Catecholaminergic and Cholinergic Neuromodulation in Autism Spectrum Disorder: A Comparison to Attention-Deficit Hyperactivity Disorder

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Abstract

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder characterized by social impairments and restricted, repetitive behaviors. Treatment of ASD is notoriously difficult and might benefit from identification of underlying mechanisms that overlap with those disturbed in other developmental disorders, for which treatment options are more obvious. One example of the latter is attention-deficit hyperactivity disorder (ADHD), given the efficacy of especially stimulants in treatment of ADHD. Deficiencies in catecholaminergic systems (dopamine (DA)), norepinephrine (NE)) in ADHD are obvious targets for stimulant treatment. Recent findings suggest that abnormalities in catecholaminergic systems may also be a factor in at least a subgroup of ASD. In this review we scrutinize the evidence for catecholaminergic mechanisms underlying ASD symptoms, and also include in this analysis a third classic ascending arousing system, the acetylcholinergic (ACh) network. We complement this with a comprehensive review of DA-, NE-, and ACh-targeted interventions in ASD, and an exploratory search for potential treatment-response predictors (biomarkers) in ASD, genetically or otherwise.

Based on this review and analysis we propose that 1) stimulant treatment may be a viable option for an ASD subcategory, possibly defined by genetic subtyping; 2) cerebellar dysfunction is pronounced for a relatively small ADHD subgroup but much more common in ASD and in both cases may point towards NE- or ACh-directed intervention; 3) deficiency of the cortical salience network is sizable in subgroups of both disorders, and biomarkers such as eye blink rate and pupillometric data may predict the efficacy of targeting this underlying deficiency via DA, NE, or ACh in both ASD and ADHD.

Keywords: Autism Spectrum Disorder, Attention-Deficit Hyperactivity Disorder, Clinical Pharmacology, Dopamine, Norepinephrine, Acetylcholine, Cerebellum, Purkinje Cells, Genetics, Salience Network, Biomarkers

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1. Introduction

1.1 Neurobiological Correlates of ASD

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by behavioral (including social) deficits (American Psychiatric Association 2013). In the DSM-5 the two foremost criteria for ASD, often referred to as the core deficits, are social deficits and restricted and repetitive behaviors. In addition to these core deficits, patients with ASD suffer from a wide range of impairments. Examples of such impairments are deficits in learning (Klinger et al. 2007; Schreibman et al. 2015), executive function (Craig et al. 2016), language (Tager-Flusberg 2006; Edgar et al. 2015), aggression (Kanne and Mazurek 2011), hyperactivity (Lecavalier 2006), sleeping (Malow et al. 2006; Deserno et al. 2019) and sensory processing (Marco et al. 2011). Many view ASD as a very heterogeneous disorder (Masi et al. 2017). While high-functioning groups can - at least in part - effectively participate in society, low-functioning ASD patients show higher severity of symptoms (e.g. no verbal communication) and cannot function independently (Lord et al. 2004; Whitby and Mancil 2009; Baghdadli et al. 2012; Masi et al. 2017). Due to the great heterogeneity of ASD in addition to the complex nature of social communication and interaction, it is hard to identify effective biological/pharmacological treatments for ASD patients. To date, there are no effective medications that treat the core deficits of ASD and many treatments tend to focus on other symptoms such as irritability (Cory 2010).

As to the underlying neurobiological correlates, ASD has been linked to abnormal function or structure of prefrontal cortex (PFC; Carper and Courchesne 2005; Stoner et al. 2014; Zhu et al. 2015), amygdala (Baron-Cohen et al. 2000), cerebellum (Becker and Stoodley 2013; Hampson and Blatt 2015), insula (Uddin and Menon 2009; Kosaka et al. 2010), basal ganglia (Nayate et al. 2005), as well as numerous other brain regions (Stoner et al. 2014). Others have linked the dysfunction of broader systems or networks to ASD. Examples are the broken mirror neuron hypothesis and the dysfunction of the salience network (SaN; Ramachandran and Oberman 2006; Uddin and Menon 2009). The focus on only one or a group of neural structures has not led to a unifying hypothesis of ASD, as no consistent pathology has emerged for the disorder - no genetic or neurobiological factors are very consistently present in ASD, nor are they specific when compared to other psychiatric disorders (Amaral et al. 2008; de la Torre-Ubieta et al. 2016; Müller 2007). Müller (2007) suggests that ASD should be viewed as a distributed disorder in which most — if not all — brain networks are affected. Therefore, examining connectivity between and within brain regions and neural networks could yield a more comprehensive picture of the neurobiological deficits underlying ASD.

Connectivity within well-defined networks in relation to ASD has been an area of great interest (e.g. Anderson et al. 2011; Duan et al. 2017; Kana et al. 2014; Kleinhans et al. 2008; Mizuno et al. 2006; Monk et al. 2009; Nair et al. 2013; Nomi and Uddin 2015; Uddin et al. 2013; Wass 2011). Sridharan et al. (2008) suggest that the SaN is responsible for switching between the activation of the default-mode network (DMN) and executive control networks (ECN; Seeley et al. 2007; Menon and Uddin 2010). Whereas the DMN is often regarded as the resting-state network that activates when no task is being performed, the ECN activates during the performance of tasks (Seeley et al. 2007; Sridharan et al. 2008; Toro et al. 2008; Raichle 2015). Some authors suggest that the anterior insula, an important structure in the SaN, is aberrantly connected in ASD (Uddin and Menon 2009; Ebisch et al. 2011; Guo et al. 2019). Similar ideas have been proposed for the DMN and ECN (Farrant and Uddin 2016; Moseley et al. 2015; Murdaugh et al. 2012). Nevertheless, results from over- and under-connectivity investigations are — likely in part due to methodological problems and the heterogeneity of ASD cohorts — inconsistent and reproducibility has been limited (Müller et al. 2011).

Understanding neural connectivity is an important first step in identifying how the brain effectuates important functions. However, a connection diagram of the brain should indeed be seen as a first step, and not as the final answer to comprehending how nervous systems realize function. One potential complication, as evidenced in animal studies, is that connectivity is dynamic and can change over time (Brezina 2010; Marder 2012; Bargmann and Marder 2013). Such dynamic changes over time occur across several years in interaction with the environment (Lawrence et al. 2019), but also within a matter of (milli)seconds (Marder 2012). Almost all current human ASD studies have assessed connectivity as being static within a single functional magnetic resonance imaging (fMRI) scanning session, while such connections are likely dynamic (Brezina 2010; Marder 2012; Falahpour et al. 2016). One study did consider these dynamic changes when studying ASD patients. Using fMRI, Falahpour et al. (2016) compared conventional ‘static’ scanning procedures with ‘dynamic’ scanning procedures that take into account physiological change during the scanning period (Allen et al. 2014). Using the static procedure, previous findings were replicated: ASD patients showed aberrant connectivity in the DMN. In contrast, the dynamic scanning procedure showed that ASD patients did not differ from control subjects in peak connectivity but did show greater intraindividual variability of functional connectivity during the scanning period. Thus, connections in ASD are not ‘broken’ but show higher levels of intraindividual variability across time (Falahpour et al. 2016; London 2018). Variability of connectivity, as opposed to under- or over-connectivity, may contribute to the pathology of ASD. It is therefore important to consider what drives

the variability of connectivity. One obvious perspective is the role of the classic ascending modulating neurotransmitter systems, or neuromodulatory systems.

