctis et al., 2009; Moran, 2013; Paxton et al., 2008). What is known about how those who were already on an altered developmental pathway in terms of attention, activity, and social behaviors in early childhood fare during adolescence and adulthood is the topic of the next paragraphs.

2.1.2. ADHD
From approximately age 12 on, ADHD symptoms present with a differential rate of decline with inattention remaining relatively stable or declining only at a modest rate, and in contrast hyperactivity/impulsivity waning more strongly and remitting more abruptly (Arnold et al., 2014; Holbrook et al., 2016; Mick et al., 2004). In a similar vein, hyperactivity-impulsivity in middle childhood predicts the presence of inattentiveness in early adolescence, but not vice versa; hyperactivity-impulsivity may thus exacerbate inattentiveness over time (Greven et al., 2011). However, although adults with ADHD do not (anymore) “climb on things” or “act as driven by a motor” (www.dsm5.org), less overt or disturbing forms of hyperactivity remain (Wasserstein, 2005). A recent study using objectively measured head and leg movements indicated that adults with ADHD still present with marked overactivity (Teicher et al., 2012), suggesting that textbook descriptions of the fading of hyperactivity in adolescence and young adulthood may be somewhat overestimated. Impairments associated with ADHD during adolescence are for the most part not due to comorbid conditions. Girls may grow less out of their symptoms than boys (Owens et al., 2009). Well known is further that ADHD symptoms persist into young adulthood in many cases with marked inattention, distractibility, organization difficulties, and poor task efficiency (Cheung et al., 2015; Copeland et al., 2013; Ebejer et al., 2012; Faraone et al., 2006; Fergusson et al., 1997; Karam et al., 2015; Langley et al., 2010; Spencer et al., 2007; van Lieshout et al., 2016), although substantial recovery rates and/or significant decrease of comorbid problems and functional impairment have also been reported (Costello et al., 2011; Gao et al., 2015; van Lieshout et al., 2016). Most consistent predictors of ADHD persistence are lower IQ and higher symptom severity in childhood (Cheung et al., 2015; Costello and Maughan, 2015; Ebejer et al., 2012; Gao et al., 2015; Karam et al., 2015; Langley et al., 2010; Spencer et al., 2007). Recent studies suggest that adult ADHD cases may in fact not have the typical childhood origins of the disorder (Moffitt et al., 2015; Agnew-Blais et al., 2016; Caye et al., 2016), suggesting that, for some, age of onset or full manifestation of ADHD may be later than currently assumed and that adult forms of ADHD may constitute a mix of persistent cases and later-onset cases with different etiologies.

2.1.3. ASD
Even more than ADHD has ASD been thought of as a life-long persistent disorder. There is a strong stability over the life course, wherein social problems seem the most persistent component of the behavioral phenotype in adolescence and adulthood (Seltzer et al., 2004) with perhaps some reduction in middle adulthood (Bastiaansen et al., 2011; Howlin et al., 2013). Accordingly, a study on how adolescents with ASD spend their free time showed that they spend little time engaged in conversations or doing activities with peers (Orsmund and Kuo, 2011), thereby missing out on practicing social skills (Glick and Rose, 2011), in turn, aggravating social problems. Another study showed that more than half of the adolescents and young adults with ASD at follow-up had not gotten together with friends or talked on the phone with a friend in the previous year (Liptak et al., 2011). In college students it was found that reduced social contact is thwarted, as in social anxiety, and does not reflect lack of desire for contact (Hintzen et al., 2010). Within the restricted interests and repetitive behaviors domain, repetitive behaviors are less frequent and less severe among older than younger individuals (Esbensen et al., 2009). In contrast, rigidity and insistence on sameness tend to remain stable or increase as investigated up to the age of 19 (Lord et al., 2015; Richler et al., 2010; Zohar and Dahan, 2016). It is unknown how these behaviors develop across adulthood. Finally, unusual sensory processing, another important symptom in ASD, extends across the lifespan, is very common, and takes highly variable, yet similarly severe, forms (Billstedt et al., 2007; Crane et al., 2009). Overall, recent reports indicate that ASD symptoms may become milder and that a subset of previously diagnosed individuals no longer meet criteria for ASD in adolescence or adulthood (Magiati et al., 2014). This so-called ‘optimal outcome’ is predicted by a relatively high IQ, the development of communicative and language skills at an early age and milder symptoms in the social domain compared to the persisters (Magiati et al., 2014). Moreover, studies diverge somewhat on whether theory of mind problems as a relatively robust marker of ASD in childhood are still present in adulthood and old age. A meta-analysis shows theory of mind impairments across the lifespan (Chung et al., 2014). A recent study indicates theory of mind impairments cannot be identified in elderly with ASD (Lever and Geurts, 2016), suggesting viewing ASD as a static life-long disorder for all cases is no longer supported by recent findings.

