Non-mental diseases associated with ADHD across the lifespan: Fidgety Philipp and Pippi Longstocking at risk of multimorbidity?

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Abstract

Throughout recent years, it became clear that children, adolescents and adults with ADHD are at increased risk of developing not only mental comorbid disorders but also seem to have a higher risk of non-mental diseases. The underlying trajectories leading to such brain-body comorbidities or co-occurrences are often unclear - are there direct causal relationships from one disorder to the other, or does the sharing of genetic and/or environmental risk factors lead to their occurring together more frequently? In our narrative review, we compiled recent evidence for associations between ADHD and non-mental diseases across the lifespan and discuss potential shared pathomechanisms and genetic background, as well as pharmacological treatments in comorbid or co-occurring conditions. We focus on non-mental dieases that have the strongest evidence for positive associations with ADHD so far, or are of particular interest for the treatment of ADHD. We conclude that non-mental diseases are common in ADHD and may add to the disease burden of the patient across the entire lifespan. Insufficient attention to such comorbid or co-occurrent conditions may result in missed diagnoses and suboptimal treatment in those suffering from ADHD.

3-12 keywords: attention-deficit/hyperactivity disorder, adult ADHD, somatic disorders, non-mental disease, asthma, obesity, migraine, diabetes mellitus type II, epilepsy, genetic

Highlights

- ADHD patients have an increased risk of non-mental diseases over the life span
- For Epilepsy, migraine, elimination disorders, asthma and obesity, there is the best evidence as comorbid or co-occurring conditions
- Other non-mental diseases might be rather differential diagnosis or share similar risk factors
- Diagnosing non-mental diseases in ADHD patients is important for optimizing the treatment of both conditions

Introduction

Attention-deficit-/hyperactivity disorder (ADHD) is among the most common neurodevelopmental disorders in children, with a worldwide prevalence of about 5% in childhood. In about two-thirds of these cases ADHD persists into adulthood (Faraone, Biederman, & Mick, 2006). A review of twin studies confirmed high heritability estimates of 70-80% for the disorder in both childhood and adulthood (Faraone & Doyle, 2001; Faraone & Larsson, 2019; Polderman et al., 2015), and recent large-scale molecular genetic studies have identified the first common and rare genetic risk variants associated with childhood and/or adult ADHD (Bonvicini, Faraone, & Scassellati, 2016; Demontis et al., 2019; Rovira et al., 2020; Satterstrom et al., 2019). Furthermore, environmental and developmental factors like maternal psychosocial stress during pregnancy, preterm birth, low birth weight and hypoxia during birth as well as childhood maltreatment seem to influence the risk of developing ADHD, sometimes by interaction with genetic variants (Palladino, McNeill, Reif, & Kittel-Schneider, 2019; Tole et al., 2019). It is well established that ADHD can lead to severe impairment in psychosocial functioning over the lifespan. Moreover, children and adults with ADHD very commonly develop additional mental disorders including anxiety disorders, affective disorders, oppositional-defiant and conduct disorders (childhood), personality disorders (adulthood) and substance use disorders (adolescence/adulthood) (Gross-Lesch et al., 2013; Jacob et al., 2014; McGough et al., 2005). Recent studies additionally indicated a premature mortality before the age of 40 years in comparison to non-ADHD general population, which was primarily due to accidents as well as suicide (Dalsgaard, Ostergaard, Leckman, Mortensen, & Pedersen, 2015). The phenotype of childhood ADHD and as well co-occuring mental disorders as accident proneness have been already described by Heinrich Hoffmann in his children's book 'Shockheaded Peter' in 1845. Heinrich Hoffmann was also the director of a psychiatric hospital in Frankfurt. In his story about 'Fidgety Philip' he pictured the prototype of the predominant hyperactive subtype of ADHD in this book which also had an accident at the end of the story (Thome & Jacobs, 2004). Astrid Lindgren's stories about "Pippi Longstocking" that were firstly published in 1944, describe ADHD and also a hint of oppositional-defiant disorders in a girl (Bode, 2006). However, besides the

known mental co-occurring disorders and impairments in psychosocial functioning that have been already described in those figures from literature, lately, it has also become clear that non-mental diseases seem to be highly frequent in ADHD and contribute substantially to the loss of quality of life in the patients (Instanes, Klungsoyr, Halmoy, Fasmer, & Haavik, 2018). A recently published systematic review of co-occurrence of non-mental diseases in adult ADHD concluded that there might be evidence for significant associations of adult ADHD with obesity, asthma, sleep disorders, migraine, and celiac disease. Additional non-mental diseases and syndromes that have been linked, although less strongly in that previous review, with adult ADHD are elimination disorders, restless legs syndrome, epilepsy, and allergic and immunological disorders (Instanes et al., 2018). Similar associations have been reported for childhood and adolescent ADHD, however some of the non-mental diseases vary widely in their prevalence between children and adults (Schmitt, Romanos, Schmitt, Meurer, & Kirch, 2009). A systematic review of co-occurring non-mental diseases in children with ADHD reported a significant association with amongst others allergic diseases and type 1 and 2 diabetes mellitus (Muskens, Velders, & Staal, 2017).

The first aim of this narrative review was to provide a survey of the existing literature about co-occurrence of specific non-mental diseases associated with ADHD across the lifespan, as well as the temporal sequence of co-occurrence. We focused on diseases with the most robust evidence for association with ADHD and those of special interest for the treatment of ADHD (neurological disorders, diseases of the digestive system and urinary system, endocrine and metabolic diseases, autoimmune and allergic disorders and respiratory disorders). As the risk of cardiovascular events in ADHD patients due to stimulant medication is still a strongly debated clinical topic, we included cardiovascular diseases in this review, even though the existing evidence suggests that an increased risk for cardiovascular diseases in ADHD is rather low (Instanes et al., 2018). The second aim was to explore which of the significantly associated non-mental diseases might be caused by shared pathomechanisms and shared genetic risk variants. In the description of such risk factors, we largely relied on recent large-scale family and molecular genetic studies. Finally, we discuss if treatment of the co-occurring disease could also have an effect on ADHD symptoms and vice versa.

Methods

Our goal was to provide a conceptual synthesis of the associations between ADHD and non-mental diseases across the lifespan and not a systematic review. For those co-occurring diseases for which published studies with sufficient sample sizes exist, systematic reviews and meta-analyses have already been published by others, which we describe and cite as part of the review. We searched PubMed and Web of Knowledge (including the databases *WOS, BCI, CCC, DRCI, DIIDW, KJD, MEDLINE, RSCI, SciELO, ZOOREC*) without year limitation prior August 2020 and lastly updated in April 2021. We were using the following search terms for the respective paragraphs/diseases of interest as described above:

'*ADHD*' OR *'attention deficit'* OR *'hyperactive*'* OR *'hyperkinetic'* together with (AND) *'epilepsy'/'migraine'/'restless legs syndrome'/'neurometabolic disorders'/'neurodegernative disorders'/'dementia'/Parkinson'/'elimination disorders'/'enuresis'/'daytime urinary incontinence'/'fetal incontinence'/'encopresis'/'constipation'/'celiac disease'/'inflammatory bowel disease'/'Crohn's disease'/' ulcerative colitis'/'obesity'/'diabetes mellitus'/'thyroid gland'/hypothyroidism'/hyperthyroidism'/'cardiovascular disease'/'hypertension'/'heart failure'/ 'atopic disorders'/'allergy'/'asthma'/autoimmune disorders'/.*

We only excluded case reports and case series as well as very small studies with n<=20 from the integration in our review. Additionally, we excluded data from animal models. -

Results

Neurological disorders

a. **Epilepsy**

Epilepsy is a heterogeneous collection of seizures disorders defined by recurrent unprovoked seizures, affecting approximately 1% of the population (Ngugi, Bottomley, Kleinschmidt, Sander, & Newton, 2010; Russ, Larson, & Halfon, 2012). Most epilepsies have their onset during the first decade of life,

with a second peak on onset after 65 years of age with a roughly equal sex distribution (Cross, 2011). The association between seizures and epilepsy and especially childhood ADHD is well-established, with a 2- to 4-fold higher prevalence of epilepsy and single unprovoked seizures reported in individuals with ADHD, compared to the general population (Aaberg et al., 2016; Brikell et al., 2018; Chou et al., 2013; S. M. Davis et al., 2010; Hesdorffer et al., 2004). Conversely, children with epilepsy have a 3 to 5-fold increased prevalence of ADHD and as many as 50% suffer from sub-threshold ADHD symptoms, making it one of the most common co-occurring neurodevelopmental disorders in epilepsy (Aaberg et al., 2016; Bertelsen, Larsen, Petersen, Christensen, & Dalsgaard, 2016; A. E. Williams, Giust, Kronenberger, & Dunn, 2016). Children with ADHD and epilepsy have greater rates of co-occurring autism, intellectual disability, and academic underachievement, compared to children with either disorder alone (Reilly, 2011). Although ADHD and epilepsy in adults has been less researched, one study found that adults with epilepsy and ADHD reported higher rates of depression, anxiety, lower quality of life, and more impaired psychosocial functioning, compared to adults with epilepsy alone (Ettinger et al., 2015). A small recent study that investigated 200 adult epilepsy patients reported 35% positive screening for ADHD, with the most cognitively impaired patients showing the highest rates of ADHD symptoms and clinically diagnosed co-occurring ADHD (Ashjazadeh, Sahraeian, Sabzgolin, & Asadi-Pooya, 2019). As some forms of childhood epilepsy remit with age (Puka et al., 2020), the co-occurence between ADHD and epilepsy might be less prevalent in adult services than in children and adolescents. Therefore there is less data about the prevalence of epilepsy in adult ADHD, however, it seems that at least in adult patients with epilepsy the rate of ADHD is about 2 to 3-fold higher than in general population (Instanes et al., 2018).

The relationship between ADHD and seizures and epilepsy is complex and likely multifactorial. Several mechanisms have been proposed to explain the overlap, including adverse effects of antiepileptic drugs (AEDs) and chronic seizures on attention, cognition and behavioral symptoms. In one of the largest investigation to date, including 906, 379 Danish children, febrile seizures before age five were associated with a 30% increased prevalence of ADHD, and diagnosed epilepsy with a nearly 3-fold increased rate of ADHD. An even higher ADHD prevalence was observed among children with a history

of both febrile seizures and epilepsy (Bertelsen et al., 2016). Although the evidence is variable (Auvin, 2018), some studies suggest that earlier age at seizure onset (Kwan & Brodie, 2001), frequency and duration of seizures (McCusker, Kennedy, Anderson, Hicks, & Hanrahan, 2002) and complex (treatment refractory) epilepsy (Davies, Heyman, & Goodman, 2003) are associated with ADHD in a dose-response like manner. Conversely, several studies have established that ADHD symptoms can precede the onset of seizures and are observed in AED-naïve patients, supporting the notion that either a partial bidirectional relationship exists between the disorders or a variability in onset of both disorders (Chou et al., 2013; Hermann et al., 2007; Hesdorffer et al., 2004).