Neuromodulation is the altering of activity within a neural network by electrical, mechanical or chemical means (Krames et al. 2009).¹ Nervous systems have a wide range of such neuromodulatory systems (Brezina 2010; Marder 2012). This review focuses on the three classic neuromodulatory systems: NE from the locus coeruleus (LC), DA from the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc), and acetylcholine (ACh) from the nucleus basalis of Meynert (NBM; Andén et al. 1966; Aston-Jones and Cohen 2005a; Foote and Morrison 1987; McCormick 1989, 1992; Mesulam 2000; Stahl 2008). These ascending projections have widespread potent and sustained – or more transient (e.g. Aston-Jones and Cohen 2005a, b; Schutte et al. 2020) - modulatory effects on neurotransmission in the forebrain (Andén et al. 1966; Foote and Morrison 1987; McCormick 1989, 1992; Robbins 2000; Stahl 2008; Marder 2012). In addition, focusing on these three systems in relation to ASD also provides a window on potential underlying mechanisms that overlap with those disturbed in other developmental disorders, for which treatment options are more obvious. The prime example is attention-deficit hyperactivity disorder (ADHD), given the efficacy of especially stimulants in treatment of ADHD (Wilens 2008; Huss et al. 2017).

1.2 Comparing ASD to ADHD

Indeed, neuromodulatory neurotransmitters have been of particular interest in relation to attention-deficit hyperactivity disorder (ADHD; del Campo et al. 2011; Robbins 2000; Robbins and Arnsten 2009). ADHD is a neurodevelopmental disorder characterized by hyperactivity, impulsivity and inattention (American Psychiatric Association 2013). Although ASD and ADHD differ (i.e. age of onset and typical introverted vs. extraverted profiles), the disorders do share many similarities. For example, ASD and ADHD show overlap in genetic risk factors (Ronald et al. 2008; Niklasson et al. 2009; Geschwind 2011) and there is a high level of comorbidity between the two disorders (Clark et al. 1999; Simonoff et al. 2008; Rommelse et al. 2011; van Steensel et al. 2013; Antshel et al. 2013; Stevens et al. 2016). Both disorders also have a higher prevalence in boys than girls (Barkley 2006; Bruchmüller et al. 2012; American Psychiatric Association 2013; Loomes et al. 2017). Additionally, ASD and ADHD patients show impaired social cognition and suffer comparable deficits in

¹ Although some contemporary work uses the term neuromodulation in relation to transcranial magnetic stimulation, transcranial direct-current stimulation or implants to modulate neural activity (e.g. Krames et al. 2018; Nobusako et al. 2017; Sokhadze et al. 2016), here we use this term in relation to neurotransmitters in the brain.

executive functioning (Sinzig et al. 2008; Mazza et al. 2014; Caillies et al. 2014; Bora and Pantelis 2016; Craig et al. 2016).

Dysfunction of the DA and NE systems has often been suggested as the neurobiological mechanism underlying ADHD (e.g. del Campo et al. 2011; Faraone 2018; Robbins and Arnsten 2009; Xing et al. 2016). For example, genes coding important proteins for catecholaminergic neuromodulation have often been implicated in the disorder and current ADHD medication such as methylphenidate (MPH) targets DA and NE (Faraone 2018; Faraone et al. 2011; Faraone and Larsson 2019; Huss et al. 2017; Maia et al. 2017; Myer et al. 2018; Stahl 2013).

When compared to ASD, similar findings have been reported in regard to connectivity in ADHD: intraindividual variability of connectivity seems to be abnormal (R. Wang et al. 2015; X. H. Wang et al. 2018). More specifically, the DMN seems to show lower intraindividual variability in connectivity, while the rest of the brain shows higher intraindividual variability in connectivity (de Lacy and Calhoun 2018). In a case study, Salgado et al. (2007) describe a patient with a brainstem lesion who showed ADHD symptoms (e.g. inattention). These symptoms could be ameliorated by MPH (Salgado et al. 2007). This illustrates the important role of the brainstem catecholamines in ADHD symptoms and how ADHD medication can help restore abnormal neuromodulation (see Johnston et al. 2014).

If ASD and ADHD are characterized by similar neuromodulatory disturbances, targeting the same neurotransmitter systems as current ADHD medication may prove helpful for the treatment of ASD. To illustrate more generally, such off-label application of stimulants has also proven valuable in other contexts such as subpopulations within major depressive disorder (Candy et al. 2008; Corp et al. 2014). In this review, catecholaminergic and cholinergic neuromodulation will be examined in relation to ASD and ADHD – with a focus on the SaN, cerebellum and genetics (to be further introduced later). These neuromodulatory systems will be described in detail and related to the symptomatology of ASD and ADHD. Subsequently, human trials with pharmacological agents targeting the catecholaminergic and cholinergic systems in ASD will be discussed. This will provide insight into which pharmacological agents could help the treatment of ASD and whether such treatments could be similar to the current pharmacological treatment of ADHD.

2. The Locus Coeruleus-Norepinephrine Neuromodulatory System

2.1 Connectivity of the Locus Coeruleus

The LC is a bilateral nucleus in the brainstem containing ~60,000 NE neurons that project throughout almost the entirety of the brain (Andén et al. 1966; Aston-Jones and Waterhouse 2016; Aston-Jones and Cohen 2005a; Mouton et al. 1994; Szabadi 2013). Classically, the LC-NE system was thought to influence the level of arousal and was suggested to be important in the modulation of whole brain states (Jouvet 1969; Berridge and Waterhouse 2003). The widespread projections of the system are in line with such an idea. However, recent evidence shows that individual neurons in LC have idiosyncratic projections (Chandler et al. 2014; Kebschull et al. 2016). Furthermore, ensembles of LC-NE neurons can signal specific neural sites (reviewed in Chandler et al. 2019; Totah et al. 2018). This challenges the classical idea that the LC-NE system projects homogeneously across neural sites and suggests that the system may be more flexible than previously thought.

Research in rodents has shown that ACC and prefrontal areas receive the most abundant LC-NE projections (Schwarz et al. 2015). Uniquely, insular cortex receives input from both LC-NE neurons and prefrontal NE neurons (Robertson et al. 2013). Using viral-genetic tracing methods, Schwarz et al. (2015) were able to elucidate afferent projections to LC. Afferent projections come from many sites including cortical areas and amygdala. Notably, Purkinje cells (PC) in the cerebellum provide a considerable fraction of the input into LC and do not project to any LC-NE output sites (Schwarz et al. 2015). In turn, LC seems to modulate cerebellar associative synaptic plasticity at climbing fiber-PC synapses (Carey and Regehr 2009). This indicates reciprocal neural actions between LC and cerebellum.

2.2 Norepinephrinergic Neuromodulation in ASD and ADHD

In an extensive review, London (2018) described how the LC-NE system may be involved in the symptomatology of ASD. Although mostly based on indirect evidence, LC-NE system dysfunction has the potential to explain many symptoms and impairments reported in ASD and ADHD patients. Potential aberrant LC-NE system functioning in ASD can explain deficits in learning, attention, language, sensory processing and emotional functioning, but can also explain abnormalities in the autonomic nervous system and sleeping problems (London 2018). ADHD patients show all of the impairments listed above, although sometimes these impairments differ in severity (Cohen et al. 2000; Bruce et al. 2006; Geurts and Embrechts 2008; Tonhajzerova et al. 2009; Konofal et al. 2010; Ghanizadeh 2011; Musser et al. 2011; Craig et al. 2016; Gregory et al. 2017a, b; Chevrier et al. 2019). The impairments mentioned above can be linked to the LC-NE system (London 2018),

which likely functions aberrantly in ADHD (Darcq and Kieffer 2015; Xing et al. 2016; Faraone 2018; Faraone and Larsson 2019). Thus, potential impaired LC-NE system functioning can explain a wide range of symptoms and impairments that are reported in both ASD and ADHD. It is important to establish if, and in what way, the LC-NE system functions differently in ASD and ADHD when compared to the healthy population so that pharmacological targets may be identified.