2.1.4. ADHD-ASD co-occurrence
Recent reports suggest that the co-occurrence of ASD and ADHD symptoms is—similar to the separate symptom domains—not stable across development. A recent review on co-occurrence patterns (and underlying mechanisms) from infancy to preschool years concluded that the co-occurrence of ASD and ADHD increases with age in this developmental time window, with attention problems forming a significant linking pin between both disorders, although the behavioral, cognitive and sensory correlates of these attention problems partly diverge between the two conditions (Visser et al., 2016). In community and twin samples in childhood age (often spanning up to adolescent age), comorbidity is strong with mixed ASD/ADHD symptom profiles being much more common than single disorder profiles, possibly driven by one strong general psychopathology factor indicating severity and chronicity of problems (Lundström et al., 2011; Noordhof et al., 2015; Ronald et al.,
One study indicated that in adolescence particularly, the presence of persistent ADHD symptoms is strongly related to ASD symptoms (St. Pourcain et al., 2011). Reports of ASD-ADHD symptom association in adults are scarce and nearly all controlled for age without examining potential age-changes in the co-occurrence. Studies including young adults (~18–35 years) suggest a mostly modest phenotypic overlap in ASD-ADHD symptoms (~0.30–0.45) (Lundström et al., 2011; Polderman et al., 2014; Reersen et al., 2008), possibly somewhat stronger for symptom domain specific analyses (repetitive behavior, inattention and hyperactivity-impulsivity: Polderman et al., 2014). In a smaller adult sample that also includes elderly aged individuals (17–78 years), an overall ASD and ADHD score correlates modestly (~0.30), primarily driven by the inattention rather than the hyperactivity/impulsivity domain of ADHD (Polderman et al., 2013), although interpretation of these findings is hampered by the wide age range.

2.1.5. Summary

In childhood the vast majority of individuals show a mixed ASD/ADHD symptom profile. ADHD and ASD symptoms persist into young adulthood in the majority of cases, and although a substantial proportion of individuals with ADHD and a smaller proportion of individuals with ASD show a reduction is symptom levels (and/or impairment levels), the symptoms and associated functional impairments often remain. Most consistent predictors of symptom improvement from adolescence on are higher IQ and milder symptom severity in childhood. The symptom domains within ADHD and ASD appear to undergo somewhat different developmental trajectories, with inattention and social problems being the most stable deficits, respectively, albeit improvement in these domains is also occurring. These findings illustrate that, next to their stability, symptoms of both ADHD and ASD undergo changes from early childhood until adulthood; changes that may reflect normal ongoing developmental processes, disorder-specific driven processes, improved development of secondary strategies to compensate for the primary deficits associated with ASD and ADHD, effects of intervention and changing environmental demands, or any combination of the above. The ASD-ADHD co-occurrence patterns are likely to be different for the various problem domains within ADHD and ASD. Preliminary data suggest the association between ASD and ADHD traits may be somewhat lower in adult age than in childhood/adolescence. That symptom presentations of both ADHD and ASD vary substantially across the lifespan, together with preliminary findings that ADHD-ASD co-occurrence may not be stable over the lifespan, suggests that the mechanisms behind their co-occurrence show changes across the lifespan as well.