Shared pathomechanisms

Children with ADHD show more often electroencephalogram (EEG) abnormalities compared to the general population, including subthreshold epileptiform discharges and rolandic spikes as well as subsequent seizures (Holtmann, Becker, Kentner-Figura, & Schmidt, 2003; Kanazawa, 2014; Socanski, Aurlien, Herigstad, Thomsen, & Larsen, 2015; Socanski, Herigstad, Thomsen, Dag, & Larsen, 2010). A recent study reported that a history of asphyxia and prematurity were associated with EEG abnormalities and seizures within the ADHD population (Kartal, Aksoy, & Deda, 2017). Pre- and perinatal complications (e.g., low birth-weight, gestational age, pre-eclampsia, maternal infections during pregnancy) are well-established risk factors for both epilepsy and ADHD (D'Onofrio et al., 2014; Larsson, Sariaslan, Langstrom, D'Onofrio, & Lichtenstein, 2014; Pettersson, Larsson, D'Onofrio, Almqvist, & Lichtenstein, 2019; Silva, Colvin, Hagemann, & Bower, 2014; Walsh et al., 2017), suggesting such complications may act as shared risk factors for ADHD and epilepsy co-occurence. Other neuronal features, including frontal lobe dysfunction and adrenergic system dysregulation have been implicated in both epilepsy and ADHD (A. E. Williams et al., 2016). A comparison of cases versus control differences in structural brain features from the ENIGMA ADHD and epilepsy groups found a significant correlation between the two disorders (P. M. Thompson et al., 2020).

Shared genetic background

Due to evidence of an apparent bidirectional relationship and shared neuropathology, it has been suggested that ADHD and epilepsy may arise from a shared genetic vulnerability, predisposing individuals to broad neurodevelopmental dysfunction (Moreno-De-Luca et al., 2013). Several family studies have reported an increased rate of ADHD in relatives of individuals with epilepsy, and one large population study used a sibling design to show a moderate genetic overlap between ADHD and epilepsy (Brikell et al., 2018; Gonzalez-Heydrich et al., 2012; Halmoy, Klungsoyr, Skjaerven, & Haavik, 2012). However, whilst gene discovery in ADHD and epilepsy is rapidly advancing (Demontis et al., 2019; International League Against Epilepsy Consortium on Complex Epilepsies. Electronic address, 2014), data from genome wide association studies (GWAS) have so far showed no evidence for a significant genetic overlap between the disorders (Brainstorm et al., 2018). However, the absence of a significant association may still reflect low power due to modest sample sizes of GWAS of both ADHD and epilepsy. Studies of rare genetic variants have reported an increased burden of deletions, duplications, and de novo mutations in overlapping genomic regions across neurodevelopment disorders, including ADHD and epilepsy (Lo-Castro & Curatolo, 2014), suggesting that genetic syndromes due to rare mutations might underlie the etiology and co-occurrence of ADHD and epilepsy in some cases, rather than common genetic variation. The potential impact of rare variants on population prevalence of co-occurring ADHD and epilepsy however remains unclear and may not explain the full range of comorbidity.

Treatment

Pharmacotherapy is pertinent issue for diagnosis and treatment in co-occurring ADHD and epilepsy, for several reasons. First, in-utero exposure to certain AEDs and in particular valproate has been found to increase the risk of off-spring ADHD over and above the already know risk of malformations linked to valproate use during pregnancy (Bromley, 2016; Christensen et al., 2019; Cohen et al., 2011). Thus, seizure management during pregnancy requires careful consideration and may be one of many factors linking maternal epilepsy to an increased risk of offspring ADHD (Brikell et al., 2018; Halmoy et al.,

2012). Second, certain AEDs, in particular barbiturates and to a lesser extent phenobarbital, phenytoin, carbamazepine, and valproate are correlated with attention and hyperactivity problems, with polypharmacy more likely being problematic than monotherapy (A. E. Williams et al., 2016). Third, there are longstanding concerns that stimulant ADHD drugs may lower the convulsive threshold, interfere with seizure control and in rare cases, lead to new onset seizures in previous seizure free patients. However, current evidence suggests that at least the occurrence of new onset seizures does not differ by ADHD treatment in epilepsy free ADHD individuals (Wernicke et al., 2007; Wiggs et al., 2018). Although evidence is sparse and based on small sample sizes, methylphenidate has not been found to increase the risk of new onset seizures in ADHD children with EEG abnormalities (Gucuyener et al., 2003; Holtmann et al., 2003). Further, current research does not support an increased risk of seizures in patients with a seizure history, nor in patients with controlled or refractory epilepsy (Auvin et al., 2018). One small clinical study (Santos et al., 2013), and two large population-based drug-register studies using a within-individual comparison design to adjust for confounding factors constant within an individual during the study period (e.g. genetic liability, disorder history, early life risk factors) even found a decreased number of seizures associated with methylphenidate treatment (Brikell et al., 2019; Wiggs et al., 2018). In a small open-labeled trial, methylphenidate was found to be safe and to improve quality of life ratings in patients with difficult to treat epilepsies (Radziuk et al., 2015). The International League Against Epilepsy's 2018 consensus paper on management of ADHD in children with epilepsy states that methylphenidate is effective and well tolerated in children with both controlled and refractory epilepsy. Similar evidence is lacking for atomoxetine and amphetamine-derivatives, highlighting the need for further research (Auvin et al., 2018). Although these findings do not support the hypothesis of an increased risk of seizures related to methylphenidate, findings need to be replicated in other populations, using complimentary analytic methods. Further, there is still a dearth of knowledge regarding the safety of ADHD treatment in patients with epilepsy and additional neurodevelopmental disorder comorbidities, where polypharmacy and severity of neurodevelopmental insults may be of greater concern.

b. Migraine

Migraine is a multifactorial episodic headache disorder, with attacks of pain and time-limited neurological dysfunction. Lifetime prevalence in the general population is around 15-20%, with females being affected more than twice as often as males. Heritability estimates for migraine based on twin studies are between 30% and 60% (Anttila, Wessman, Kallela, & Palotie, 2018; Sutherland & Griffiths, 2017; Wang et al., 2016).

Clinical and epidemiological studies have shown an association between ADHD and migraine across the lifespan (Arruda, Arruda, Guidetti, & Bigal, 2017; Carpenet, Guichard, Tzourio, & Kurth, 2019; Fasmer, Halmoy, Oedegaard, & Haavik, 2011; Hansen et al., 2018; T. Lateef et al., 2019; Salem et al., 2018).. In line with this, a positive correlation between prescription of migraine and ADHD medications was found in the total Norwegian population for age groups between 20 and 50 years and for both sexes, with ORs ranging from 1.8 to 2.8 (Fasmer et al., 2012). Other studies in as well clinical ADHD populations as general population showed that associations between the two disorders were stronger for adults (OR 1.8 to 2.2) (Fasmer, Halmoy, et al., 2011; Hansen et al., 2018), but were also seen to a smaller extend in adolescents in a systematic review that included 12 studies investigating adolescents and only two with adults or all ages in a registry (OR 1.3) (Salem et al., 2018). In a very recent study using health insurance data, children with ADHD (n= 258,662) showed an increased rate of migraine (OR = 2.49; 95% CI = 2.37-2.61) compared to gender-, age-, and region-matched non-ADHD children (n= 2,327,958) (Akmatov, Ermakova, & Batzing, 2021). Similar findings were shown in a study in which 5,671 school children between 5-12 years were assessed for ADHD and migraine/other headache simultaneously. Here, the authors reported a significant higher prevalence of ADHD in children with migraine overall in comparison to non-migraine children (10.8% vs. 2.6%, RR = 4.1, 95% CI = 2.7-6.2), EM (10.2% vs. 2.6%) but not with other types of headaches (Arruda, Arruda, Guidetti, & Bigal, 2020). An increase of the co-occurrence with age most likely is due to the fact that typically migraine starts later in life and ADHD is also remitting in about one-third of the affected children when they reach adolescence or adulthood. Associations were also stronger for girls compared to boys, as well as for hyperactivity-impulsivity compared to inattention (Arruda et al., 2017; Carpenet et al., 2019).

However, migraine is also more common in girls and women as stated above. Using the Philadelphia Neurodevelopmental Cohort, Lateef and coworkers found that youth with migraine had a higher ADHD prevalence compared to those with non-migraine headache (OR 1.3) (T. Lateef et al., 2019). However, they also more often showed additional various non-mental diseases and other mental disorders, including anxiety and mood disorders (OR 1.3 and 1.9). After adjustment for these disorders, migraine and non-migraine headache did not show a higher co-occurrence with ADHD any longer.

Furthermore, ADHD co-occurrence increases with migraine frequency (Arruda et al., 2017) and visual aura symptoms (Carpenet et al., 2019; Hansen et al., 2018). Migraine is also associated with other mental disorders such as depressive and anxiety disorder (Fasmer et al., 2012), and with non-mental diseases such as obesity (Bigal, Liberman, & Lipton, 2006) and asthma (T. M. Lateef et al., 2009; Peng et al., 2016), all of which are also related to ADHD. A recent study in adolescents showed stronger associations of migraine with affective disorders and anxiety disorders than pure ADHD, however, the ADHD diagnosis was only assessed by parent report (Hommer, Lateef, He, & Merikangas, 2021).

Shared pathomechanisms

The co-occurrence of ADHD and migraine may be a consequence of shared comorbidities or related pathophysiological mechanisms, including neurotransmitter imbalances for dopamine, noradrenaline, or GABA (Salem et al., 2018), studies are still lacking.

Shared genetic background

Evidence for the existence of pleiotropic, common genetic factors influencing migraine and ADHD stems from a recent analysis of shared heritability in common brain disorders, which found genetic correlation of migraine with ADHD (r=.26), depression (r=.32), and Tourette's Syndrome (r=.19) (Brainstorm et al., 2018). Most remarkably, migraine was the only neurological disorder that had significant shared heritability with mental disorders, although it has to be mentioned that sample sizes were underpowered.

Treatment

Adverse effects of stimulant treatment could also contribute to an increased rate of headaches and potentially migraine (Salem et al., 2018). However, there is also a small pilot study showing that amphetamine treatment could ameliorate chronic tension headache and migraine in non-ADHD patients (Haas & Sheehe, 2004).

c. Restless legs

Restless legs syndrome (RLS) is a highly prevalent neuropsychiatric disorder that may occur in childhood ("pediatric RLS"), yet becomes much more prevalent (up to 10%) in adulthood; this increase in RLS prevalence has to be kept in mind when considering comorbidity patterns with ADHD (Allen et al., 2003). The lead symptoms are given in the name; as soon as the patient is required to sit or lie still, the legs become "restless" (i.e., the patient experiences impairing paresthesia). This is hard to tolerate and only gets better once the patient starts to move again, therefore patients may appear "hyperactive". Generally, symptoms alleviate when the patient walks around, which patients then often do when symptoms become unbearable during bedtime. RLS patients consequently suffer from sleep problems and insomnia, with associated daytime impairments (Allen et al., 2003). The behavioural pattern seen in RLS can pose challenges in the differential diagnosis of ADHD and RLS; in adulthood, the disorders can easily be disentangled by proper examination and anamnesis, but in childhood, the delineation of (the rather uncommon) pediatric RLS from ADHD can be more difficult.

In childhood, a large body of evidence exists for comorbidity of RLS and ADHD (e.g. (Pullen, Wall, Angstman, Munitz, & Kotagal, 2011) and an extensive review by Angriman et al.(Angriman, Cortese, & Bruni, 2017)). Specifically, in 374 children that were diagnosed with restless legs, 25% (94/374) were also diagnosed with ADHD which is about 3.5-fold higher than expected in general population. However, a control population was not included in this study (Pullen et al., 2011). A recent population based study in 7072 adolescents reported 7.6% participants that displayed clinically relevant ADHD symptoms and ADHD symptoms were positively associated with restless legs syndrome (OR = 1.47, 95% CI = 1.02-2.11)(Liu, Liu, Liu, Sun, & Jia, 2020). The most convincing study in adults so far is a cross-

sectional study in 25,336 blood donors from Denmark, where 5.2% screened positive for RLS and 2.6% for ADHD, and the OR for having ADHD was 3.6 in RLS patients (Didriksen et al., 2019). Additionally, in a rather large sample (n=1,632) of community-based adults, adult ADHD was also found significantly associated with RLS (OR=3.2) (Roy et al., 2018). However, the association disappeared when controlling for sleep problems; although it should be noted that this may be an overly conservative approach, given the almost complete overlap of RLS with poor sleep. A smaller, cross-sectional study of adult ADHD found significantly increased OR for self-reported RLS (OR=14.5) (Bjorvatn et al., 2017). Taken together, these data are not easily explained by diagnostic inaccuracy and collectively argue for significant co-occurrence of ADHD and RLS across all age groups.