Molecular Genetics

Genetically, some genes have been identified that may influence the development of the LC-NE system, which may be affected in ASD and ADHD. Dopamine β -hydroxylase (DBH) is an enzyme that catalyzes the conversion of DA into NE (Kaufman and Friedman 1965; Stahl 2013). Alterations of *DBH*, the gene coding DBH, can lead to a relative increase in DA levels and a relative decrease in NE levels, which is highly relevant for LC-NE functioning. *DBH* seems to play a role in ADHD (Tong et al. 2015; Wigg et al. 2002; Zhang et al. 2004; but see Inkster et al. 2004). For example, *DBH* gene variant rs129882 was found to be associated with ADHD in a large sample (Tong et al. 2015). In ASD, *DBH* has also been implicated and maternal levels of DBH seem to play a role (Robinson et al. 2001; Jones et al. 2004; Yrigollen et al. 2008; Jwaide et al. 2020). Furthermore, in an ASD sample, *DBH* was associated with both ASD and ADHD behaviors (Barrie et al. 2018). Another potentially relevant NE-related gene is *SLC6A2*, which codes for the NE reuptake transporter. Although some studies report associations between *SLC6A2* and ADHD (Bobb et al. 2005; Faraone et al. 2011; Hawi et al. 2013; Sengupta et al. 2012), others report no such association (de Luca et al. 2004; McEvoy et al. 2002). Sengupta et al. (2012) suggest that sex, subtypes of ADHD phenotypes and specific haplotype blocks of the *SLC6A2* gene are important factors to consider (see X. Zhu et al. 2004). Other evidence shows that *SLC6A2* is important in identifying whether MPH can be an effective treatment for ADHD patients. Specifically, two polymorphisms, rs28386840 and rs5569, were found to be associated with decreased MPH efficacy in ADHD patients (Yang et al. 2004; Myer et al. 2018). The one study examining a relation between *SLC6A2* and ASD did not reveal a significant association (Park et al. 2014).

Purkinje Cells and Cerebellum

As stated, PCs in the cerebellum have substantial projections to the LC (Schwarz et al. 2015). Notably, abnormalities of PCs, such as lower total number of cells or decreased density, are some of the most replicable neurobiological findings in ASD – approximately 75% of patients show abnormalities in PCs (Fatemi et al.

2002; Whitney et al. 2009; Passarelli et al. 2013; Hampson and Blatt 2015). Some evidence indicates that PC numbers are also decreased in ADHD, but more research is necessary (Rout et al. 2012; Passarelli et al. 2013). As Rout et al. (2012) note, decreased PC numbers may only be observed in an ADHD subtype with cerebellar abnormalities as revealed from more global neuroimaging assessment (see Durston et al. 2011). Currently, the genetic underpinnings of PC abnormalities in ASD are still beginning to be understood (Hampson and Blatt 2015). One study by Rout et al. (2012) reported increased serum levels of antibodies against glutamic acid decarboxylase 65 (GAD65) in ASD and ADHD patients when compared to healthy subjects (GAD65-antibodies were not present in any of the healthy subjects). GAD65 is important in γ -aminobutyric acid (GABA) synthesis. Serum from the ASD and ADHD groups was subsequently applied to mouse cerebellum, where the antibodies reacted with PCs. Application of these antibodies ultimately resulted in PC death (Mitoma et al. 2003; Rout et al. 2012). Increased antibodies against GAD65 may therefore contribute to PC abnormalities in ASD and ADHD, but research in larger samples is required. Aberrant efferent PC projections in ASD and perhaps ADHD unto LC may lead to LC-NE dysfunction. However, the reverse is also conceivable. As stated, the LC modulates cerebellar associative synaptic plasticity, which influences PC firing (Carey and Regehr 2009). Therefore, anomalous LC-NE functioning can lead to disturbed PC activity. The last option is that the reciprocal projections between LC and cerebellum in both directions are anomalous, which would also indicate LC-NE and PC/cerebellar dysfunction.

Functional Networks

Among its widespread projections, LC innervates two important nodes of the SaN: ACC and insular cortex (Seeley et al. 2007; Robertson et al. 2013; Schwarz et al. 2015). Neuromodulation may play an important role in SaN regulation since this network shows a high level of dynamic changes over time when compared to other networks (Chen et al. 2016). Dysfunction of SaN has been suggested to underlie ASD and has been implicated in ADHD (Uddin and Menon 2009; Aboitiz et al. 2014; Sidlauskaitė et al. 2016). Interestingly, when compared to ECN, DMN and SaN, similar functions have been proposed for the LC-NE system (Aston-Jones and Cohen, 2005a, b). According to Adaptive Gain Theory, the LC has two modes. A *phasic* mode in which phasic activity is relatively high and tonic activity is moderate and a *tonic* mode which shows the reverse pattern. When in *phasic* mode, metabolic resources are used to process task-relevant stimuli, and this improves current task performance. In contrast, when in *tonic* mode, metabolic resources are no longer used to focus on the task and is linked to distractibility. Importantly, in *tonic* mode, resources are used to identify salient stimuli in the

environment (Aston-Jones and Cohen, 2005a, b; Aston-Jones and Waterhouse, 2016). Whereas ECN and LC's *phasic* mode are important during task performance, DMN and SaN can be linked to LC's *tonic* mode. Furthermore, Zerbi et al. (2019) reported altered levels of intrinsic connectivity within the DMN and SaN in rodents after LC activation. These data further implicate the role of the LC-NE system in network modulatory effects.

Altogether, accumulating evidence from genetic, network and cellular studies is emerging for aberrant functioning of the LC-NE system in ASD and ADHD. LC-NE dysfunction may explain numerous symptoms observed in both disorders and NE could therefore be a potential pharmacological target for ameliorating such symptoms. However, note that some of the presented evidence is somewhat indirect and more direct evidence is needed to precisely identify in what way the LC-NE system functions aberrantly in ASD and ADHD. One possibility is that mutual connections between LC and cerebellar PCs are instrumental in this respect, pointing to a possible efficacy of NE-directed treatment in a majority of ASD patients, and perhaps a minority of ADHD patients.

3. The Dopaminergic Neuromodulatory System

3.1 Connectivity of VTA and SNc

The DArgic neuromodulatory system has two important DArgic nuclei in the brainstem: the SNc and VTA (Beier et al. 2015; Mesulam 2000). It is important to consider the differences between these two nuclei. Firstly, the SNc and VTA have different efferent and afferent projections (Watabe-Uchida et al. 2012). The SNc mainly innervates unto dorsal striatum (DS; Lerner et al. 2015; Morales and Margolis 2017). Moreover, evidence shows that the medial SNc and lateral SNc have independent efferent pathways to medial and lateral DS, respectively (Lerner et al. 2015). In turn, lateral DS was found to project unto SNc (Watabe-Uchida et al. 2012; Lerner et al. 2015). VTA was found to project to nucleus accumbens (NAc), PFC and amygdala (Beier et al. 2015, 2019; Chandler et al. 2013; di Michele et al. 2005; Morales and Margolis, 2017). Afferent projections unto VTA come from many areas including NAc, amygdala and ventral pallidum (Watabe-Uchida et al. 2012; Beier et al. 2015, 2019).