2.2. Developmental change in associated executive functioning (EF) problems

2.2.1. Typical development

Problems in EF are common in a range of psychiatric disorders, and particularly in neurodevelopmental disorders like ASD and ADHD (Doyle, 2006; Hosenbocus and Chahal, 2012; Rommelse et al., 2011). EF is a core component of self-regulation abilities and includes, for example, efferent attention, inhibitory control, and working memory. EF becomes more differentiated from early childhood to adolescence to adulthood (Lee et al., 2013; Mungas et al., 2013) and different subcomponents of EF develop at a different rate during adolescence (Boelema et al., 2014). Despite such developmental improvements, EF shows considerable rank order stability over time (Berman et al., 2013; Boelema et al., 2014; Eijgsti et al., 2006). Individual differences in EF in childhood predict adult social and occupational outcomes (Kern et al., 2009; Miller et al., 2012a,b). There is a functional dependency between the development of EF and social interaction: the development of EF facilitates the cognitive skills that are important for social interaction (e.g., theory of mind), and possibly also vice versa (Alessandri et al., 2014; Baribeau et al., 2015; Bernier et al., 2012, 2015; Best et al., 2009; Fiske et al., 2014; Luengo Kanacri et al., 2013; Moriguchi, 2014; Pellicano, 2010; Rinsky and Hinshaw, 2011; Tseng and Gau, 2013). This illustrates the extensiveness of problems that may result from EF impairments, as well as the multiple ways as to how EF impairments may link to the behaviors that define both ADHD and ASD. Commonly assumed is that following its rapid development through childhood and adolescence, EF remains relatively fixed throughout adulthood, only to decline in late adulthood (Deater-Deckard, 2014). However, rather than such stage-like development, EF development may additionally be characterized as dynamic, where errors can (temporarily) emerge in previously mastered skills (Barber et al., 2013; Borst et al., 2015). Furthermore, recent studies report improvements in EF also in participants between 30 and 50 years of age (Fortenbaugh et al., 2015; Hartshorne and Germain, 2015; Hsu et al., 2014; Lucenet et al., 2014; Lukács and Kemény, 2015; Rantanen et al., 2007; Veroude et al., 2013) which is much longer than previously assumed. These recent findings suggest that EF processes have an inverted U-shaped rather than a fixed plateau-shape during adulthood. As such, EF development is ongoing after adolescence (Rebok et al., 2014), driven by both developmental, genetic, and environmental (e.g., parenting, exercise, diet, socio-environmental) factors (Daly et al., 2015; Hsu et al., 2014; Kesse-Guyot et al., 2014).

2.2.2. ADHD

In studies on EF impairments in ADHD, longitudinal studies are scarce, particularly in adolescence and beyond. It has previously been proposed that age-related improvement of EF may go hand in hand with the ADHD symptom decline in adolescence (Halperin and Schulz, 2006). Longitudinal empirical studies so far confirm that EF deficits in ADHD may in part resolve or become milder with age when entering adolescence and young adulthood (van Lieshout et al., 2013). Core EFs proposed to be etiologically related to ADHD are less evidently present in adolescence (despite the presence of ADHD), suggesting that part of the children may ‘grow out’ of early EF deficits (Thissen et al., 2014). However, there are also findings that EF deficits remain stable into adolescence (Biederman et al., 2007, 2008). In addition, resolving may only pertain to experimental tasks and not to questionnaire ratings of complex daily life EF (Barkley and Fischer, 2011), as these do not fully tap into the same underlying construct (Boyer et al., 2014; Faridi et al., 2015; Fuermaier et al., 2015; Toplak et al., 2013). Moreover, EF impairments are evident in both young adults whose ADHD diagnoses persist and in those whose ADHD symptoms have remit (Miller et al., 2012a). Another finding that contrasts with the fading of EF impairments from adolescence on is that ADHD symptoms put adolescents at risk for decreased IQ (which partly overlaps with EF) two years later (Rommel et al., 2015), suggesting that the symptoms themselves – when still present in adolescence – may stand in the way by deteriorating chances to reach normative adult EF. In adulthood meta-analyses and reviews –based on cross-sectional data– do suggest EF impairments are present (Alderson et al., 2013; Boonstra et al., 2005; Hervey et al., 2004), and may remain intertwined with ADHD regardless of age (Biederman et al., 2011; Seidman, 2006), or remission (Biederman et al., 2009; Miller et al., 2007). Also in older individuals with ADHD, EF problems are present (Das et al., 2015; Semeijn et al., 2015). Pending future longitudinal studies with repeated EF assessments, we conclude that EF impairments are likely present in adult and old-age ADHD, but it is unknown how stable the impairments are from childhood age onwards, and if older age is associated with a steeper EF decline that sets in earlier in adults with ADHD.
2.2.3. ASD