Shared pathomechanisms

If diagnosed correctly, RLS can be treated with dopaminergic compounds such as L-DOPA or dopamine receptor agonists (see for example German guidelines https://www.dgn.org/leitlinien/2386-ll-06-2012-restless-legs-syndrom-rls-und-periodic-limb-movement-disorder-plmd). In line with this, RLS is thought to be due to a dysfunction of dopaminergic regulation of the basal ganglia. As dopamine neurotransmission also plays important roles in ADHD, a pathophysiological link of LS and ADHD seems conceivable. Another etiological factor that may link ADHD and RLS is iron deficiency (Picchietti & Picchietti, 2010). Finally, the sleep problems eventually caused by RLS might lead to ADHD-related symptoms such as irritability or attention deficits (Cortese et al., 2005), mimicking or worsening ADHD.

Shared genetic background

Known risk factors for RLS are manifold, and the syndrome has a strong polygenic component (Winkelmann, Schormair, et al., 2007). Apparent monogenic forms of RLS exist, and eight linkage loci have been found so far, but no gene has yet been identified by positional cloning. However, most forms of RLS show a complex mode of inheritance, which might provide an etiological link with ADHD and is also supported by a family-based genetic study (Gao, Lyall, Palacios, Walters, & Ascherio, 2011). An early genome-wide study identified three genome-wide significant associations with RLS (*MEIS1*,

BTBD9, and *MAP2K5*) (Winkelmann, Schormair, et al., 2007). While none of these were associated with ADHD (Schimmelmann et al., 2009), this early study was highly underpowered, and later studies did find links to endophenotypes of ADHD for *BTBD9* (Alemany et al., 2015) and *MAP2K5* (Fliers et al., 2012). One risk gene that might contribute to both conditions is *NOS1,* which codes for neuronal nitric oxide synthase 1 (Reif, 2010; Reif et al., 2009; Winkelmann, Polo, et al., 2007). Taken together, ADHD and RLS may share genetic and non-genetic risk factors, show significant and non-random co-occurrence, and have reciprocal relationships affecting their symptom presentations.

Treatment

Treatment of RLS in ADHD follows current RLS guidelines and can effectively be done with L-DOPA or dopamine receptor agonists (see also above). However, interactions with stimulant medication must be considered, although clinical experience suggests that this does not pose a major problem (Cortese et al., 2005) as well in children and adolescents as in adults. However, L-DOPA only improve restless legs symptoms but not ADHD core symptoms in patients suffering from both disorders (England et al., 2011).

d. Rare neurometabolic disorders that mimic ADHD

The nervous system relies on an adequate supply of nutrients and metabolites to maintain its functions. Not surprisingly, the brain is highly sensitive to metabolic alterations, as brain functions are affected in hundreds of known neurometabolic disorders (NMD; https://www.omim.org/). NMDs are often caused by the lack or dysfunction of an enzyme, transporter, or cofactor necessary for specific chemical reactions in the body, often originating in peripheral organs. Symptoms of NMDs are highly variable, ranging from early life mortality, to progressive neurological manifestations, to minor biochemical alterations that hardly affect quality of life. ADHD symptoms have been reported in several NMDs, including succinic semialdehyde dehydrogenase deficiency, 3-methylcrotonyl-CoA carboxylase deficiency, succinyl-CoA: 3-oxoacid CoA transferase deficiency, fumaryl-acetoacetate

hydrolase deficiency (tyrosinemia type 1), mucopolysaccharidosis III (Sanfilippo disease), acute porphyria, argininosuccinate lyase deficiency and other urea cycle and mitochondrial disorders, Wilson's disease, and phenylketonuria (PKU) (Instanes et al., 2018; Simons, Eyskens, Glazemakers, & van West, 2017).

Shared pathomechanisms and genetics

NMDs are often caused by single, penetrant genetic mutations. Here, we describe PKU and tyrosinemia as examples. PKU is the most common and widely studied autosomal recessive amino acid metabolism disorder. Classical PKU is caused by genetic defects in the gene encoding phenylalanine hydroxylase, resulting in neurotoxic accumulation of phenylalanine. The result is a severe neurological impairment, causing intellectual disability if early diagnosis and a strict dietary treatment are not performed (Schuck et al., 2015). Multiple mechanisms of PKU damage to the nervous system have been suggested, including inhibitory action of excess levels of phenylalanine on tyrosine hydroxylase, which is the rate limiting enzyme in dopamine synthesis (Stevenson & McNaughton, 2013) and hence may well interfere with disturbed dopamine neurotransmission as found in ADHD.

The same is true for tyrosinemia which is caused by a genetic mutation in the fumarylacetoacetase gene that leads to a deficiency in the encoded enzyme, which catalyzes the cleavage of tyrosine metabolites to acetoacetic acid and fumaric acid (Russo, Mitchell, & Tanguay, 2001). Similar to PKU, tyrosinemia patients have increased levels of an aromatic amino acid (tyrosine) which may also interfere with the synthesis of monoamine transmitters, including dopamine (van Ginkel et al., 2016). In recent studies of children with tyrosinemia type 1, a strong correlation was observed between symptoms of ADHD and blood levels of tyrosine, supporting a direct role of this amino acid in the pathogenesis (Barone et al., 2019; van Ginkel et al., 2016). Intriguingly, a lack of tyrosine hydroxylase resulting in decreased synthesis of dopamine and noradrenaline mainly leads to neurological symptoms (DOPA-responsive dystonia) and few psychiatric symptoms (Fossbakk, Kleppe, Knappskog, Martinez, & Haavik, 2014).

Treatment

ADHD symptoms in NMDs might be treated using similar pharmacological and non-pharmacological interventions as for primary (idiopathic) ADHD, however, there are no randomized controlled trials investigating the efficacy and safety of stimulants in NMD patients with ADHD features (Barone et al., 2019). The clinical diagnosis and management of ADHD symptoms in NMDs represent multiple challenges. In severe cases of NMDs, which require specialized diets or pharmacological interventions, the diagnosis and treatment of ADHD may be delayed; a phenomenon known as "diagnostic overshadowing" by the primary disease (Hendriksen, Peijnenborgh, Aldenkamp, & Vles, 2015). On the other hand, in mild and progressive cases of NMDs presenting with psychiatric symptoms, the underlying metabolic disturbance may go undetected if the newborns are not generally screened for those like the phenylketonuria screening. It might be useful to include other NMDs in the newborn screening to prevent neuropsychiatric symptoms in later life. This may have catastrophic consequences, as NMDs can be lethal or produce irreversible brain damage. Fortunately, many NMDs can be successfully treated with dietary or pharmacological intervention, and the list of treatable conditions is gradually increasing.

Unfortunately, no complete overview exists of which diseases are most likely to produce ADHD symptoms, and how these conditions should be diagnosed and treated. As of April 2019, the Online Mendelian Inheritance in Man database (OMIM) database (https://www.omim.org/) contains a total of 24,936 entries and 16,061 gene descriptions; only 79 of these entries refer to ADHD. Most of these entries refer to chromosomal loci identified by early linkage studies, candidate gene studies, and animal studies of ADHD. Most loci have not been replicated or implicated in recent GWAS studies, and their relevance for ADHD is still unclear. Few of the known metabolic syndromes with CNS symptoms, including ADHD symptoms, are listed under this heading. This illustrates the need for a more systemic approach towards this important clinical problem.

e. Neurodegenerative disorders

In all areas of ADHD literature, the absence of studies in the elderly is striking. Beyond mid-adulthood, hardly any information on ADHD can be found. Only a few studies have investigated the prevalence of ADHD in older adults. These studies have reported prevalence estimates ranging from 1.00% to 6.20% (Torgersen, Gjervan, Lensing, & Rasmussen, 2016). The available epidemiological evidence is also limited, but suggests a link between ADHD and neurodegenerative disorders. A small study matched 149 controls to 109 patients with dementia with Lewy bodies (DLB) and 251 patients with Alzheimer's disease (AD) (Golimstok et al., 2011). 48% of the DLB patients had ADHD symptoms or an ADHD clinical diagnosis earlier in life, 15% of the AD patients, and 15% of the controls, suggesting an ADHD association with DLB but not AD. Using the National Health Insurance Research Database of Taiwan, Tzeng et al. matched 675 individuals diagnosed with ADHD and 2025 without ADHD. The hazard ratio for the association of ADHD and dementia was 4.0 (95% CI = 2.5- 6.4). However, use of medication for ADHD did not modify dementia risk (Tzeng et al., 2017). An additional study investigated hospital discharge data on dementia and ADHD. Here, hints were found that a preexisting ADHD was higher in the Lewy Body Dementia patients (IRR: 1.21, 95% C.I. 1.08-1.35). The higher prevalence of ADHD in Alzheimer dementia patients was not significant anymore after adjusting for diabetes mellitus (Fluegge & Fluegge, 2018).

Shared pathomechanisms

There are several hypotheses that could explain an overlap between ADHD and neurodegenerative disorders like dementias and Parkinson's disease. One potential explanation is that there is a substantial overlap of cognitive symptoms in ADHD and neurodegenerative disorders, which often renders a differential diagnosis difficult. Cognitive symptoms that occur in ADHD as well as in prodromal AD include subjective memory complaints (e.g. forgetfulness), deficits in working memory, and difficulty in engaging and sustaining attention (Callahan, Bierstone, Stuss, & Black, 2017). Age of onset is obviously critical to tease the two conditions apart, but this is often difficult in old age. There are conflicting theories as to whether neuropathological processes underlying ADHD and prodromal

AD are similar, or whether these two conditions are completely unrelated (Callahan et al., 2017). Psychosocial factors that are likely to act as mediators between ADHD and neurodegenerative disorders include childhood adversity, lifestyle and lifelong mental co-occurring disorders. Maltreatment during early childhood and a low socioeconomic status during early life are thought to potentially interact with brain development, thereby increasing the risk to develop ADHD (Richards, 2013). Atypical brain development influenced by such early-life social conditions also renders the adult brain more susceptible to neurodegenerative pathology in late life (Seifan, Schelke, Obeng-Aduasare, & Isaacson, 2015). Further shared biological risk factors for dementia and ADHD include low birth weight, prematurity and fetal distress. These factors often lead to impaired neurodevelopment, thereby rendering the brain more vulnerable to ADHD (Thapar, Cooper, Eyre, & Langley, 2013) and potentially increasing the risk for neurodegeneration later in life (Seifan et al., 2015). ADHD is also often associated with poorer social functioning, leading to higher divorce rates and greater social isolation (Klein et al., 2012). Since a socially active lifestyle later in life is protective against neurodegeneration (Fratiglioni, Paillard-Borg, & Winblad, 2004), social isolation that often comes with ADHD is likely to add to dementia risk.