3.2 Dopaminergic Neuromodulation in ASD and ADHD

Recently, the DA system has also been implicated in ASD. Pavál (2017) posits that two DArgic pathways play an important role in the core deficits of ASD: the mesocorticolimbic (MCL) pathway and the nigrostriatal (NS)

pathway. VTA projections unto PFC and NAc make up the MCL-pathway. This pathway is important in reward processing and shows hypoactivation in ASD patients (Dichter, Felder, et al. 2012; reviewed in Pellissier et al. 2018). In ASD, the value of social rewards is thought to be greatly reduced, which results in a lack of social motivation (Dawson et al. 2005; Chevallier et al. 2012). Social motivation theory suggests that a lack of social motivation is the underlying cause of many social impairments in ASD (Chevallier et al. 2012; Dichter, Damiano and Allen. 2012). Thus, aberrant MCL-pathway functioning is thought to underlie the social impairments of ASD (Pavál 2017). However, note that others posit that dysfunction of the Social Brain Network (i.e. inferior frontal gyrus, amygdala and fusiform face area) can explain impaired social motivation (Misra 2014), which would imply that social motivation can be impaired without MCL-pathway abnormalities. The NS-pathway consists of SNc projections unto DS. This pathway plays an important role in motor aspects of goal-directed behavior (Lewis et al. 2007; Howe and Dombeck 2016). For example, increased sensitivity of striatal and cerebellar DA D2 receptors underlies motor impairments in Parkinson's disease (Rinne et al. 1990). Both optogenetic and pharmacological stimulation of the DA D1 receptor in the NS-pathway results in repetitive and stereotyped autistic-like behavior in mice (Lee et al. 2018). These data implicate the NS-pathway in the core behavioral deficit of ASD (Horev et al. 2011; Pavál 2017; Lee et al. 2018). However, accumulating evidence opposes the functional distinction between the MCL- and NS-pathways (Rossi et al. 2013; Ilango et al. 2014; Haber 2016). For example, rodents will self-administer stimulation to the SNc, implying that this structure plays a role in reward, although not a part of the MCL-pathway (Ilango et al. 2014). Nonetheless, even if the pathways are not functionally distinct, evidence suggests that DArgic dysfunction may underlie the core symptoms of ASD.

It is generally accepted that dysfunction of the DA system plays a vital role in ADHD pathology (Levy and Swanson 2001; Faraone et al. 2005; Tripp and Wickens 2009; Faraone and Mick 2010; Purper-Ouakil et al. 2011; Faraone 2018). DA dysfunction in ADHD has been linked to deficits in executive functions and learning (Swanson 2003; Silvetti et al. 2013) but also to inattention, hyperactivity and impulsivity (Swanson 2003; Genro et al. 2010). The development of SN and VTA connectivity has been shown to be disturbed in ADHD (Tomasi and Volkow 2012). Furthermore, dysfunction of the MCL-pathway has been associated with ADHD-behaviors (Stark et al. 2011) and the NS-pathway has been linked to hyperactivity in the disorder (Genro et al. 2010). These data indicate dysfunction of the MCL- and NS-pathways in ASD and ADHD.

Molecular Genetics

Irregularities in genes that are involved in the development of the DA system have been identified in ASD and ADHD. *SLC6A3* is a gene that codes for the DA reuptake transporter, which has a high density in striatum and NAc (Brooks 2016; Salatino-Oliveira et al. 2018). This gene has often been implicated in ADHD (Faraone et al. 2011, 2014; Faraone and Larsson 2019; Gizer et al. 2009). For example, a meta-analysis reported a relation between a polymorphism of the *SLC6A3* and increased DA transporter presence in striatal areas as determined by positron emission topography (PET; Faraone et al. 2014). This polymorphism has also been linked to ADHD in adults (Franke et al. 2010). With respect to ASD, although some contradictory results regarding *SLC6A3* involvement have been reported (e.g. Makkonen et al. 2008), most studies indicate that *SLC6A3* is associated with the disorder (Hamilton et al. 2013; Nguyen et al. 2014). Genes coding the different DA receptors in relation to ASD and ADHD have also been investigated. Strong evidence suggests *DRD4* and *DRD5* are associated with ADHD, while weaker evidence suggests an association between ADHD and receptor genes *DRD1* and *DRD2* (Faraone et al. 2011; Gizer et al. 2009). Moreover, multiple studies report *DRD3* to have no association with ADHD (Faraone et al. 2005; Genro et al. 2010). In ASD, many DA receptor genes have been implicated. *DRD1*, *DRD2*, *DRD3*, *DRD4* and *DRD5* have all been associated with the disorder (Hettinger 2009; Gadow et al. 2010; Taurines et al. 2011; Staal et al. 2012; Nguyen et al. 2014). Moreover, associations between polymorphisms in *DRD3*, *DRD4* and repetitive behaviors in ASD patients have been reported (Gadow et al. 2010; Staal et al. 2012). This directly links DA dysfunction to ASD symptomatology. Taurines et al. (2011) compared the mRNA expression of *DRD4* and *DRD5* between ASD, ADHD and control groups. The data showed lower *DRD4*-mRNA in ASD and ADHD groups. Moreover, the ASD group showed lower *DRD5*-mRNA when compared to the ADHD and control groups (Taurines et al. 2011). Altogether, genetic factors seem to contribute to dysfunction of the DA system in both ASD and ADHD. Although genetic abnormalities in the DA system are shared between the two disorders, there are also important differences such as the role of *DRD3*.

Functional Networks

As discussed, the SaN has been implicated in ASD and ADHD symptomatology. The SN has been shown to be connected with the SaN in humans using diffusion tensor imaging (Zhang et al. 2017). Additionally, functional connectivity between SN, VTA and SaN nodes has been reported in an fMRI study (Seeley et al. 2007). In an extensive review, the importance of the DA system in SaN functioning has been described (Peters et al. 2016).

The authors suggest that cortico-striatal-thalamic loop circuits can regulate SaN functioning (Alexander et al. 1986; Peters et al. 2016; McCutcheon et al. 2019). More specifically, VTA and rostral SN pars reticularis innervate unto thalamic and striatal areas, which subsequently modulate cortical nodes of the SaN (del Campo et al. 2011; Peters et al. 2016; Haber 2016). In line with this, deep brain stimulation of NAc and SN was found to boost activity in cortical SaN nodes (Alexander et al. 1986; Peters et al. 2016). In turn, a PET study showed that repetitive transcranial magnetic stimulation of dorsal lateral PFC increased DArgic transmission in caudate nucleus and thalamus (Strafella et al. 2001). This shows that SaN nodes and subcortical areas can reciprocally activate one another (Alexander et al. 1986; Peters et al. 2016). Functionally, the DA system and SaN have been proposed to have similar roles. Contemporary studies suggest that DArgic modulation not only influences reward learning and goal-directed behavior, but also plays a role in directing attention toward salient stimuli in the environment (Horvitz 2000; Koob and Volkow 2010; Kroemer et al. 2014; Peters et al. 2016). Together, this illustrates the importance of the DA system in SaN functioning.

In sum, dysfunction of the DA system likely contributes to the symptomatology in ASD and ADHD. Whereas there is strong evidence for the relation between DA dysfunction and ADHD, such evidence is relatively still emerging for ASD. Nevertheless, genetic evidence strongly implicates DA dysfunction in both disorders as *DBH*, *SLC6A3* and DA receptor genes have been implicated in ASD and ADHD. Moreover, the influence of the DA system on the SaN can help explain symptomatology in ASD and ADHD. Importantly, the DA system can be targeted by available pharmacological treatments, which could improve the future treatment of ASD. Further research should focus on elucidating exactly how the DA system is altered in ASD and ADHD, so that specific targets within the system may be identified.

4 The Nucleus Basalis-Acetylcholine Neuromodulatory System

4.1 Connectivity of the Nucleus Basalis

The NBM is an important cholinergic nucleus positioned in the basal forebrain and has widespread projections across the brain (Liu et al. 2015; McCormick 1989; Mesulam 2000; Mesulam et al. 1983; Mesulam and Geula 1988). There are two types of cholinergic receptors: nicotinic (nAChR) and muscarinic receptors (mAChR; Fuenzalida et al. 2016; Jensen et al. 2005; Stahl 2013). Comparable to the LC-NE system, the cholinergic system has classically been thought to modulate arousal (Aston-Jones and Cohen 2005a; Phillis 1968; Szerb 1967). More recently, this system has been implicated in memory and attentional functions (H. M. Arnold et al. 2002; A. K. L. Liu et al. 2015; Mesulam 2000; Mueller et al. 2017), but also in cognitive flexibility and social

communication (Ragozzino et al. 1998; Karvat and Kimchi 2014; L. Wang et al. 2015; Liu et al. 2018). No viral-tracing genetic studies have been performed to precisely examine the topography of the NBM. Nonetheless, the connections of the NBM have been examined, primarily in animal studies. NBM has widespread cortical projections, which are relatively more ventral when compared to the DA and NE systems (Kenemans and Ramsey 2013; Liu et al. 2015; Mesulam et al. 1983; Mesulam and Geula 1988). Furthermore, NBM has been shown to be connected to frontal areas and visual cortex (Nagasaka et al. 2017; Huppé-Gourgues et al. 2018). Additionally, connections between the NBM and ventral striatal areas have been described (Shu et al. 2019). Also, NBM and amygdala have reciprocal projections to one another (Aitta-aho et al. 2018; Mesulam 2000; Mesulam et al. 1983; Woolf and Butcher 1982).