A review on EF across the lifespan in ASD concludes that there are age-related improvements in EF from childhood to adolescence in autism (O’Hearn et al., 2008). Findings of individual studies diverge considerably, including findings of stability of EF deficits (Andersen et al., 2015; Chen et al., 2016) and small sample sizes combined with small age-ranges hinder firm conclusions on developmental change of EF over the course of adolescence and into adulthood. Despite developmental gains, it is clear that most adolescents with ASD do not have normative EF (Geurts et al., 2014). Developmental gaps in daily life EF in adolescents with ASD appear largest in adolescence (Rosenthal et al., 2013; van den Bergh et al., 2014). These more complex real life EF deficits remain present in adulthood (Wallace et al., 2016). Adolescent and adult ASD literature showed that less efficient EF strategies are used by individuals with ASD, relying more on a trial-by-trial feedback processing manner instead of developing an effective reward-based working memory to guide behavior (Charman et al., 2011; Solomon et al., 2015). A recent account of elderly with ASD emphasized that, given the near absence of studies, the trajectories of change in cognitive (and social) functioning in ASD in old age are unknown (Happé and Charlton, 2012). It may be hypothesized that cognitive functioning declines more steeply in affected individuals compared to normative decline, as has been reported in relation to immediate visual recall in one of the few studies in elderly individuals with ASD so far (Davids et al., 2016; Geurts and Vissers, 2012). Alternatively, declines may follow the normative pattern observed in older age. One study, including patients with widely varying diagnoses (but including pervasive developmental disorders) shows a similar age-related executive decline in EF for patients and typically developing participants, although the patients start out with significantly lower EF (Janssen et al., 2014). Alternatively certain functions may be spared or even continue to improve in ASD (Happé and Charlton, 2012). Preliminary support for the latter was recently found by showing that typical aging effects on cognition appear less evident or parallel – but not increased – in individuals with ASD (Lever and Geurts, 2015; Lever et al., 2015). This could potentially suggest that ASD may partially protect against an age-related decrease in cognitive functioning, e.g. through lifelong exercising of compensatory strategies.

2.2.4. ADHD-ASD co-occurrence

No studies have been conducted linking EF impairments to symptoms of both ASD and ADHD in adolescents or adults. Given the strong intertwining of EF and ASD/ADHD, it seems likely that this relationship undergoes age related changes as well. To what extent EF can be seen as causally giving rise to and determine the course of the symptoms over the lifespan is still under debate (van Lieshout et al., 2013; Rommelse et al., 2016; Sonuga-Barke and Coghill, 2014; Yerys et al., 2007). Alternative proposals have been that EF may protect against the development of ASD/ADHD symptoms that are caused by other factors (Johnson et al., 2015) or alternatively that EF impairments act as epiphenomena (secondary deficits) potentially indicative of a more severe/chronic form of the disorder. For further insight into this issue, longitudinal studies are needed that follow up childhood diagnosed people into adulthood and repeatedly assess EF, ASD and ADHD. If (partly) causal to ADHD/ASD symptoms, changes in EF will have their impact on co-occurrence patterns of ADHD and ASD across the lifespan (Rommelse et al., 2016).

2.2.5. Summary

In summary, EF determines which behaviors we initiate, continue, adjust and stop. EF is subject to experience-dependent developmental change throughout the lifespan. EF deficits in children with ADHD and ASD measured with simple experimental tasks may in part resolve or become milder with age when entering adolescence and young adulthood, but more complex and daily life EF in adolescents with ASD/ADHD still seems to lag much behind that of typical controls, and it is currently unknown if this gap will also start to close as in simpler EF tasks. To what extent EF declines more steeply in ASD/ADHD affected adults, follows a normative pattern or alternatively is relatively spared in ASD/ADHD compared to normative cognitive decline is currently unknown and requires further studies. In any case, to the extent that EF impairments give rise to the symptoms of ADHD and ASD, respectively, developmental changes in EF across the life course are likely to alter co-occurrence patterns between ADHD and ASD.

2.3. Interim discussion literature review

From this literature review we distil that:

1. Both ADHD and ASD symptom constellations are not at all stable across development – with some symptom dimensions (attention problems, social problems, rigidity/insistence on sameness) being much more persistent than other symptom dimensions (hyperactivity/impulsivity and repetitive behaviors);

2. Studies on ADHD in adulthood have been more frequent than on ASD in adulthood. Diagnosing ADHD in adulthood has been more controversial than diagnosing ASD in adulthood, which probably stimulated adult ADHD research, compared to adult ASD research (Asherson et al., 2010; Hechtman, 2011; Wick and Zanni, 2009). Most research on ADHD and on ASD beyond childhood has been cross-sectional;

3. The co-occurrence of ADHD and ASD seems to vary with age as well, with strongest co-occurrence in adolescence. It is likely that there are subgroups within the ADHD-ASD spectrum with a different lifespan course;

4. Longitudinal studies that assess both ADHD and ASD beyond the childhood years are rare. Studies in old age are nearly absent. Therefore, currently there is very limited knowledge how the early alterations in attention, behavioral regulation, and social functioning in ADHD and ASD cascade to downstream maturational, learning (through less/ atypical experiences), or compensating alterations beyond the childhood years;