Co-occurring mental disorders are very common in ADHD, reaching up to 77% in adulthood (Sobanski et al., 2007). Among those co-occurring disorders, depression has the highest prevalence in ADHD individuals (Sobanski et al., 2007). It has been shown that depression in midlife is associated with higher rates of AD later in life (Dotson, Beydoun, & Zonderman, 2010; Ownby, Crocco, Acevedo, John, & Loewenstein, 2006) through suggested mechanisms such as oxidative stress, mitochondrial dysfunction and inflammation that lead to neurodegenerative cell death (Kim, Nunes, Oliveira, Young, & Lafer, 2016). Other mediators that might convey a higher rate of neurodegenerative disorders in ADHD patients include health-compromising behaviors as well as socioeconomic and psychosocial factors (Callahan et al., 2017). Individuals with ADHD are more prone to smoking and substance abuse compared to their age-matched peers (Erskine et al., 2016). This might be influenced by a lack of inhibitory control and difficulty regulating impulsivity (Ortal et al., 2015). Smoking and alcohol abuse have been linked to an accelerated decline in cognitive functions in older age, especially in the domains

of memory and executive functioning (Lafortune et al., 2016). Most likely, the mechanism underlying cognitive decline in response to substance abuse is compromised vascular health (Baumgart et al., 2015). In addition to substance abuse, diminished inhibitory control in individuals with ADHD often leads to disorders that are associated with overeating, such as obesity and diabetes. Both disorders are known to have a negative impact on vascular health and increase dementia risk (Baumgart et al., 2015). Disorders of inflammation (Akiyama et al., 2000; Donev & Thome, 2010; Mitchell & Goldstein, 2014; Verdile et al., 2015) and measures of oxidative stress (Joseph, Zhang-James, Perl, & Faraone, 2015; Mattson, 2002; Pohanka, 2014; Verdile et al., 2015; Wang et al., 2014) are also associated with both ADHD and neurodegenerative disorders. These risks may be exacerbated by other shared risk factors such as pesticide (Bouchard, Bellinger, Wright, & Weisskopf, 2010; Kuehn, 2010; Mostafalou & Abdollahi, 2017) and pollution exposure (Calderon-Garciduenas et al., 2004; Moulton & Yang, 2012; van den Hazel et al., 2006).

An important socioeconomic factor that potentially acts as a mediator between ADHD and neurodegenerative disorders is the "cognitive reserve". Cognitive reserve describes the ability of the brain to withstand damage or neuropathology by recruiting a variety of brain networks and/or cognitive strategies developed through different life exposures (Baumgart et al., 2015). Proxies of cognitive reserve include education (Garibotto et al., 2008; Garibotto et al., 2012) and occupational attainment (Garibotto et al., 2008; Stern et al., 1995). Behavioral and cognitive difficulties that are common symptoms of ADHD often lead to limited educational and occupational attainment (Biederman & Faraone, 2006; Hechtman et al., 2016). Lastly, socioeconomic factors, psychosocial factors, and health-compromising behaviors have strong interactions with each other and are often thought to be causally related with each other. Their effects as mediators on the potentially increased rate of neurodegenerative disorders in ADHD are often multifactorial and highly complex (Callahan et al., 2017).

Shared genetic background

ADHD and AD do not appear to be strongly genetically associated with each other, as indicated by the low (0.10) and non-significant genetic correlation (via LD score regression) between the two disorders (Brainstorm et al., 2018; Demontis et al., 2019). Therefore the association of ADHD and dementias on the genetic level might be rather indirect, mediated by disorders which contribute to dementia risk and are directly genetically correlated with ADHD, such as major depression, substance abuse, obesity and diabetes mellitus type 2 (Demontis et al., 2019; Fluegge & Fluegge, 2018). Additionally, major depression and substance abuse disorders do not share a heritability with AD (Brainstorm et al., 2018). A recent study could not find a genetic correlation of ADHD and Parkinson's disease analyzing the summary statistics obtained from the largest meta-analysis of genome-wide association studies of ADHD (20,183 cases; 35,191 controls) and PD (26,421 cases; 442,271 controls)(G. H. Li et al., 2020).

Treatment

Dementia medication, such as choline-esterase inhibitors, has not proven to be effective in treating ADHD (Biederman et al., 2006). For the NMDA-antagonist memantine used for treatment of dementias, there are some pilot studies that potentially suggest improved ADHD symptoms. However, high quality studies are missing (Mohammadzadeh, Ahangari, & Yousefi, 2019). Methylphenidate might be beneficial for treating apathy in AD patients, but again studies of high quality have not been conducted, hampering further conclusions (Ruthirakuhan, Herrmann, Abraham, Chan, & Lanctot, 2018).

2. Diseases of the digestive and urinary system

a. Elimination disorders

Elimination disorders comprise enuresis (EN), daytime urinary incontinence (DUI) comprising different subtypes and fecal incontinence (encopresis, FI) with or without constipation (von Gontard, 2013). They are particularly common in children and show a decreasing prevalence from childhood over adolescence into adulthood. An increased rate of ADHD as well as oppositional-defiant disorder (ODD) has been described in children with elimination disorders at school entry (Niemczyk, Equit, Braun-

Bither, Klein, & von Gontard, 2015). In a clinical sample of 97 children (age 4-17 years) with elimination disorders (enuresis, encopresis and combined) found an increased rate of mental disorders, most commonly ADHD, compared to 50 children without an elimination disorder(Gizli Coban, Onder, & Surer Adanir, 2021). Similar findings were reported in a study of a clinical sample ofv1638 children visiting an incontinence clinic, of which of 28.3% (n = 463) had an ICD-10 psychiatric diagnosis, mainly ODD and ADHD, and 28.6% (n = 463) were overweight or obese. However, this study did not include a control population (von Gontard et al., 2020). In a population based retrospective cohort analysis using a Taiwanese health insurance database, in a total of 1,146 children with enuresis, an increased prevalence of ADHD was reported (OR=3.156, 95% CI: 2.446, 4.073) as well as other mental disorders (anxiety disorder, major depression, autism spectrum disorder). However, ADHD was the third most common mental disorder in the enuresis children after intelligence disability (OR=4.0, 95% CI: 2.48-6.43) and disruptive behavior disorders (OR=3.75, 95% CI: 1.8-8.0) (Tsai et al., 2020). Regarding elimination disorders in clinical samples of ADHD patients, in adolescents with ADHD, an OR >2 for enuresis was found in a population-based study (Jameson et al., 2016). In a study of 331 children (aged 6-10 years) diagnosed with ADHD, a rate of nighttime enuresis of 33.5% was reported which is about 3-fold higher than reported in general population (Khazaie, Eghbali, Amirian, Moradi, & Ghadami, 2018; von Gontard, Overs, Moritz, Thome-Granz, & Hussong, 2019). No data on the prevalence of FI in adolescents exist, and no research on any elimination disorder is available in adults. A recent literature review has summarized the current clinical knowledge on mental disorders co-occurring in elimination disorders (von Gontard & Equit, 2015). In particular, DUI and FI are more frequent in children with ADHD and ODD or conduct disorder (CD).

Shared pathomechanisms

For EN, shared genetic mechanisms have been postulated (see below). In addition, chronicity of EN and the combined occurrence of different elimination disorders is increased in ADHD, most likely due to behavioral sequelae of the disorder which lead to lack of compliance with effective behavioral intervention of elimination disorders (Kovacevic, Wolfe-Christensen, Rizwan, Lu, & Lakshmanan, 2018).

In addition, for DUI and fecal incontinence especially in the presence of ADHD and ODD/CD, shared environmental risk factors have been suggested, such as early life stress, a lack of parental warmth and developmentally appropriate parental supervision and support. Some patients may have also experienced physical or sexual abuse. Additionally, urinary tract infections, medication such as risperidone, alcohol or substance abuse, and diabetes mellitus can trigger DUI, but also EN in genetically predisposed individuals (von Gontard, Vrijens, et al., 2019). For the etiology of FI with obstipation, nutritional aspects (lack of fibre intake and insufficient fluid intake), insufficient exercise, and infrequent toileting play a major role.

Shared genetic background

The current etiological model for the comorbidity of ADHD with elimination disorders comprises shared genetic risk for ADHD and EN, based on family, twin and linkage studies (Bailey et al., 1999). Still, specific molecular mechanisms have not yet been described (von Gontard & Equit, 2015). A recent GWAS compromising 3882 nocturnal enuresis cases and 31,073 controls found that the polygenic risk score for ADHD was significantly positively associated with nocturnal enuresis (OR 1.06, 95% CI: 1.01-1.10) (Jorgensen et al., 2021).

Treatment

Diagnosis and intervention should be based on national and international guidelines, such as AWMF (www.awmf.org), NICE (www.nice.org.uk), the International Children's Continence Society (Neveus et al., 2006), or Rome-III (Rasquin et al., 2006). As a rule, the treatment of elimination disorders consists primarily of behavioral therapy, only as a secondary step, targeted medication either for some subtypes of enuresis or of constipation should be added. Stimulant treatment of ADHD improves compliance with behavioral intervention, and thus needs to be started prior to intervention targeting elimination disorders.

b. Diseases of the digestive system: Celiac disease and inflammatory bowel diseases

In the general population, the prevalence of celiac disease is estimated about 0.5-1.4 % worldwide (Singh et al., 2018). In a study of 111 pediatric celiac patients, 20.7% had a learning disorder and/or ADHD, in comparison to 10.5% of a pediatric control population without celiac disease recruited from the same hospital (Zelnik, Pacht, Obeid, & Lerner, 2004). However, a larger study (362 ADHD vs. 390 healthy controls) did not find increased celiac disease rates in childhood ADHD patients (Gungor, Celiloglu, Ozcan, Raif, & Selimoglu, 2013). In contrast to this, a Swedish register study found increased rates of neuropsychiatric disorders (including ADHD) in children and adolescents with celiac disease (n= 10,903) in comparison with siblings without celiac disease (n= 12,710) (Butwicka et al., 2017). In a small study of children and adolescents with inflammatory bowel disease, a significantly increased number of ADHD diagnoses was found; however, when Crohn's disease and ulcerative colitis were analysed separately, no increased prevalence of ADHD was found (Ben-Or, Zelnik, Shaoul, Pacht, & Lerner, 2015). In their systematic review, Instanes et al. reported a positive association of adult ADHD and celiac disease and hints of a general association with disorders of the digestive system. A narrative review published online in 2016 included eight studies about an association between ADHD and celiac disease. The authors here found that only three out of eight studies reported a positive association between ADHD and CD which however had severe methodological limitations (regarding diagnostic procedures and missing control groups). Therefore the authors of this review concluded that at the moment there is no conclusive evidence for a causal relationship between ADHD and celiac disease (Erturk, Wouters, Imeraj, & Lampo, 2020).

Shared pathomechanisms

Hypotheses suggesting how ADHD (or mental disorders in general) and celiac disease or inflammatory bowel diseases might be causally related describe that autoimmune and inflammatory mechanisms could potentially play a role. It has been suggested that the ingestion and cleavage of gluten into

immunogenic peptides could lead to leaking of peptides through the intestinal wall. These peptides may then be able to traverse the blood-brain-barrier, and potentially induce low grade inflammation in the brain (Clappison, Hadjivassiliou, & Zis, 2020). However, human studies providing strong evidence for those theories are lacking (Dunn, Nigg, & Sullivan, 2019).

Shared genetic background

A significantly increased frequency of several autoimmune disorders, including celiac disease, was found in first-degree relatives of patients with ADHD in a Swedish registry study (X. Li, Sjostedt, Sundquist, Zoller, & Sundquist, 2019). In contrast, the analysis of Tylee et al. could not show an association between ADHD and celiac disease (J. P. Davis, Dumas, Briley, & Sussman, 2018).

Treatment

Gluten-free diets have been more extensively investigated in autism-spectrum disorder and less so in ADHD (Ly et al., 2017). Interestingly, a recent study found significantly increased ADHD symptoms in newly diagnosed adult celiac disorder patients in comparison to healthy controls, which normalized after treatment with a gluten-free diet for 12 months (Kristensen et al., 2019). Possibly, celiac disease leads to ADHD-like symptoms, rather than reflecting true comorbidity. Larger studies are needed to clarify the relationship between celiac disease and ADHD.