4.2 Cholinergic Neuromodulation in ASD and ADHD

Cholinergic neuromodulation is altered in ASD. Cholinergic neurons in the NBM have been shown to be altered in size, number and structure in ASD patients (Kemper and Bauman 1998). Moreover, decreased levels of the ACh precursor choline have been reported in ASD (Sokol et al. 2002; Friedman et al. 2006). Furthermore, epibatidine - a marker for $\alpha 4\beta 2$ -nAChRs (Jensen et al. 2005) - shows altered binding in frontal, parietal, striatal and cerebellar regions in ASD patients (Perry et al. 2001; Lee et al. 2002; Martin-Ruiz et al. 2004; Ray et al. 2005; Mukaetova-Ladinska et al. 2010; Deutsch et al. 2010; Marotta et al. 2020). Notably, decreased cerebellar binding of $\alpha 4$ -nAChRs may lead to PC loss (Lee et al. 2002). Additionally, multiple preclinical ASD mouse models appear to suffer cholinergic deficits (Artoni et al. 2019; Marotta et al. 2020). For example, the BTBR mouse model for ASD is an inbred mouse strain that is characterized by a deletion within the *Itpr3* gene (Meyza and Blanchard 2017). BTBR mice show repetitive behaviors, impairments in social communication and aberrant nicotinic cholinergic neurotransmission (L. Wang et al. 2015). Nicotine administration in BTBR mice ameliorated these characteristic ASD-like behaviors (L. Wang et al. 2015). Another study in BTBR mice reported similar effects when donepezil - an acetylcholinesterase inhibitor - was administered (Karvat and Kimchi 2014). Although mAChRs have not been investigated extensively in relation to ASD, one study did report a 30% decrease in M1 receptor binding in ASD patients (Perry et al. 2001; Lee et al. 2002; Mukaetova-Ladinska et al. 2010). More research is necessary to understand potential abnormalities of the muscarinic system in ASD.

The cholinergic system has also been implicated in ADHD. Compared to healthy subjects, there is a larger percentage of smokers among ADHD patients and these patients have lower percentages of quitting

smoking (Pomerleau et al. 1995; Moolchan et al. 2000). This increase of consuming nicotine-containing substances could be a form of self-medication among ADHD patients (Levin and Rezvani 2002; but this could also be due to the increased impulsivity in ADHD, see Sousa et al. 2011) – similar ideas have been proposed for schizophrenia patients (Kumari and Postma 2005). As discussed briefly, ADHD patients show a wide range of impairments such as decreased inhibition, impulsivity and executive functioning. Impaired cholinergic neurotransmission has been suggested to play a role in these cognitive deficits of ADHD (Potter et al. 2006, 2014). For example, one placebo-controlled study showed that nicotine administration improved performance on the Stroop task and also decreased stop-signal reaction time (SSRT) in ADHD patients (Potter and Newhouse 2004). Logemann et al. (2014) could not replicate the nicotinic effect on SSRT in healthy subjects, but strong responders to nicotine did show an enhanced stop-P3 electroencephalogram component when nicotine was administered (Kenemans 2015). The nicotinic system has also been suggested to be involved in impulsivity, further underlining the importance of the cholinergic system in ADHD (Ohmura et al. 2012). Similar to ASD, mAChRs have not yet been thoroughly investigated in relation to ADHD. Nonetheless, mAChRs do appear to have decreased binding capacity in ADHD patients (Johansson et al. 2013). More research is needed to elucidate the role of mAChRs in ADHD.

Molecular Genetics

Based on an analysis of genome-wide association study data, cholinergic receptor genes have been identified as candidate genes in ASD (Lee et al. 2012). Specifically, *CHRNA7* (coding the $\alpha 7$ -nAChR (Jensen et al. 2005)), has been associated with ASD, as has been *CHRFAM7A* (Bacchelli et al. 2015) - an exclusively human and highly polymorphic hybrid gene consisting of a duplicated portion of *CHRNA7* fused to exons A-E of *FAM7A* (Gault et al. 1998; Wall et al. 2009; Pinto et al. 2010; Casey et al. 2012; Huguet et al. 2013; Bacchelli et al. 2015; Gillentine and Schaaf 2015; Gillentine et al. 2017). *CHRNA7* has also been implicated in ADHD (Baccarin et al. 2020; Gillentine et al. 2017; Gillentine and Schaaf 2015; Sinkus et al. 2015; Valbonesi et al. 2015), but not all studies have not replicated this finding (Kent et al. 2001; Faraone et al. 2005; Ross 2012). *CHRFAM7A* has also been associated with ADHD (Baccarin et al. 2020; Williams et al. 2012), but replication is required to confirm this association. Another gene, *CHRNA4*, codes for the $\alpha 4$ -nAChR and has been identified as a candidate gene for ASD, but this gene seems to only play a role in specific cases (i.e. combinations with other genes or pathologies; Moessner et al. 2007; Oikonomakis et al. 2016; Wall et al. 2009). Conversely, evidence for the involvement of *CHRNA4* in ADHD is strong, as multiple studies have reported an association

of ADHD with the gene (Todd et al. 2003; Lee et al. 2008; Wallis et al. 2009; Faraone and Mick 2010; Mastronardi et al. 2016). Moreover, *CHRNA4* has been linked to attentional problems and to SaN functioning (Todd et al. 2003; Sadaghiani et al. 2017).

Functional Networks

The cholinergic system may play a role in SaN functioning. Striatum, ACC and insula have the highest density of $\alpha 4\beta 2$ -nAChRs in the brain as determined by PET (Gallezot et al. 2005; Picard et al. 2013). As stated, these areas are crucial SaN nodes (Seeley et al. 2007; Peters et al. 2016). Sadaghiani et al. (2017) reported that *CHRNA4* polymorphism rs1044396 increased activity in ACC, insula and anterior prefrontal areas. Of note, rs1044396 showed no activity-altering effects in DMN and ECN (Sadaghiani et al. 2017). As mentioned previously, the cholinergic system seems to be involved in inhibiting responses (Kenemans 2015; Logemann et al. 2014). Nicotine administration improves performance on stopping tasks in ADHD patients (Potter and Newhouse 2004; Potter et al. 2006). Interestingly, Peters et al. (2016) reported that stopping and SaN show a remarkable overlap in activated brain areas. Kenemans and Ramsey (2013) posit that the cholinergic system is involved in salience detection (Furey et al. 2008). For example, when physostigmine, an acetylcholinesterase inhibitor, is administered, visual cortex showed enhanced activity to the first (and novel) trial, but not to subsequent trials (Furey et al. 2000). Furthermore, amygdala has also been suggested to be involved in salience detection (Kenemans and Ramsey 2013; Sander et al. 2003). Amygdala is innervated by both the NBM as well as non-NBM cholinergic nuclei in the brainstem (Aitta-aho et al. 2018). In turn, amygdala innervates multiple neuromodulatory nuclei such as NBM, LC, VTA and SNc (Cardinal et al. 2002; Watabe-Uchida et al. 2012; Beier et al. 2015, 2019; Schwarz et al. 2015). These connections of the amygdala allow this structure to modulate activity of multiple neuromodulatory nuclei which modulate SaN functioning.