5. EF – a core component of self-regulation and functionally interdependent with social skills – undergoes substantial changes with age. Initial evidence suggests that based on ratings of complex EF behaviors in daily life, these ratings – rather than laboratory EF tasks – show the greatest deviance in adolescence relative to normative development. With no longitudinal data beyond adolescence, it is uncertain if this gap will becomes smaller;

6. EF likely relates to ADHD and ASD at all ages but this has not been systematically studied;

7. Little is known about symptom variability during the life course (in particular adulthood and old age), i.e. the rising and abating of symptom severity in relation to individual and environmental changes (Adler and Newcorn, 2011). The recent discussions in relation to late onset ADHD (Agnew-Blais et al., 2016; Caye et al., 2016; Moffitt et al., 2015) suggest the presence of earlier (different type) subthreshold problems only to become full syndromal ADHD beyond the DSM-5 age of onset criterion of ADHD. Such rising of symptoms during adolescence or adulthood suggests that symptoms may also (temporarily) wane. What is well-known, however, is that waning of symptoms does not go hand in hand with the waning of daily life impairments (Copeland et al., 2015; Sibley et al., 2012; Wu and Gau, 2013).
3. Empirical illustration of a lifespan approach in studying co-occurring ASD and ADHD symptomatology

We supplement the literature review with an empirical illustration. Participants came from various clinical, high risk, community, and healthy samples. A total of 17,173 ASD and ADHD symptom ratings were obtained from participants aged 0 to 84 years. In the Supplementary file, an overview of the number of paired ASD-ADHD ratings by study and instrument are listed. Prior to statistical modeling, we plot the association between ASD and ADHD separately for major developmental periods. Fig. 3 shows the graph for different developmental groups. Within toddlerhood, the correlation between ADHD and ASD was estimated as 0.06, within preschool as 0.24, within childhood as 0.51, within adolescence as 0.60, within young adulthood as 0.50, within middle adulthood as 0.50 and finally within late adulthood as 0.39. These correlations by developmental period thus show an asymmetric inverted-asymmetric-u-shaped association between ASD and ADHD across the lifespan. Please see the Supplementary material for sample characteristics, statistical testing, confirmation of these correlations using curvilinear regression analyses with age as continuous variable, and sensitivity analyses (Fig. 3).

4. Discussion

In this discussion we will first reflect on the methodological obstacles that stand in the way of a lifespan approach. Next, we will discuss how we may understand the curvilinear pattern of association across the lifespan found in the empirical illustration by relating it to the lifespan literature reviewed above.

4.1. Obstacles and opportunities using a lifespan approach and long term goals

Even though our lifespan data were “only” at the symptom level, we encountered already multiple methodological difficulties. These current shortcomings largely reflect the difficulties involved in studying ASD and ADHD across the lifespan, rather than limitations of our own work. While some of these may be easily solved, other apparent shortcomings have no easy or immediate solution. We will discuss these issues of our own work in more detail in the hope to move the field of ASD-ADHD research forward towards a lifespan approach.

First, one major issue was the change in informant when reaching adulthood and thus, how to disentangle rater effects from the “true” association between ASD and ADHD. This “break” in informants somewhere around the age of 18 may be seen as problematic in all published research so far. Although parent report is usually considered preferable to child-report in studies reporting on ASD and ADHD symptoms (and in case of ASD, also considered preferable to teacher report), for both disorders is has not been established when, if at all, developmental maturation is such that self-report on own ADHD and ASD symptoms becomes the more valid source of information for studying course, impairments, and outcome (e.g., Barkley et al., 2002; Horwitz et al., 2016; Kessler et al., 2010; Pirenhumbert et al., 2006). In adolescence, the optimal source of information is combined reports from the parent and a core academic teacher (Sibley et al., 2012). Beyond adolescence, the safest conclusion is probably that a multi-informant approach is most optimal, but, the issue has not received much empirical attention so far, and most studies in adulthood rely on self-report, in sharp contrast with gold standards in childhood. Similarly at the other end of the lifespan, a second informant added importantly to picking up on early cognitive decline (Gifford et al., 2015). In the present study, we cannot exclude the possibility that the decreasing correlation between ADHD and ASD between late adolescence and young adulthood is (partly) due to the change from parent to child report, however, informant switch cannot explain the steady increase in co-occurrence up to young adulthood, nor the decrease from age 18 on to old age. Future research should nonetheless determine if our current findings replicate for different informants. Another long-term goal would be to systematically investigate the possible benefits from multi-informant assessment of ADHD and ASD in adulthood.