3. Endocrine and metabolic disorders

a. Obesity

Obesity is of major public concern, primarily due to the high frequency, associated high economic burden and decrease in life expectancy (Cortese et al., 2016; Engin, 2017b). A diagnosis of obesity is given to individuals whose body mass index (BMI) is calculated to be over 30, using the equation weight in kilograms divided by height in metres squared (kg/m^2) (WHO Obesity and overweight Available online: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (accessed on Apr 11, 2019)). Heritability estimates for obesity are substantial (~74% (Elks et al., 2012)). Obesity has

frequently been reported as significantly associated with ADHD (de Zwaan et al., 2011; Gungor, Celiloglu, Raif, Ozcan, & Selimoglu, 2016; Instanes et al., 2018; Spencer, Faraone, Tarko, McDermott, & Biederman, 2014; Waring & Lapane, 2008), although this can seem contradictory, as individuals with ADHD are often characterized as 'hyperactive' (Foster et al., 2003) thought to go along with decreased body weight. In 2016, two meta-analyses investigating the link between ADHD and obesity were published (Cortese et al., 2016; Nigg et al., 2016). Sample sizes were large (728,136 and 703,397 individuals, respectively), and both studies found a significant association between ADHD and obesity (OR 1.2-1.3). The pooled prevalence of obesity was increased by ~70% in adults and ~40 % in children with ADHD. In those reviews, as well studies that investigated the prevalence of obesity in ADHD (n=17 studies) as studies that investigates prevalence of ADHD in obese population (n=2) were included. Health insurance data confirmed those findings and report an increased prevalence of obesity (OR = 2.85; 95% CI = 2.80-2.91) in children with ADHD (Akmatov et al., 2021). Regarding the life span perspective, obesity prevalence seem to increase with age which is true for ADHD patients as well as for the general population. However, there is an interesting follow-up study, reporting that also adult male persons with a remitted ADHD have an increased rate of obesity in later life compared to healthy controls without a history of childhood ADHD (Cortese et al., 2013). A longitudinal study of 140 girls with ADHD also confirmed a higher obesity rate in young adulthood in comparison to non-ADHD controls (n=88). In childhood, there were no significant differences in BMI between the groups, but in young adulthood, 40.2% of the ADHD females met criteria for obesity in comparison to 15.4% of the controls (Porter, Henry, Halkett, & Hinshaw, 2021) .

Shared pathomechanisms

There are several possibilities which could explain an association between ADHD and obesity. These include ADHD increasing the risk of obesity, obesity (or factors associated with it) causing/mimicking ADHD symptoms, and shared genetic risk factors/neurobiology (Cortese et al., 2016). Firstly, ADHD has been suggested to contribute to obesity through its impulsive and inattentive symptomatology (Cortese & Castellanos, 2014). Impaired inhibitory control (due to impulsive tendencies) could result

in overeating, night eating, snacking and preference for fast foods as well as food high in carbohydrates (i.e. convenience products, “cafeteria diet”: high fat, high sugar meals), whereas decreased attention could result in lack of awareness of food intake and poor meal planning, contributing to irregular eating patterns. This hypothesis has recently been strengthened by an analysis of the IMAGEN cohort, hinting at a shared neural substrate of impulsivity traits and BMI as well as the PRS scores of ADHD and BMI, which consists of shared common associations with whole-brain grey matter and similarities in a reward-related impulsivity fMRI task (Barker et al., 2021). Secondly, it is possible that factors associated with obesity may also be underlying the development of ADHD-like symptoms, although this has only been shown for variables affecting sleep (such as shorter or later sleep) (Cortese & Vincenzi, 2012).

Shared genetic background

Chen et al. conducted a family study of 472,735 index males born during 1973-1992. They concluded that ADHD and overweight/obesity share familial risk factors, which are not limited to those causing overweight/obesity through the mediation of ADHD (Q. Chen et al., 2017). Significant genetic correlations have been identified between both ADHD-BMI (r=0.21-0.32) (Demontis et al., 2019) and ADHD-obesity (r=0.29-0.34) (Demontis et al., 2019), suggesting that shared neurobiological or metabolic dysfunction may explain at least part of the association between the disorders. Specifically, the biological processes of circadian rhythm and dopaminergic neurotransmission have been implicated (Nigg et al., 2016). Altered circadian functioning (e.g. sleeping problems) has been significantly associated with both ADHD (Coogan & McGowan, 2017) and BMI/obesity (Um, Hong, & Jeong, 2017), and may contribute to obesity by disrupting temporal eating patterns and causing changes in metabolic hormones (Engin, 2017a). However, genetic evidence for an influence of circadian rhythm on the overlap between ADHD and obesity is limited (Mota et al., 2020). Dysregulation of dopaminergic signaling is thought to lead to ‘reward deficiency syndrome’, which is characterized by insufficient positive reinforcement to rewards (Cortese & Vincenzi, 2012). In an attempt to compensate for this lack of sensitivity, individuals may develop a dependency on

'unnatural' immediate awards, such as overeating (Volkow, Wang, & Baler, 2011). This hypothesis has been further strengthened by a recent study using GWAS statistics, which found that dopaminergic genes were enriched among genes linked to both ADHD and obesity (Mota et al., 2020). A recent study using the data from 1982 Pelotas (Brazil) Birth Cohort at age 30-year follow-up with 3630 participants could confirm a positive association of BMI (OR = 1.05; 95% CI, 1.00-1.09) and fat mass (OR = 1.04; 95% CI, 1.00-1.07) with ADHD. Furthermore, the polygenic risk score for BMI was nominally associated with ADHD (OR = 1.65; 95% CI, 1.02-2.65) (Martins-Silva et al., 2021).

Treatment

In children, adolescents and adults with ADHD, stimulant treatment can lead to weight loss (Mellstrom, Forsman, Engh, Hallerback, & Wikstrom, 2018; R. Weisler et al., 2009). One of the meta-analyses described above showed that ADHD was no longer found significantly associated with obesity in pharmacologically-treated patients (Cortese et al., 2016), supporting previous research (Levy, Fleming, & Klar, 2009).

b. Diabetes mellitus

Diabetes mellitus (DM) is an endocrine and metabolic condition requiring lifelong treatment. There are three main types of DM: type 1 DM (T1DM) or immune-mediated diabetes, type 2 DM (T2DM) caused by insulin-resistance, and gestational DM (GDM) characterized by glucose-intolerance during pregnancy (American Diabetes, 2010). DM affects 425 million people worldwide, and its incidence is estimated to increase by about 4-5% each year (Cho et al., 2018).

Recent epidemiological studies suggest increased rates of autoimmune and metabolic diseases, including DM (Butwicka et al., 2016; Chen, Lee, Yeh, & Lin, 2013; Q. Chen et al., 2018; Kapellen, Reimann, Kiess, & Kostev, 2016; P. R. Nielsen, Benros, & Dalsgaard, 2017), among individuals with ADHD. Several population registry studies investigated the co-occurrence of ADHD and DM in children. Two such studies reported an increased rate of T1DM in children with ADHD (up to 1.5-fold) (Butwicka et al., 2016; Butwicka, Frisen, Almqvist, Zethelius, & Lichtenstein, 2015; P. R. Nielsen et al., 2017). One

of the few studies investigating T2DM showed a significant 3-fold increase in the rate of T2DM in children with ADHD compared to controls, but did not find increases in T1DM (Chen et al., 2013).

Studies in adults also report increased prevalence of T2DM in individuals with ADHD, while no study to date has investigated the co-occurrence of T1DM in ADHD in adults. A recent longitudinal study of nearly 36,000 adolescents and young adults with ADHD and 72,000 age- and sex-matched controls, followed up after 10 years, reported that individuals with ADHD were more likely than controls to develop T2DM in adulthood (hazard ratio [HR]=2.84) (M. H. Chen et al., 2018). Similarly, an investigation of over 5,5 million individuals aged 18 to 64 years (of whom 61,129 had ADHD) selected from the Swedish population registers showed increased prevalence of T2DM in adults with ADHD compared to those without ADHD (3.9% in ADHD compared to 1.6% in adults without ADHD) (Q. Chen et al., 2018). Data from the National Health Interview Survey of a national representative sample of the USA, revealed a positive association of ADHD and diabetes mellitus of OR 1.54 (95% CI, 1.16-2.04) which was not modified by obesity (Xu, Liu, Yang, Snetselaar, & Jing, 2021). There is a paucity of studies investigating the prevalence of ADHD in patients suffering from diabetes mellitus. A small study of 230 T1DM children reported an ADHD prevalence of 10.4%. The children with co-occurring ADHD and T1DM displayed a higher complication rate and a poorer control of their T1DM (Vinker-Shuster, Golan-Cohen, Merhasin, & Merzon, 2019).

A recent meta-analysis investigated the association of maternal diabetes and ADHD in the offspring, using data from three case-control studies and six cohort-studies (Zhao et al., 2019). While maternal diabetes was not significantly associated with an increased rate for ADHD in the offspring in the highly heterogeneous case-control studies, the cohort studies indicated a significant effect (risk ratio of 1.40), although publication bias was identified (Zhao et al., 2019). A further recent study also investigated the rate of ADHD in the offspring of mothers with DM (522 with T1DM, 7,822 with T2DM, and 29,534 with GDM), and 290,000 children of control mothers (Xiang et al., 2018). Children of mothers with a T1DM diagnosis had the greatest ADHD prevalence (57%), followed by children of mothers with T2DM (43%), and children of mothers with GDM requiring antidiabetic medications (26%) (Xiang et al., 2018).

Shared pathomechanisms

There is currently little information on shared pathogenicity for ADHD and the different types of DM. As ADHD is associated with obesity (Cortese et al., 2016; Nigg et al., 2016), and obesity is a main risk factor for T2DM, this indirect relationship might be the most important shared pathomechanism for T2DM similarly as is the case in bipolar disorder (Kittel-Schneider et al., 2020). Additionally, ADHD patients show poorer lifestyle habits and sleep disturbances, which may also contribute to the risk of T2DM (Landau & Pinhas-Hamiel, 2019).

Shared genetic background

The possibility of genetic risk factors contributing to the observed associations between ADHD and DM was highlighted by the recent GWAS of ADHD, where a significant genetic correlation was observed between clinically diagnosed ADHD and increased risk for T2DM (rg=0.18, P=7.80×10−5) (Demontis et al., 2019). However, it is still unclear whether the correlation between T2DM and ADHD is direct or rather indirect, mediated through the increased prevalence of obesity as a main risk factor of T2DM.

Regarding diabetes mellitus type 1 (T1DM), a Swedish register study showed that children of T1DM patients had a significantly increased rates of ADHD (Hazard Ratio 1.29 (95% CI 1.15-1.42). T1D in mothers was more strongly associated with ADHD in children (HR 1.35 [95% CI 1.18-1.55]) compared to T1D in the fathers (HR 1.20 [95% CI 1.03-1.41])(Ji, Chen, Sundquist, & Sundquist, 2018). In the analysis of Tylee et al., T1DM was rather negatively genetically correlated with ADHD (Tylee et al., 2018). However, it remains unclear whether this reflects an underlying shared genetic factor, or the diabetic metabolic state of mothers potentially leading to increased rates of ADHD in the exposed children.