In sum, cholinergic neurotransmission is affected by genetic and molecular abnormalities in both ASD and ADHD. The direct genetic and molecular influences of nAChRs within the SaN as well as the indirect influences via the amygdala make the cholinergic system crucial for proper SaN functioning. Therefore, dysfunction of the cholinergic system may underlie SaN dysfunction in ASD and ADHD. Dysfunction in salience detection can explain a myriad of symptoms in these disorders and normalizing this system may be a viable target for pharmacological interventions.

5. Pharmacological Interventions in ASD

As reviewed, the catecholaminergic and cholinergic systems play a role in ASD and ADHD symptomatology. Pharmacological interventions can target these systems which may help alleviate symptoms (Stahl 2013). Currently, the atypical antipsychotics risperidone and aripiprazole are the only FDA approved medications for ASD and these drugs are generally prescribed to treat irritability (Bonnot and Holzer 2012). In practice however, other off-label medications such as stimulants are prescribed to treat ASD patients (Murray et al. 2014). It is important to consider how prescribed medications affect ASD symptomatology and if these medications are tolerable within the ASD population. Table 1 shows all current randomized and placebo-controlled pharmacological trials in human ASD patients. Only drugs targeting the catecholaminergic and cholinergic - and sometimes serotonergic - systems are considered.

5.1 Norepinephrinergic Interventions in ASD

Propranolol

Propranolol exerts its effects on NE modulation in both the central and autonomic nervous systems (Mansur et al. 1998). Multiple placebo-controlled studies have reported improvements in ASD, including normalization of facial scanning, enhanced (non-)verbal communication and improved social functioning (Beversdorf et al. 2013, 2014; Zamzow et al. 2014, 2016). London et al. (2020) reported propranolol to lower aggressive and self-injurious behaviors, but the study was not placebo controlled. Additionally, while in some studies anxiety was unaffected, others reported a decrease in anxiety (Sagar-Ouriaghli et al. 2018). Furthermore, in one study propranolol administration boosted functional connectivity in the DMN in both healthy subjects and ASD patients, while another study reports increased functional connectivity in language areas in the left hemisphere (Narayanan et al. 2010; Hegarty et al. 2017). Intraindividual variability of functional connectivity was not assessed in these studies. Although studies have investigated the effects of propranolol on specific symptoms of ASD (i.e. facial scanning and language), the core deficits (i.e. social impairments and repetitive and restricted behavior) have not often been assessed (but see Beversdorf et al. 2013, 2014). Additionally, most propranolol trials have small sample sizes and do not directly assess outcome measures that are clinically relevant, such as irritability, ADHD symptomatology and stereotypical behavior. It is necessary to conduct double-blind placebo-controlled trials to properly assess the possible effects of propranolol on the core deficits of ASD and to assess propranolol's potential effects in clinical treatments.

Table 1. Overview of human RCTs targeting DA, NE and/or ACh in ASD.

Drug	Study	Participants	Age ^a	Outcome Measures	Effect Size (<i>d_{av}</i>) ^b
Propranolol	Beversdorf et al. (2008)	18 subjects, of which 9 ASD patients	29.3 (9.9)	Verbal problem solving	0.41
	Beversdorf et al. (2011)	28 subjects, of which 14 high-functioning ASD patients	18.9 (4.2)	Semantic verbal fluency; letter fluency	0.43; <i>n.s.</i>
	Beversdorf et al. (2013)	- ^c	- ^c	Social functioning	sig. ^c
	Beversdorf et al. (2014)	- ^c	- ^c	Social functioning	sig. ^c
	Bodner et al. (2012)	27, of which 14 high-functioning ASD patients	18.9 (2.4)	Working memory	0.72
	Zamzow et al. (2014)	28, of which 14 high-functioning ASD patients	18.3 (2.7)	Mouth fixation; eye fixation	0.54; <i>n.s.</i>
	Zamzow et al. (2016)	20 ASD patients	21.4 (4.6)	Conversational reciprocity	0.40
Atomoxetine	Arnold et al. (2006)	16 ASD patients	9.3 (2.9)	Hyperactivity; social withdrawal; hyperactive/impulsive symptoms	0.40; 0.34; 1.27
	Harfterkamp et al. (2012)	97 ASD patients (all children)	10.0 (2.8)	ADHD total; inattention; hyperactive/impulsive symptoms	1.09; 0.66; 1.12
	Harfterkamp et al. (2014)	97 ASD patients (all children)	10.0 (2.8)	Hyperactivity; stereotypy	1.01; 0.79
Clonidine (Transdermal)	Fankhauser et al. (1992)	9 ASD patients	12.9 (9.6)	Global Improvement rating; social relationships, affectual reactions, sensory responses	1.39; 1.54; 0.54; 1.33
Clonidine (Oral)	Jaselskis et al. (1992)	8 ASD patients	- ^d	Hyperactivity; irritability; stereotypy; inappropriate speech	0.32; 0.64; 0.24; 0.30
Guanfacine	Handen et al. (2008)	11 ASD patients (all children)	7.3 (1.4)	Global rating of improvement; hyperactivity rated by parents; hyperactivity rated by teachers	1.33; 1.04; 1.34
	Scahill et al. (2015); Politte et al. (2018)	62 ASD patients (all children)	8.5 (2.3)	Home situation; obsessive-compulsive symptoms; hyperactivity; stereotypy; inappropriate speech; inattention; ADHD rating	0.74; 0.57; 1.21; 0.29; 0.28; 0.97; 1.45
Methylphenidate	Handen et al. (2000)	13 ASD patients with ADHD symptoms (all children)	7.4 (1.7)	Hyperactivity; inappropriate speech	1.34; 0.77
	Pearson et al. (2013)	24 ASD patients with ADHD symptoms (all children)	8.8 (1.6)	Hyperactivity; irritability; inappropriate speech; CGI total rated by parents; rated by teachers	0.86; 0.62; 0.41; 1.00; 1.35
	Quintana et al. (1995)	10 ASD patients with ADHD symptoms	8.5 (1.3)	Hyperactivity; irritability	0.63; 0.69
	RUPPAN (2005)	66 ASD patients with ADHD symptoms	7.5 (3.3)	Hyperactivity rated by parents; rated by teachers	0.40; 0.48