A second obstacle was the use of different questionnaires to assess ASD/ADHD symptoms in our study. Although all used instruments include the core problems of ADHD and ASD, they do not neatly translate into one another compared to the situation that the same instruments had been used across the lifespan. As such, it is possible that the use of different instruments applied to different developmental phases has led to different estimates of the association between ASD and ADHD. The broader problem behind this is that instrument development is still very much work in progress, especially for adults. This is due to the fact that for ASD and ADHD developmentally appropriate measures are required. That is, ASD and ADHD manifest differently across the lifespan (Lord et al., 2015; McGough and Barkley, 2004; Spencer et al., 2007; Wasserstein, 2005), and as an example, while failing to respond to one’s own name is a core feature of autism in infancy it is not later in childhood (Picci and Scharf, 2013). Instrument development is only as far as our (systematically organized) knowledge on how problems manifest during different developmental phases. A long term opportunity would be to show through longitudinal research that ASD and ADHD, when measured with developmentally appropriate items that differ across the lifespan, nonetheless show strong consistency over time. Currently, averaging across instruments (as here), and studying robustness of (current) findings based on different instruments in independent studies, may the best first step forward.

A related and third obstacle is that we used questionnaire measures of ADHD and ASD. These are typical in large datasets including our own. There are no large datasets (N>1000) currently available with interview data of both ADHD and ASD, in part due to costs, but also to the only recently abandoned DSM-IV restriction not to classify both disorders simultaneously in the same patient (APA, 2000).
Table 1

Short term opportunities to study lifespan co-occurrence of ADHD and ASD.

| Use existing cross-sectional (and preferably longitudinal) datasets to replicate or refute our reported lifespan cubic shape. Here, we brought together data from three research groups; there should be many additional datasets available. Study moderating effects of age in studies on ADHD and ASD, in particular in adults given current practice to treat age as a covariate whereby possible changes across the lifespan are missed. Use quantitative measures. Children with ADHD or ASD tend to have a mixed symptom profile with symptoms of both disorders that is captured better by dimensional than dichotomous measures. Use multidimensional quantitative measures, reflecting the heterogeneity of both conditions. This will show how different problem domains within ADHD (e.g., attention problems, hyperactivity, impulsivity) and ASD (e.g., reduced social interest, sensorimotor repetitive behaviors, communication problems, insistence on sameness) co-occur across the lifespan. Associated characteristics are also of importance herein (e.g. emotion regulation problems, sleep difficulties) (Clegg et al., 2013). Use a multi-informant approach not only in childhood but across the life course. Metacognitive ability and insight into own problems is reduced in ADHD and ASD (Hobson et al., 2006; Horwitz et al., 2016; Manor et al., 2012; Steward et al., 2014). Reliance on self-report thus misses out on an important part of the quality and quantity of the ADHD and ASD symptoms present, which can be remedied by a second informant (e.g., parent, spouse). Link longitudinal changes in ADHD and ASD symptom level to EF over parts of the lifespan. Choose important developmental periods that involve major life transitions, such as from adolescence to young adulthood (involving, for example, transitions from school to work or from living with parents to independent living). Include measures of ADHD and ASD in treatment studies of either disorder. This will show if changes in ADHD symptoms influence the course of co-occurring ASD symptoms and vice versa. Use both laboratory tasks and ratings scales to quantify the mismatch between capacities versus effectiveness of daily life use of cognitive skills like EF. The literature so far suggests that reduced cognitive capacities assessed by laboratory task may be overcome yet more complex daily life equivalents (where multiple capacities come together) are not. Study the genetic influences underlying onset and course of ASD/ADHD in twin studies. Novel genetic influences may emerge with time while early genetic influences may decrease; processes that are also likely to be at play during normative development of activity, attention, regulation of behavior and social motivation and understanding (Rommelse and Hartman, 2016). |

Another practical obstacle that plays a role here is that, just as with questionnaires, knowledge of the validity of adult interview measures is only beginning to emerge (Parr et al., 2015; Primich and Lennaco, 2012). Although a strong case may be made that given the mixed and heterogeneous symptoms profiles of ADHD and ASD dimensional measures are superior to categorical measures (e.g., Chaste et al., 2015; Kiser et al., 2015), extensive interview data should be considered superior to “quick and dirty” questionnaire data, this given that interview data can generate both dichotomous and dimensional scores and can be obtained from any informant. Thus, the conclusions reached here on the lifespan association between ADHD and ASD would perhaps be different if interview data had been used and this needs to be established. A more general long-term goal is further study the added value of adult interviews and observational measures relative to questionnaires (e.g., Bastiaansen et al., 2011).