Treatment

No significant interactions between anti-diabetic medication and stimulant drugs have been reported so far (May & Schindler, 2016). Further, it has been demonstrated that methylphenidate can affect glucose uptake in rats, providing a potential mechanism for these observations (Porrino & Lucignani,

1987). Such an effect could potentially mask DM-induced blood glucose changes, hindering timely intervention, and therefore further studies should aim to clarify whether ADHD stimulant-based medication can alter blood glucose concentration. Additionally, there are studies showing that comorbid ADHD leads to a poorer glycemic control in adolescents with T1DM as well to a poorer adherence insulin pump therapy in adults (Macek et al., 2019; Merzon et al., 2020).

c. Disorders of the thyroid gland

In clinical diagnostic procedures, thyroid function is usually investigated to exclude hypo- or hyperthyroidism as somatic differential diagnoses of ADHD/ADD (Hage, Hohmann, Millenet, & Banaschewski, 2020). However, there is also evidence suggesting an association between thyroid disorders and ADHD. Several studies observed that ADHD was common in individuals with resistance to thyroid hormones (RTH) (Brucker-Davis et al., 1995; Hauser et al., 1993). A Taiwanese nationwide population-based study, including more than 75,000 newly diagnosed children and adolescents with ADHD, reported that ADHD patients were more likely to be comorbid with hyperthyroidism (1.72-fold) or hypothyroidism (2.23-fold) than controls. Likewise, a prospective study screening for thyroid abnormalities found an increased prevalence of thyroid abnormalities in the ADHD group compared to the general population, and hypothyroidism was more common than hyperthyroidism (Weiss, Stein, Trommer, & Refetoff, 1993).

Autoimmune diseases affecting thyroid function also seem to be related to ADHD risk. A Danish nationwide prospective cohort study including more than 23,000 ADHD cases suggested that a personal history of autoimmune thyroiditis increased the prevalence of ADHD in children, adolescents and young adults (P. R. Nielsen et al., 2017). Consistent with this, a Taiwanese nationwide population-based study reported that ADHD patients had a 2.53-fold higher prevalence of autoimmune thyroid disease than controls (P. H. Chen et al., 2018). Finally, in a retrospective US study determining the burden of adult ADHD in an employed population, hypothyroidism was more common in adults with

ADHD than in matched controls without ADHD, and it was especially common in adults with ADHD and comorbid depression (Hodgkins, Montejano, Sasane, & Huse, 2011).

Thyroid hormones are critical for neurological development in intrauterine and early life. Until mid-gestation, the fetus is totally dependent on maternal thyroid hormone production and transmission (Moog et al., 2017). For this reason, links between maternal thyroid hormone abnormalities and offspring ADHD have also been investigated in several studies. The Danish nationwide prospective cohort study mentioned above found a maternal history of thyrotoxicosis to increase the rates of ADHD in children, adolescents and young adults (P. R. Nielsen et al., 2017). In a meta-analysis however, maternal hormone insufficiency during pregnancy was not associated with ADHD in offspring (W. Thompson et al., 2018). A more recent systematic review suggested moderate evidence for a link between maternal thyroid hormone levels and ADHD in offspring, and for a possible association between early-treated congenital hypothyroidism and later ADHD (Drover et al., 2019). Conversely, no relationship was found between neonatal thyroid hormones and ADHD development. However, methodological limitations of included studies prevented the authors from drawing strong conclusions.

Shared pathomechanisms

As thyroid hormones are important in brain development, it is likely that maternal thyroid dysfunction during pregnancy could influence fetal brain development, and lead to an increased prevalence of ADHD. However, due to the lack of studies it remains unclear whether ADHD and thyroid disorder are co-occurring, or whether clinical symptoms of hypothyroidism as well as hyperthyroidism might rather mimic ADHD symptoms, leading to ADHD misdiagnosis.

Shared genetic background

A Swedish study showed an association of ADHD and autoimmune diseases in families, however, this was more pronounced for other autoimmune diseases than for hypothyroidism (X. Li et al., 2019). A

recent analysis of shared genetic risk showed an association between hypothyroidism and ADHD, however, this was only significant before correcting for multiple comparison (Tylee et al., 2018).

Treatment

ADHD medication does not increase the risk of secondary thyroid dysfunction (P. H. Chen et al., 2018). In a small study, it has been shown that treatment with liothyronine in children with ADHD but without resistance to thyroid hormone has no effects on the ADHD core symptoms (Weiss, Stein, & Refetoff, 1997).

4. Cardiovascular diseases

Due to the effects of stimulant medication on heart rate and blood pressure, it is importance to determine whether ADHD patients have a higher prevalence of congenital heart diseases or a higher risk of developing cardiovascular diseases later in life, such as arterial hypertension, coronary artery disease, myocardial infarction and heart failure. However, the prevalence of any cardiovascular disease in ADHD populations has not been sufficiently researched. A Swedish register study analysing the data of 5,551,807 adults aged 18 to 64 years found an increased prevalence of hypertension in adult ADHD patients, even after excluding patients with comorbid substance abuse, depression, bipolar disorder and anxiety (PR: 1.72, 95% CI: 1.56–1.89) as well as T2DM (PR: 2.11, 95% CI: 1.79–2.42) (Q. Chen et al., 2018). However, neither BMI nor obesity were taken into account in this study. Further, a recent review reported that the data regarding hypertension and ADHD are inconsistent, and not all studies found a positive correlation (Landau & Pinhas-Hamiel, 2019).

In children, a small study found mean platelet volume (MPV) was significantly increased in a children ADHD group compared to control group (Yorbik, Mutlu, Tanju, Celik, & Ozcan, 2014). However, the significance of increased MPV level in ADHD remains unclear, and it is not clear whether this could lead to an increased risk of coronary artery disease in later life. Adolescents with malformation of the great heart arteries and single ventricle congenital heart disease showed increased rates of ADHD compared to healthy controls (DeMaso et al., 2017; DeMaso et al., 2014), perhaps reflecting increased ADHD

prevalence in e.g. 22q11.2 deletion syndrome which also goes along with cardiac malformations (Schneider et al., 2014). This finding is strengthened by an Asian study that showed an increased rates of childhood ADHD and autism spectrum disorder in children with congenital heart disease (Tsao et al., 2017). Conversely, there are suggestions that children which have suffered from a perinatal or childhood stroke can develop secondary ADHD or ADHD-like symptoms (T. S. Williams et al., 2018). Similar findings have been reported in children with congenital heart disease who had cardiac surgery in the first 5 years if their life and those children seem prone to develop an ADHD-like phenotype (Cainelli et al., 2021; Holst et al., 2020).

Shared pathomechanisms

The association of obesity with ADHD is well documented, therefore this might be the factor conveying an increased risk of acquired cardiovascular disease in ADHD. Patients with ADHD also frequently have an unhealthy life style and diet, higher prevalence of nicotine and alcohol abuse, and increased risk for major depression, which is an independent risk factor for cardiovascular disease (Elliott, 1994). As the rate of obesity is already increased in ADHD children, this can lead to metabolic syndrome in later life which is a confirmed risk factor for developing cardiovascular disease in the long run (C. M. Lee, Huxley, Wildman, & Woodward, 2008). Children with congenital heart diseases show higher prevalence for ADHD or ADHD-like symptoms, however, this connection might be due to significant cerebral hemodynamic changes after birth that could impair neurodevelopment (Marino et al., 2012).

Shared genetic background

A recent cross-disorder GWAS showed a small significant correlation of ADHD genetic risk with intra-cerebral haemorrhage (ICH) genetic risk, but no significant correlations with cerebral ischemic stroke or early onset stroke (Brainstorm et al., 2018). Apart from risk for arterial hypertension, there does not seem to be an increased risk of cardiovascular disease in ADHD patients due to the mental disorder itself.

Treatment

Stimulants and atomoxetine can lead to increases in blood pressure and heart rate in children, adolescents and in adults (Liang et al., 2018). However, in the majority of patients those increases are not of clinical significance, and there is no evidence for an increased cardiovascular mortality due to ADHD medication (Hennissen et al., 2017; Liang et al., 2018; Westover & Halm, 2012). A recent systematic review reported that ADHD medications are associated with moderate elevations in resting heart rate and blood pressure. There were published adverse effects in association with ADHD stimulants including arrhythmias, non-ischemic cardiomyopathy, Takotsubo cardiomyopathy, and sudden death. But the authors concluded that there was no convincing evidence of a causal mechanisms but there is a paucity of randomized controlled trials addressing long-term safety of ADHD medications in adults (Torres-Acosta, O'Keefe, O'Keefe, & Lavie, 2020). In children with congenital heart disease and ADHD symptoms, data are rare and stimulant treatment needs to considered under individual risk-benefit assessment (Batra, Alexander, & Silka, 2012). In general, ADHD patients should still be regularly monitored regarding cardiovascular parameters when taking medication.

5. Autoimmune and allergic diseases

Celiac disease, inflammatory bowel syndrome, diabetes mellitus type I as well as autoimmune disorders of the thyroid are also autoimmune disorders but have been discussed in previous chapters.

a. Atopic disorders and allergies

Atopy describes the genetically determined disposition to react with increased IgE generation after aerogen, gastrointestinal or cutaneous contact with natural or synthetic environmental molecules and compounds (type I allergic reaction). The classical atopic disorders are allergic asthma, allergic rhinitis and atopic dermatitis (Thomsen, 2014; Wheatley & Togias, 2015). For several decades, there has been controversy as to whether ADHD is associated with atopic disorders (Schmitt & Romanos, 2009). In the last ten years, substantial evidence for a clinically relevant relation of atopic disorders and ADHD has been accumulated. Descriptively, ADHD has been found to be associated with atopic eczema (Cortese

et al., 2018; Schmitt et al., 2009), asthma (Cortese et al., 2018), and to a lesser extent, with allergic rhinitis and atopic food allergy (Feng et al., 2017; Miyazaki et al., 2017; Schans, Cicek, de Vries, Hak, & Hoekstra, 2017). The overall evidence points to an increased rate of allergic diseases in ADHD compared to general population about 50% (see below for more detail). A recent systematic review and meta-analysis found 25 studies exploring the association of asthma and ADHD. Four of those studies investigated the prevalence of ADHD in asthma patients and in comparison to non-asthma controls and the other studies explored the prevalence of asthma in ADHD children compared to non-ADHD controls. 17 studies showed a significant positive association between asthma and ADHD, OR between 1.38 and 1.69, the authors calculated a significant OR of 1.52 (95% CI 1.42-1.63) taking 23 of the studies into account(Kaas et al., 2021). In a cross-sectional study including 113,671 adolescents in Israel comorbidities of asthma phenotypes were investigated and a significant association with ADHD was reported (Machluf, Farkash, Rotkopf, Fink, & Chaiter, 2020). In a systematic review investigating the association of asthma, food allergies, allergic rhinitis, atopic dermatitis and allergic conjunctivitis, the authors included five studies, all explored the rates of allergic diseases in ADHD and non-ADHD controls. The authors showed a positive significant association with ADHD and asthma (OR: 1.80, 95% CI: 1.57 - 2.07). Despite a higher heterogeneity and inconsistency between studies, they found also hints for a higher prevalence of allergic rhinitis in ADHD children compared to the control groups (OR: 1.59, 95% CI: 1.13 - 2.23), increased rates of atopic dermatitis in ADHD vs. controls (OR: 1.43, 95% CI: 1.09 -1.88) and higher prevalence of allergic conjunctivitis in ADHD in comparison to the control groups (OR: 1.69, 95% CI: 1.04 - 2.76). There was no difference between ADHD and non-ADHD control groups with regards to food allergies (Miyazaki et al., 2017). A recent study using data from a Danish birth register, matching children with a diagnosis of atopic dermatitis to children without atopic dermatitis, revealed a significant association of ADHD and atopic dermatitis (aHR 1.91, 95% CI 1.56-2.32), but not depression (aHR 0.58, 95% CI 0.21-1.56), anxiety (aHR 1.47, 95% CI 0.98-2.22) or self-harming behavior (aHR 0.88, 95% CI 0.27-2.88) (Vittrup et al., 2021). The published data regarding adult ADHD and asthma is scarce but there is a case-control study showing an adjusted OR (aOR) of 2.9 for asthma in ADHD patients compared to general population, the aOR for rhinitis and eczema were 1.5 and 1.4

respectively (van der Schans, Aikman, de Vries, Hoekstra, & Hak, 2017). A cross-sectional study with adults showed similar results, here asthma was significantly more prevalent in the ADHD patient group compared to the non-ADHD controls (24.4% vs. 11.3% and OR = 2.54, 95% CI 1.89-3.44) (Fasmer, Riise, et al., 2011). Data from USA population based surveys including all age groups (354,416 children and adolescents and 34,613 adults) showed that atopic dermatitis was associated with ADHD in as well children (aOR 1.41, 95% CI1·03-1·26) and adults (aOR 1.61 (CI 1.25-2.06) and the ADHD risk in atopic dermatitis was then further increased by other co-occurring diseases like allergic diseases, headaches and obesity (Strom, Fishbein, Paller, & Silverberg, 2016). Even though the link between atopy/allergy and ADHD seems to be solidly established, there is remaining uncertainty about the involvement of specific atopic/allergic diseases and the underlying mechanisms engendering the co-occurrence. Furthermore, it is less clear if those potential comorbidities change over the lifespan in ADHD.