Haloperidol	Anderson et al. (1989)	45 ASD patients (all children)	4.5 (1.2)	Discrimination learning; CPRS total; withdrawal; stereotypy; fidgetiness; hyperactivity; CGI total; temper outbursts	<i>n.s.</i> ; rest sig. ^d
	Campbell et al. (1982); Anderson et al. (1984)	40 ASD patients (all children)	4.6 (- ^d)	Discrimination learning; CPRS total; CGI total	0.46; rest sig. ^d
	Remington et al. (2001)	36 ASD patients	16.3 (6.4)	Hyperactivity; CARS total; irritability; social withdrawal; irritability; inappropriate speech	sig. ^d ; rest <i>n.s.</i>
Risperidone	Luby et al. (2006)	24 ASD patients (all children)	4.0 (1.0)	CARS total	0.62
	McCracken et al. (2002); McDougle et al. (2005)	101 ASD patients (all children)	8.8 (2.7)	Hyperactivity; irritability; stereotypy; inappropriate speech; Ritvo total; sensory motor behaviors; affectual reactions; sensory responses	1.05; 1.44; 0.66; 0.33; 0.94; 0.74; 0.88; 0.79
	McDougle et al. (1998)	31 ASD patients (all adults)	28.1 (7.3)	CGI total; repetitive behavior; aggression (all after 12 weeks); sensory motor behaviors; affectual reactions; Ritvo total	0.41; 0.29; 0.39; 0.19; 0.45; 0.15
	Nagaraj et al. (2006)	39 ASD patients (all children)	5.0 (1.7)	CARS total; CGAS total	sig. ^d ; 1.06
	Shea et al. (2004)	77 ASD patients (all children)	7.5 (2.3)	Hyperactivity; irritability; social withdrawal; inappropriate speech; conduct problems; insecure/anxious; overly sensitive	0.81; 0.61; 0.38; 0.28; 0.36; 0.14; 0.32
	Troost et al. (2005)	24 ASD patients (all children)	9.1 (2.3)	Relapse of irritability	0.68
Aripiprazole	Findling et al. (2014)	41 ASD patients (all children)	10.4 (2.8)	Relapse of irritability	<i>n.s.</i>
	Ichikawa et al. (2017)	93 ASD patients (all children)	10.1 (3.2)	Hyperactivity; irritability; CGAS total; CGI total	0.71; 0.58; 0.35; 1.03
	Marcus et al. (2009)	218 ASD patients (all children)	9.7 (3.1)	Hyperactivity; stereotypy; inappropriate speech; CGI total	0.86; 0.49; 0.31; 0.77
	Owen et al. (2009)	75 ASD patients (all children)	9.2 (2.9)	Hyperactivity; irritability; CGI total; stereotypy; inappropriate speech	all sig. ^d
	Varni et al. (2012)	316 ASD patients (all children)	9.5 (3.1)	Quality of life; emotional functioning; social functioning; cognitive functioning	0.68; 0.48; 0.61; 0.45
Olanzapine	Hollander et al. (2006)	11 ASD patients (all children)	9.0 (2.5)	CGI total; irritability; aggression	all <i>n.s.</i>
Desipramine	Gordon et al. (1992)	7 ASD patients (all children)	9.6 (4.4)	Hyperactivity; CPRS total; NIHM obsessive-compulsive rating score	0.72; <i>n.s.</i> ; <i>n.s.</i>
	Gordon et al. (1993)	12 ASD patients	- ^c	Hyperactivity; autistic symptoms; anger; compulsive/ritualized behaviors	sig. ^c ; rest <i>n.s.</i>
Clomipramine	Gordon et al. (1992)	7 ASD patients (all children)	9.6 (4.4)	CPRS total; NIHM obsessive-compulsive rating score	4.00; 1.13
	Gordon et al. (1993)	12 ASD patients	- ^c	Hyperactivity; autistic symptoms; anger; compulsive/ritualized behaviors	all sig. ^c
	Sanchez et al. (1996)	8 ASD patients (all children)	6.4 (1.4)	CGI total; CPRS total	all <i>n.s.</i>

	Remington et al. (2001)	36 ASD patients	16.3 (6.4)	CARS total, hyperactivity; irritability; social withdrawal; irritability; inappropriate speech	all <i>n.s.</i>
Tianeptine	Niederhofer et al. (2003)	12 ASD patients (all children)	7.3 (3.3)	Hyperactivity; irritability; inappropriate speech; inappropriate eye contact	0.24; 0.47; 0.60; 0.18
	Wichers et al. (2021)	38 subjects, of which 19 ASD patients	30 (11)	Sustained attention; inhibition/stopping	all <i>n.s.</i>
Donepezil	Chez et al. (2003)	17 ASD patients (all children)	6.8 (1.9)	Expressive speech; receptive speech	0.19; 0.20
	Handen et al. (2011)	31 ASD patients (all children)	11.6 (. ^d)	Executive functioning	<i>n.s.</i>
Rivastigmine	Chez et al. (2004)	32 ASD patients	- ^c	Expressive speech; overall autistic behavior	all sig. ^c
Galantamine	Niederhofer et al. (2002)	20 ASD patients (all boys)	7.4 (1.2)	Hyperactivity; irritability; inadequate eye contact; inappropriate speech	0.32; 0.55; 0.22; 0.55
DMXB-A	Olincy et al. (2016)	2 ASD patients	50 and 24 years old	Inattention; social dysfunction	<i>No statistical testing performed due to low sample size</i>
Transdermal nicotine	Lewis et al. (2018)	8 ASD patients	24.0 (2.6)	Hyperactivity; irritability; social withdrawal; stereotypy; inappropriate speech; aggression	all <i>n.s.</i>
Mecamylamine	Arnold et al. (2012)	18 ASD patients (all children)	7.4 (2.6)	Hyperactivity; irritability; social withdrawal; stereotypy; inappropriate speech; repetitive behaviors; social responsiveness	all <i>n.s.</i>

^a Data presented as Mean (SD).

^b Effect size calculated using the following formulas: $Cohen's d_{av} = \frac{(M_{PostPlacebo} - M_{PrePlacebo}) - (M_{PostDrug} - M_{PreDrug})}{((SD_{PostPlacebo} + SD_{PrePlacebo} + SD_{PostDrug} + SD_{PreDrug})/4)}$ or $Cohen's d_{av} = \frac{(M_{Placebo} - M_{Drug})}{((SD_{Placebo} + SD_{Drug})/2)}$. See Lakens (2013).

^c article could not be accessed. Whenever possible, relevant information was retrieved from abstract.

^d relevant information to perform effect size calculation was not provided.

Abbreviations: *n.s.* = non-significant; sig. = significant; CARS = Childhood Autism Rating Scale; CGAS = Children's Global Assessment Scale; CGI = Clinical Global Impression; CPRS = Children's Psychiatric Rating Scale; NIHM = National Institute of Mental Health; Ritvo = Ritvo-Freeman real life rating scale; RUPPAN = Research Units on Pediatric Psychopharmacology Autism Network.

Atomoxetine

Multiple studies have investigated whether atomoxetine can ameliorate ADHD symptoms in ASD patients. All currently reviewed studies report beneficial effects of atomoxetine on hyperactivity, inattention and impulsive behavior (Arnold et al. 2006; Harfterkamp et al. 2012, 2013, 2014). One limitation of the current ASD-atomoxetine trials is that most studies have investigated the effect of atomoxetine on ADHD symptoms in ASD, but ASD symptoms have often not been assessed (but see Harfterkamp et al. 2014). However, in a non-placebo controlled trial, Jou et al. (2005) report an improvement of general behavior (e.g. less deviant) after atomoxetine treatment when compared to before starting the treatment. Additionally, one trial reported that atomoxetine can decrease stereotypical behaviors in ASD patients (Harfterkamp et al. 2014). In conclusion, although atomoxetine seems to alleviate ADHD symptoms in ASD patients, it remains unclear whether atomoxetine can aid in the treatment of ASD symptomatology.

Clonidine and Guanfacine

Two double-blind placebo-controlled trials have assessed the potential therapeutic effects of clonidine – a net NE antagonist – in ASD. One trial showed that oral clonidine may help treat hyperactivity, irritability, stereotypy and inappropriate speech (Jaselskis et al. 1992). Another study, using transdermal clonidine, administration reported beneficial effects on global improvement, social relationships, affectual reactions and sensory responses (Fankhauser et al. 1992). These trials seem promising for clonidine as a treatment option, but they are limited by their small sample sizes, as well as the side effect profile of the drug (i.e. irritability and sedation).

Lastly, the alpha-2 receptor agonist guanfacine has recently been investigated in ASD, in part due to the recent interest in extended-release guanfacine and ADHD trials investigating the drug. Guanfacine seems to have a myriad of positive effects in ASD patients. The two existing trials report beneficial effects on hyperactivity, stereotypy, inappropriate speech, inattention, ADHD-behaviors, global ratings of improvement, compulsive behaviors as well as an improved home situation (Handen et al. 2008; Scahill et al. 2015; Politte et al. 2018). Adverse effects were limited (i.e. drowsiness) and tolerability was generally high (Scahill et al. 2015; Politte et al. 2018). It is important to note that both clonidine and guanfacine can show net NE agonistic or antagonistic effects based on the dose (Svensson et al. 1975). Future studies - and potentially clinicians - should take this dose-dependent effect into account since this may affect efficacy and tolerability of these substances.