A fourth methodological difficulty in our study was the potential selection bias of samples. A drawback of using general population studies is that few (one in hundred at most for ASD, one in ten maximal for ADHD; Baxter et al., 2014; Simon et al., 2009; Thomas et al., 2015) have a clinical diagnosis of ASD or ADHD. A drawback of using clinical samples is overestimation of co-occurrence of ADHD and ASD problems, as children with multiple type problems are more likely referred than children with problems on a single domain. Here, we opted for combining samples and use all information we had, including population and clinical samples, as well as “in between” sibling and parent samples who in part have sub-threshold problems. The ideal approach, studying co-occurrence patterns in large samples of individuals with ADHD or ASD who were identified in the general population, to avoid the referral bias, is costly, and population based databases with diagnostic assessment of both ADHD and ASD based on interviews currently do not exist. Replication of our findings in other, independent, samples might be the first feasible step.

4.2. Feasible short term opportunities as a first step to advance our knowledge base

Both the literature review and the empirical illustration indicated how much is still unknown. Table 1 lists a research agenda feasible in the short term that will substantially advance our knowledge base not only on ADHD and ASD co-occurrence but also on plausible changing mechanisms across the lifespan. This will aid in refining the long term research goals.

4.3. How to interpret found curvilinear ADHD and ASD association patterns across the lifespan?

Both our findings as well as those from previous studies suggest that the co-occurrence between ASD and ADHD symptoms is highest in late adolescence. Correlations between ASD and ADHD based on adolescence are driven by those who still have the symptoms (Faraone et al., 2006; Mick et al., 2004; St. Pourcain et al., 2011) and may be particularly influenced by the social and EF impairments prevailing in this period in both ASD and ADHD (Ahmed and Miller, 2011; van den Bergh et al., 2014; Rosenthal et al., 2013; Taylor et al., 2015a, 2015b). As outlined in the review, due to reciprocal connections between EF and social interaction (Moriguichi, 2014; Pellicoano, 2010), problems in one may increase problems in the other. Adequate social adaptation and EF are needed more and more during adolescence while at the same time parents who used to provide the scaffolds to co-steer their child’s behavior are increasingly less in the position to do so (Boyer et al., 2014). It has been proposed that adolescence may form the ‘second hit’ of brain alterations (the first hit being early disruptions to neural development [even as early as prenatal development] that fundamentally compromise developing neural circuits) with the confluence of pubertal hormones, neural reorganization, and increasing social demands during adolescence interfering with the ability to transition into adult social roles and levels of adaptive functioning (Picci and Scherf, 2015). We agree and further hypothesize that adolescence is a crucial time window of (neural) plasticity to accommodate the new developmental tasks that individuals face. Suboptimal development during this sensitive time in ASD and ADHD may set the stage for irreversible changes in development later on, or vice versa, with developmental catching-up of EF and social skills. Thus, on the border of the expected transition to independent adulthood, when social adaptation and EF skills matter most, and are taxed most, symptoms of ADHD and ASD are strongly co-present in those who fail to make the normative gains commensurate with chronological age.

That ASD and ADHD symptoms correlate only mildly to modestly in very young children in our data is in line with a recent systematic literature review (Visser et al., 2016). This may possible be explained by the non-crystallized nature of problem behavior.
in most atypically developing children at that age. That is, the manifestation of ADHD and ASD symptoms is less outspoken in young children, which may hold in particular for future onset of ADHD (Mörck et al., 2013; Nelson, 2015; Sonuga-Barke and Halperin, 2010). Core features of ADHD and ASD, such as reduced self-regulation or theory of mind, involve neural systems that are too immature to already show delay or dysfunction in early life (Mungas et al., 2013; Sullivan et al., 2015). Similarly, a recent review on early co-occurrence of ADHD and ASD indicated that the behaviors involved in ASD or ADHD in young children overlap substantially more with normative behavior (characterized by normative poorly developed EF in the majority of children) than at older ages, and also constitute a red flag for multiple other (future) psychiatric disorders than ADHD or ASD (Johnson et al., 2015). As a consequence, screening measures may not be very sensitive to early cognitive and social precursors in toddlerhood in children with subsequent ADHD symptomatology (Arnett et al., 2013) and it has been argued that especially at a young age classification of a specific DSM-syndrome should be avoided (Gillberg and Fernell, 2014). Such diagnostic nonspecificity may result in relatively low co-occurrence rates at this age. In fact, recent findings on late onset ADHD may reflect that, even in the childhood years, less outspoken symptoms that do not fit a specific DSM-syndrome may be missed (Faraone and Biederman, 2016). Thus we posit that symptoms of ASD and ADHD are rather diffuse in early childhood reflecting the still emergent differentiation of cognitive abilities.