Shared pathomechanisms

Atopic disorders themselves are substantially interlinked, and the respective manifestations share a common trajectory referred to as the "atopic march". Following primary sensitization, atopic eczema is a highly frequent early manifestation affecting at least 20% of all children, and is the most common cause of disrupted sleep in infants (Smaldone, Honig, & Byrne, 2007). Even though atopic eczema in most cases is the primary clinical manifestation of atopy, the initial sensitization may have occurred before and may be attributed to the antigenic properties of food. Atopic food allergy (e.g. to cow milk protein) is often diagnosed when eczema occurs in children within the first months after birth, and in many cases a strict diet results in reductions of the food-related IgE levels and itchy rashes. However, only about half of all children with atopic eczema actually develop increased IgE levels, further complicating the search for the underlying mechanisms within the comorbidity. Moreover, it questions whether non-IgE related food allergies actually exist (Romanos et al., 2011).

Following the atopic march, allergic rhinitis and asthma are subsequent manifestations of the initial sensitization. Interestingly, the association of atopy with ADHD seems to be stronger when children develop several atopic disorders, possibly indicative of a dose-dependent effect (C. Y. Lee et al., 2016).

Nevertheless, the temporal pattern and longitudinal course of atopy opens up the possibility that the association between ADHD and asthma (and allergic rhinitis) may be engendered by previous presence of early atopic disorders such as food allergy and eczema. While the evidence in this regard is conflicting, one longitudinal birth cohort study suggested that the presence of atopic eczema in the first two years of life increases the occurrence of ADHD symptoms at the age of 10 years by 50%, even when eczema was restricted to the first two years (Schmitt et al., 2010). Furthermore, several studies revealed that the association between atopic eczema and ADHD was particularly strong in those children with impaired sleep (Romanos, Gerlach, Warnke, & Schmitt, 2010; Strom et al., 2016). Beyond childhood, asthma, insomnia and headaches were also positively associated with ADHD in adults (Strom et al., 2016).

While the existing data suggest long-term effects from early exposure to atopy, other studies explored direct effects as a potential explanation. Both atopic symptoms as well as antihistamine medication (Schmitt et al., 2018) may have behavioral effects on children, and the observed ADHD symptoms may be interpreted as phenocopy or aggravation of existing symptoms rather than a "real" comorbid expression. However, exploratory clinical studies provide little evidence that this may be the case (van der Schans et al., 2019).

Assuming shared etiological factors in the observed association between atopy and ADHD, several mechanisms have been proposed, including genetic, hormonal and environmental (Buske-Kirschbaum et al., 2013; Buske-Kirschbaum et al., 2019). Considering that cytokines may pass through the brain blood barrier, an interesting approach is to investigate the presumable effects of early immunological and inflammatory processes on brain development (see next chapter). This notion is supported by recent data suggesting that the association is only present in those children with allergic sensitization (C. F. Yang, Yang, & Wang, 2018).

Shared genetic background

Recent studies could show a familial correlation of probable genetic origin between asthma and ADHD in combined results of a meta-analysis and a Swedish population-based study, which remained

significant (OR 1.45) even after simultaneously controlling for several possible confounders in the population-based study (Cortese et al., 2018). This was also confirmed by a genome-wide cross-trait association study that identified seven genetic loci shared between ADHD and asthma (Z. Zhu et al., 2019). Another genome-wide correlation analysis also found a significant uncorrected genetic correlation for ADHD with allergy and asthma, but not atopic dermatitis (Tylee et al., 2018).

Treatment

Data from a Swedish register study suggested that ADHD is increased in children with asthma, but asthma medication does not seem to be associated with an increased prevalence of ADHD (Holmberg, Lundholm, Anckarsater, Larsson, & Almqvist, 2015). A recent small study investigating the preventive effect of the anti-histaminic agent cyproheptadine on sleeping problems and appetite loss induced by methylphenidate in ADHD children could not show any significant improvement (Kadkhoda Mezerji, Moharreri, Mohammadpour, & Elyasi, 2019). Another study suggested that early antihistamine exposure in children with atopic dermatitis might contribute to the increased risk of ADHD, however a potential causal association could not be determined in this study (Schmitt et al., 2018). There is evidence that in children with allergic rhinitis and increased ADHD symptoms, the treatment of the allergic rhinitis leads to improvement in ADHD symptoms (M. T. Yang et al., 2016). H3-receptor antagonists have also been studied for their use as ADHD medication, however, no substance from those studies is currently available for the treatment of ADHD due to discouraging clinical studies (R. H. Weisler et al., 2012).

b. Other immunological disorders

Although sparse, recent evidence has suggested an association between immune disturbances and ADHD (Lasky-Su et al., 2008; Misener et al., 2008; Oades, Dauvermann, Schimmelmann, Schwarz, & Myint, 2010), and an increasing number of studies have shown a strong association between immune disorders and the risk of ADHD (Hegvik, Instanes, Haavik, Klungsoyr, & Engeland, 2018; P. R. Nielsen et al., 2017). More specifically, significant associations were found between ADHD and several

autoimmune diseases such as psoriasis (Hegvik, Jacobsen, Fredriksen, Zayats, & Haavik, 2016), type 1 diabetes (see also above) (P. R. Nielsen et al., 2017), autoimmune hepatitis, autoimmune thyrotoxicosis (see above and (M. H. Chen et al., 2017; Valentine et al., 1997)), ankylosing spondylitis, inflammatory bowel disease (as discussed in the previous chapter) (M. H. Chen et al., 2017), multiple sclerosis, and rheumatoid arthritis. In some cases, such diseases showed a cross-generational association, with immune diseases in parents and increased prevalence of ADHD in the offspring (M. H. Chen et al., 2017; Instanes et al., 2017; P. R. Nielsen et al., 2017). Those findings were recently confirmed by an additional longitudinal cohort study, including 12,610 children exposed to maternal autoimmune disease in comparison to 50,440 unexposed children. The authors reported that any autoimmune disease was significantly positively associated with ADHD in the exposed offspring (HR, 1.30; 95% CI 1.15-1.46). Specifically, T1DM (HR, 2.23; 95% CI, 1.66-3.00), psoriasis (HR, 1.66; 95% CI, 1.02-2.70), and rheumatic fever or rheumatic carditis (HR, 1.75; 95% CI, 1.06-2.89). Additionally, a meta-analysis was conducted and again, any autoimmune disease (2 studies: HR, 1.20; 95% CI, 1.03-1.38), T1DM (4 studies: HR, 1.53; 95% CI, 1.27-1.85), hyperthyroidism (3 studies: HR, 1.15; 95% CI, 1.06-1.26), and psoriasis (2 studies: HR, 1.31; 95% CI, 1.10-1.56) were shown to be associated with ADHD rates in exposed children of mothers with autoimmune disorders(T. C. Nielsen et al., 2021).

Shared pathomechanisms

Studies searching for immunological markers in ADHD patients have not provided conclusive findings, likely due to small sample sizes and a high heterogeneity among the biological markers searched for. Cytokines are involved in the modulation of the immune system, and elevated pro-inflammatory cytokine levels were observed to interfere with brain development and several neurotransmitter systems (Buske-Kirschbaum et al., 2013; Jasoni, Sanders, & Kim, 2014). Variable levels of pro-inflammatory cytokines (e.g. IL-6, IL-10, TNF-alpha) have been found in the serum/plasma of patients with ADHD, with some reports showing an increase compared to healthy controls (O'Shea et al., 2014; Oades et al., 2010), while other studies found no imbalances between those with and without ADHD.

A recent study showed significant positivity for anti-Yo antibodies (autoantibodies against Purkinje cells of the cerebellum) and a higher immunoreactivity against anti-Purkinje cell antibodies in a cohort of patients diagnosed with ADHD (Donfrancesco et al., 2016; Passarelli et al., 2013). Increased serum levels of anti-basal ganglia antibodies (i.e. antistreptolysin O (ASO)) (Sanchez-Carpintero, Albesa, Crespo, Villoslada, & Narbona, 2009; Toto et al., 2015) as well as antibodies against the dopamine transporter (Giana et al., 2015) have also been detected. Furthermore, children of mothers with elevated levels of maternal thyroid peroxidase antibodies also were observed to have more ADHD symptoms (Modesto et al., 2015). Increasing literature has also shown the possible association between a parental history of immune abnormalities and ADHD in offspring (M. H. Chen et al., 2017; P. R. Nielsen et al., 2017). For example, higher frequencies of several immune system disorders (e.g. rheumatoid arthritis, T1DM, autoimmune thyroiditis, multiple sclerosis) have been found among mothers and fathers of offspring with ADHD compared with parents of control subjects (Instanes et al., 2017) as also described above in more detail.

Most of the ADHD-associated immune disorders share a common immune background, i.e. an imbalance in the Th17/Treg axis (Ryba-Stanislawowska, Werner, Brandt, Mysliwiec, & Mysliwska, 2016), which might provide additional insight into the pathomechanisms underlying comorbidity. Th17 cells play a role in the defense against bacteria, but also in autoimmunity and in allergic diseases classically considered as Th2-mediated disorders (Meller et al., 2015; Oboki, Ohno, Saito, & Nakae, 2008; Patel & Kuchroo, 2015), with an increase in these cells predisposing to autoimmunity or allergy (Angkasekwinai et al., 2007; Bettelli et al., 2006). A balanced Th17/Treg cells axis is needed for proper immune function and for preventing autoimmune phenomena. Increasing evidence suggests that in addition to microglia, T cell activity (especially Th17 and Treg cells) might be needed for proper brain development and functioning of areas playing a role in mood, behavior and cognition, such as the hippocampus (Lewitus & Schwartz, 2009; Lewitus et al., 2009). This brain area has also been implicated in ADHD (Plessen et al., 2006).

Shared genetic background

Recent GWAS data analysis suggests a genetic correlation of ADHD with rheumatoid arthritis and psoriasis (Tylee et al., 2018). The *SLC9A9* gene, which is a gene traditionally implicated in multiple sclerosis, has also been implicated in the etiology of ADHD (Esposito et al., 2015; Zayats et al., 2015; Zhang-James, Middleton, Sagvolden, & Faraone, 2012).

Treatment

Methylphenidate (one of the most prescribed pharmacological treatment for adults and children with ADHD (Safer, 2016) may induce a transient suppression of T helper cells (Auci, Fikrig, & Rodriquez, 1997). Similarly, desipramine (a tricyclic antidepressant that has been used for the treatment of ADHD) has been shown to decrease serum $CD4^{+}IL17^{+}$Th17 cell levels and to increase $CD4^{+}CD25^{+}$FoxP3 Treg cell levels (Zhang et al., 2013). A recent study showed that elevated serum IL17 levels at baseline were selectively associated with a greater reduction in depression severity with bupropion-escitalopram combination treatment, but not with escitalopram in monotherapy or with the combination of venlafaxine-mirtazapine (Jha et al., 2017). Moreover, bupropion (a dopaminergic antidepressant commonly used for the treatment of co-occurring depression in ADHD patients) has also been shown to reduce IL-17-mediated inflammatory responses and joint swelling in a murine antigen-induced arthritis model (Ebbinghaus, Gajda, Boettger, Schaible, & Brauer, 2012). Conversely, acetaminophen (paracetamol) has been shown to increase Th17 cells in the liver (X. Zhu & Uetrecht, 2013), and an association between ADHD diagnosis and the use of acetaminophen during pregnancy has been shown in several studies (Ystrom et al., 2017), supporting the idea of an Th17/Treg axis imbalance in the etiopathogenesis of ADHD.

Outlook

In our narrative review, we focused on the most robust and/or relevant non-mental diseases of childhood and adult ADHD that have partly been described in previous systematic reviews and meta-analysis. In many cases, we find that information on co-occurring diseases in adults with ADHD is

lacking, and a full lifespan perspective for a single co-occurring non-mental disease can hardly ever be deduced from current literature. Most striking is the virtually complete absence of any information about ADHD and associated non-mental diseases in the elderly. In a previous review, we drew similar conclusions about studies related to mental comorbidity of ADHD (Franke et al., 2018). There is thus an urgent need for additional studies, including longitudinal designs, that allow a more complete picture of ADHD across the lifespan to be drawn.

In investigating the modality of the association between ADHD and other diseases through review of potential shared genetic and environmental factors and what is known about effects of treatment, we observed that in several cases, non-mental illnesses might constitute differential diagnoses rather than co-occurring diseases. For celiac disease, for example, several interventional studies show an improvement of ADHD symptoms after treatment for celiac disease. The same might be true for rare neurometabolic disorders: if the underlying non-mental disease can be treated, the ADHD-like symptoms might be improved. Though neurometabolic and celiac disease are often diagnosed in childhood and adolescence, mild forms can go undiagnosed until adulthood. Thyroid disorders form another case where differential diagnoses might lead to different treatment decisions: hypothyroidism as well as hyperthyroidism can mimic ADHD symptoms in both children and adults.

In several cases, the association between ADHD and a non-mental disease might be rather indirect, this could, for example, be the case for the co-occurrence with type II diabetes mellitus, which may be conveyed by the increased prevalence of obesity in ADHD. A similar picture could be true for the potential increased rates of neurodegenerative disorders in ADHD, which appear to be rather mediated by shared psychosocial and environmental risk factors than by shared neurobiological risk factors. The data for epilepsy, migraine, elimination disorders, asthma, restless legs syndrome and obesity hint at being truly associated as an co-occurring disease of ADHD over the lifespan (see also Figure 1). In general, interventional studies investigating ADHD symptoms before and after the sufficient treatment of the non-mental disease are needed.

From a clinical point of view, the described co-occurring diseases prompt for careful, but age-specific screening of patients diagnosed with ADHD, as differential diagnoses or as co-occurring conditions

because treatment of those could positively influence ADHD symptoms and/or improve general health in ADHD patients. After birth, screening for neurometabolic disorders is an imperative as such, but might also serve as a preventive measure for ADHD. In childhood, there is a wide range of relevant disorders that may be co-occurring with ADHD or prompt its symptoms. Taking a thorough history for elimination disorders and atopic as well as auto-immune disorders (including T1DM, autoimmune thyroid and gastrointestinal disorders) is warranted. Pediatric RLS can be mistaken for ADHD, however in the case of true c-occurrence, RLS treatment alleviates RLS but not ADHD symptoms. Additionally, children suffering from epilepsy should be evaluated for possible ADHD. In adulthood, attention should be paid to detect thyroid disorders (at least measuring TSH at the initial assessment is recommended). Also, comorbid migraine becomes increasingly common in ADHD with age and should be asked for in the diagnostic interview (also vice versa).

Throughout the lifespan, obesity is an important problem of patients with ADHD. The routes to obesity are likely manifold and heterogeneous (see above), leaving ample opportunity for preventive measures e.g. changes of food preference, avoiding of snacking, and food restriction. Addressing obesity may have a pronounced preventive effect on T2DM, other metabolic disorders, cardiovascular disease and, ultimately, also neurodegenerative disorders. The risk towards the latter might also be affected by targeting smoking, sedentary lifestyle (prevalent in ADHD, e.g. due to increased screen time) and other unhealthy behaviors. All of those behaviors are addressed by adequate pharmacological and non-pharmacological treatment of ADHD. This underscores the huge public health improvement potential of diagnosing and treating ADHD correctly (as also pointed out in cost models, e.g. (Libutzki et al., 2019), which in many occasions/countries still lacks the informed and insightful approach necessary from the different disciplines diagnosing and treating ADHD in children and adults, including psychiatrists, psychologists, pediatricians and general practitioners.

Where shared neurobiological mechanisms between ADHD and co-occurring non-mental diseases do exist, a deeper investigation of those will be useful in identifying the mechanisms that underlie the links between the diseases. Recent work by us and others, for example, identifies dopamine signaling as one of the main biological pathways shared by ADHD and obesity through genome-wide association

approaches (Mota et al., 2020). Consistent with this finding, altering dopamine signaling through methylphenidate treatment is known to normalize the rates of obesity in ADHD (Cortese & Castellanos, 2014). Extending such neurobiological work to other ADHD-non-mental disease combinations may thus not only increase our knowledge about the underlying pathways contributing to the co-occurrence, it could also help to identify novel treatment targets.

In summary, there is a huge potential for improving health across the lifespan for those with ADHD in understanding the causes and consequences of lifespan co-occurring diseases across the entire spectrum of diseases, not stopping short at mental disorders. Knowing about ADHD and associated diseases has consequences for diagnostics and treatment in both children and adults. However, there is insufficient attention for the lifespan perspective yet in most of the existing scientific studies into ADHD co-occurring diseases, and blind spots exist for ADHD and its associated non-mental diseases in old age, and for longitudinal investigations that go across different phases of life. Large-scale studies, like those making use of population registries (e.g. those of the Scandinavian countries), provide perfect opportunities for such important work. Also the large population studies that are now coming available (e.g. UK Biobank, All of Us, Million Veteran Study) increase our opportunities to learn more about ADHD – a prerequisite being that questions about ADHD diagnosis and symptoms are included in the surveys, which seems less often the case in those studies collecting data from adults. As those data also provide neurobiological and genetic data, performing mechanistic studies can provide new insights into ADHD and associated diseases, potentially identifying novel biological pathways and treatment targets.

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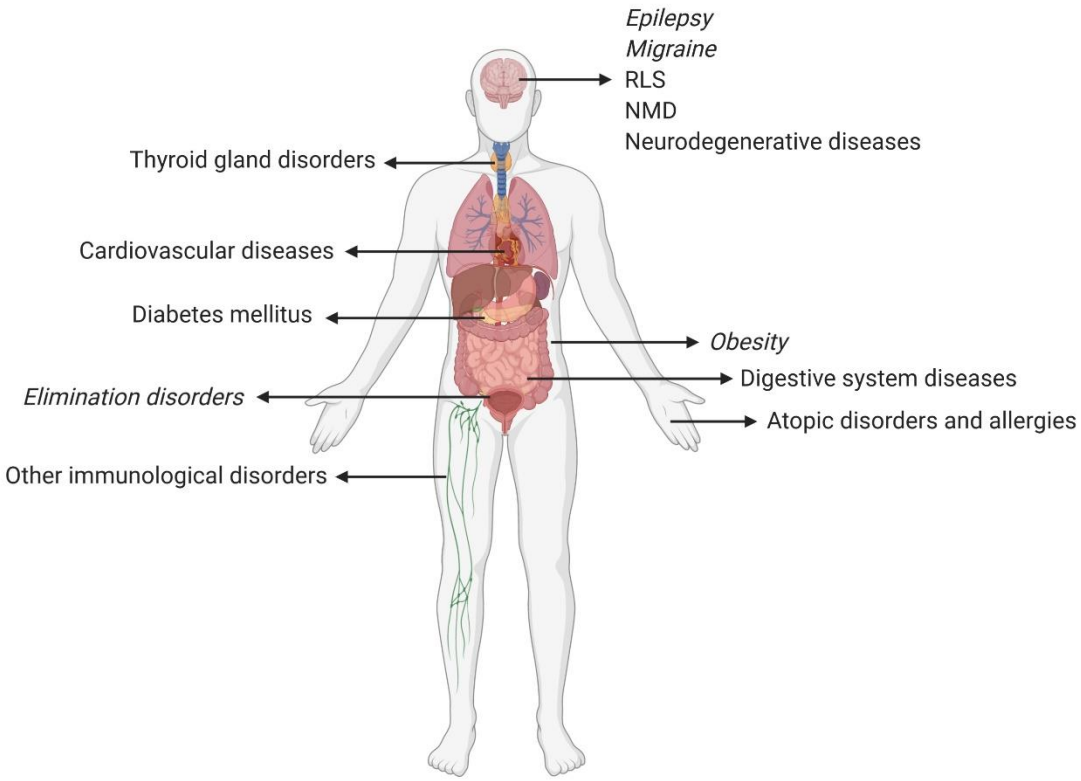
Conflict of interest

CMF receives royalties for books on ASD, ADHD, and MDD. SKS has received author's and advisory honoraria from Takeda/Shire and Medice Arzneimittel Pütter GmbH in the last 3 years. BF has received educational speaking fees from Medice Arzneimittel Pütter GmbH. JH has received educational speaking fees from Lilly, HB Pharma, Biocodex, Medice Arzneimittel Pütter GmbH, Takeda/Shire. TB served in an advisory or consultancy role for Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Shire, and Infectopharm. TB received conference support or speaker's fees from Lilly, Medice, and Shire. TB received royalities from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press. AR serves on advisory boards and receives speaker's honoraria from Medice, Shire/Takeda, Janssen, neuraxpharm, Servier and SAGE. Jonna Kuntsi has given talks at educational events sponsored by Medice; all funds are received by King's College London and used for studies of ADHD. In the past year, SVF received income, potential income, travel expenses continuing education support and/or research support from Takeda, OnDosis, Tris, Otsuka, Arbor, Ironshore, Rhodes, Akili Interactive Labs, Sunovion, Supernus and Genomind. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. He also receives royalties from books published by Guilford Press: *Straight Talk about Your Child's Mental Health*, Oxford University Press:

Schizophrenia: The Facts and Elsevier: ADHD: *Non-Pharmacologic Interventions.* He is Program Director of www.adhdinadults.com. JB has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Takeda/Shire, Roche, Medice, Angelini, Janssen, and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties. YG has received persona fees and non-financial support from Medscape, non-financial support from Shire/Takeda, and personal fees from Studentlitteratur, all outside the submitted work. J.A.R.Q was on the speakers' bureau and/or acted as consultant for Eli-Lilly, Janssen-Cilag, Novartis, Shire, Takeda, Bial, Shionogui, Lundbeck, Almirall, Braingaze, Sincrolab, Medice and Rubió in the last 5 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Janssen-Cilag, Rubió, Shire, Takeda, Shionogui, Bial, Medice and Eli-Lilly. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 5 years: Eli-Lilly, Lundbeck, Janssen-Cilag, Actelion, Shire, Ferrer, Oryzon, Roche, Psious, and Rubió.
HL has served as a speaker for Evolan Pharma and Shire/Takeda and has received research grants from Shire/Takeda; all outside the submitted work. All other authors declare no conflict of interest.

Figure 1: Non-mental diseases associated with ADHD



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