Just like ADHD and ASD being less specific in their manifestation in early childhood, this may also hold to some extent at the older end of the lifespan. Found gradual attenuation of co-occurrence of symptoms across the adult lifespan into older age here may indicate, like in young children, that symptoms become less specific given a gradual overall reduction in brain functioning due to aging, most prominently EF. Developmental and old age-related performance decrements in EF may be due to the undifferentiated and inefficient manner in which both children and older adults recruit the neural processes associated with EF (Friedman et al., 2009). Children and elderly may use similar undifferentiated and inefficient EF strategies just like in childhood, old age shows reciprocal associations between EF and theory of mind, but now enhancing cognitive decline (Bottiroli et al., 2016; Moran et al., 2012; Moran, 2013; Palmer et al., 2014; Phillips et al., 2011; Rakoczy et al., 2012). Although there is marked variation among individuals, reduced brain functioning may already start in young adulthood and may occur sooner and more steeply in those who experienced (any) chronic psychiatric complaints during their lives, leaving scars of less reserve in the brain (Janssen et al., 2014; Oberman and Pasqual-Leone, 2013). Thus, like the red flags of behaviors that may forebode different psychiatric disorders in childhood there may be, in an analogous fashion, undifferentiated red traces from a history of psychiatric problems in older adulthood. In addition, late onset brain degenerative diseases may set in, such as mild cognitive impairments or early stages of dementia, again with symptoms that may be similar to ADHD (McShane et al., 1998; Pose et al., 2013) or ASD (Sandoz et al., 2014), spreading out the neural impairments and further diffusing symptom manifestation. Such an account of diffusing symptoms would fit the “de-differentiation of cognitive function” hypothesis stating that with increasing age, differentiation of different cognitive functions reduces (de Frixas et al., 2009; Hülür et al., 2015). In all, we posit that key symptoms of ADHD and ASD become less specific in adulthood and especially in late adulthood, due to decreasing brain functioning, thereby explaining decreasing correlations.

In sum, we interpret the pattern of lifespan co-occurrence at the symptom level as reflective of lifespan EF development, which is altered in ADHD and ASD compared to normative development. This drives the correlations between particularly the attention and social domains of ADHD respectively ASD, which are the most persistent problems throughout the lifecycle. We additionally hint at possible mismatches with environmental demands, strengthening correlations between ADHD and ASD symptomatology particularly in adolescence when first steps in adult role-taking are required yet EF and social skills lag most behind. We plea for a strong research focus on adolescence which may after childhood be a second crucial time window for either irreversible changes in development or catching-up patterns explaining more optimal outcomes. Finally, we suggest that early childhood and late adulthood resemble one another in terms of diagnostic non-specificity of symptoms, overlapping both in early childhood and in old age with normative behaviors of a developing, respectively, aging brain, and with flags of upcoming, respectively, scars of lifelong experienced, (any type) psychiatric problems. A full lifespan approach into old age meets with many methodological obstacles and is therefore a longer term yet important research goal. These interpretations of our findings are necessarily speculative since we did not empirically study the proposed mechanisms. Rather they are meant to be hypothesis-generating for future research.

Authorship contributions

NR and CH developed the study concept. Data analyses were performed by CH. Data interpretation was done by CH, NR, HG, CH and NR drafted the paper, and JB, BF and HG provided critical revisions. All authors approved the final version of the paper for submission.

Conflict of interest

None of the authors report potential conflicts of interest.

Acknowledgements

We want to thank the researchers (Marike Altink, Yvette de Bruijn, Cathelijne Buschgens, Ellen Fliers, Anoek Oelemans, Iris Oosterling, Sascha Roos, Saskia de Ruiter, Daphne van Steijn, Janne Visser, Anne van Lammeren, Ernst Horwitz) who collected data or shared their (unpublished) data with us. We additionally want to thank TRAILS (www.trails.nl).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2016.09.003.

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