5.3 Dopaminergic Interventions: Stimulants and (a)typical antipsychotics in ASD

Stimulants

ADHD patients are commonly prescribed stimulants such as MPH or amphetamines (Murray et al. 2014). MPH also reportedly lowers ADHD symptoms such as hyperactivity, inattention and impulsivity in ASD patients (e.g. Pearson et al. 2013; Quintana et al. 1995). Nonetheless, ASD patients have a lower chance of responding to MPH and suffer from adverse effects more often than ADHD patients (Handen et al. 2000; RUPPAN 2005). McCracken et al. (2014) showed that efficacy and tolerability of MPH in ASD patients is mediated by genes: *DRD1*, *ADRA2*, *COMT*, *DRD3*, *DRD4*, *SLC6A3*, *SLC6A4*, *DRD2* and *DRD3*. Similar genes mediate the efficacy of MPH in ADHD, as *SLC6A3*, *DRD4* and *COMT* have been implicated (Myer et al. 2018). Although MPH increased social skills and the clinical global impression in ASD in some studies, a meta-analysis showed that MPH does not significantly affect the core deficits of ASD (Sturman et al. 2017). However, this could be due to the low number of studies assessing the core deficits or genetic mediation of efficacy and tolerability of MPH (McCracken et al. 2014).

Antipsychotics

Haloperidol is a typical antipsychotic that mainly antagonizes D₂ergic neurotransmission. Administration of haloperidol was found to decrease hyperactivity in two reports (Anderson et al. 1989; Remington et al. 2001). Furthermore, compared to placebo haloperidol beneficially impacted global impression and children's psychiatry rating scale scores in two studies (Campbell et al. 1982; Anderson et al. 1984; Remington et al. 2001). Inconsistent results are found when examining discrimination learning. One trial reports a significant, albeit modest, increase in discrimination learning (Campbell et al. 1982; Anderson et al. 1984), while another trial reports no such effects (Anderson et al. 1984). Although, in one study haloperidol decreased ASD symptoms such as withdrawal and stereotypy (Anderson et al. 1989), these effects were not replicated in a later trial (Remington et al. 2001).

The atypical antipsychotics risperidone and aripiprazole seem to share therapeutic effects in ASD. Both drugs decrease hyperactivity and irritability and both drugs seem to benefit the clinical global impression (Cohen et al. 2013; Table 1). Additionally, the drugs have overlapping side effects such as weight change, altered appetite, drowsiness and sedation. A trial comparing risperidone to aripiprazole in ASD revealed that the efficacy and tolerability are comparable (Ghanizadeh et al. 2014). Nonetheless, differences between the effects of risperidone and aripiprazole are also reported. While risperidone has been found to reduce aggression and

autistic behaviors (McDougle et al. 1998; Nagaraj et al. 2006; Luby et al. 2006), aripiprazole improved quality of life (Varni et al. 2012). Although these atypical antipsychotics may reduce overall autistic behaviors in some studies, adverse effects are often problematic and these medications are not tolerable in many patients (Orsolini et al. 2016). Genetic studies may help identify genes that mediate efficacy and tolerability of atypical antipsychotics in the treatment of ASD. Note that one trial investigating another atypical antipsychotic, olanzapine, showed no significant therapeutic effects (Hollander et al. 2006). Lastly, none of the reviewed studies have assessed the effects of MPH or (a)typical antipsychotics on the DA MCL- and NS- pathways in ASD. Investigating such effects in ASD may provide insight into the potential therapeutic effects of these agents on the core deficits of the disorder (Pavál 2017).

5.4 Cholinergic Interventions and Tricyclic Antidepressants in ASD

Cholinergic Agents

Drugs targeting the cholinergic system in ASD have not been extensively researched. The most researched cholinergic drug in relation to the disorder is donepezil. Donepezil reportedly increased both receptive and expressive speech, but did not influence executive functioning or overall autistic behaviors when compared to placebo (Chez et al. 2003; Handen et al. 2011). One placebo-controlled galantamine study has been conducted which reports improvements in hyperactivity, irritability, eye-contact and inappropriate speech (Niederhofer et al. 2002; also see Ghaleiha et al. 2014 where galantamine was added to the existing prescribed medication). Rivastigmine seems to improve expressive speech and overall autistic behaviors, but not enough research has been conducted to properly assess how these agents may benefit future treatment (Chez et al. 2004). A relatively new drug DMXB-A, an $\alpha 7$ -nAChR agonist, improved neurocognition in schizophrenia patients (Olincy et al. 2006). In a sample of only two ASD patients, the drug decreased inattention and decreased social dysfunction in one of these patients (Olincy et al. 2016). Transdermal nicotine administration showed no significant effects in a placebo-controlled trial (A. S. Lewis et al., 2018; Table 1). The nicotinic antagonist mecamylamine also showed no significant effects in a placebo-controlled trial (Arnold et al. 2012; Table 1). As stated, cholinergic drugs have only been scarcely researched in relation to ASD. Double-blind placebo-controlled studies are necessary to understand how these agents can potentially aid future treatment of ASD.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) exert their effects by influencing multiple neurotransmitter systems, often targeting serotonin, NE, DA and ACh. TCAs have also been investigated in relation to ASD. Across two trials, desipramine seemed to decrease hyperactivity but compulsive and autistic behaviors remained unaffected (Gordon et al. 1992, 1993). In contrast, the same trials showed that clomipramine did decrease ASD symptoms, compulsive behaviors and also hyperactivity (Gordon et al. 1992, 1993). However other clomipramine trials did not replicate such effects (Sanchez et al. 1996; Remington et al. 2001). Another TCA, tianeptine, seems to decrease hyperactivity, irritability, inappropriate speech and inappropriate eye contact (Niederhofer et al. 2003). A recent fMRI study showed that tianeptine did not behaviorally affect sustained attention or inhibition/stopping in ASD patients, but the drug did normalize ECN activation during tasks (Wichers et al. 2021). Overall, although some trials report beneficial effects of TCAs in ASD, most trials show little to no significant therapeutic effects of this class of medications.

6. Discussion

As reviewed, dysfunction of catecholaminergic and cholinergic neuromodulation play a role in the symptomatology of ASD and ADHD (Faraone et al. 2005; Potter et al. 2006; Faraone and Mick 2010; Pavál 2017; London 2018). Importantly, the dysfunction of these neuromodulatory systems seem to share similarities - as well as differences - between both disorders at the level of genetics, functional networks and at the cellular level that may provide guidance for the development of biological/pharmacological treatment options.

Accumulating evidence suggests overlapping genetic abnormalities in the catecholaminergic and cholinergic systems in ASD and ADHD (Faraone et al. 2005; Nguyen et al. 2014; Bacchelli et al. 2015; Faraone and Larsson 2019). However, note that many of the reported studies concerning the genetics of the catecholaminergic and cholinergic systems have limited effect sizes and replication of many findings has been scarce.

At a functional-network level, aberrant SaN functioning seems to play a role in both disorders, and may be explained by disturbances in the NE-, DA-, or ACh- neuromodulatory systems (Sadaghiani et al. 2017; Zerbi et al. 2019). The extent of the contribution of these three systems to dysfunctional SaN may differ between ASD and ADHD, as well within these populations. This in turn may be directly related to the effectiveness of either NE- or DA- or ACh-directed interventions in either population. Therefore, more specific, personalizing biomarkers may be useful in designing intervention strategies especially in relation to ASD. One further clue is

that there are also differences in the genetic associations (*DRD3*, specific for ASD, and *SLC6A2*, specific for ADHD).

One further difference between ASD and ADHD in the dysfunction of neuromodulatory systems is the role of PCs. PC functioning is affected by especially by NE and ACh neuromodulatory systems, and has been implicated in ASD pathology, but less strongly in ADHD (Rout et al. 2012). Therefore, targeting PCs may be suitable for ASD patients, and a specific subgroup of ADHD patients (see Durston et al. 2011). Given the role of the NE and ACh systems in PC function, it seems useful to further investigate NE- and ACh-targeting agents as effective treatments in ASD. Trials so far have yielded promising results, especially for the NE-reuptake inhibitor atomoxetine, for alpha-2 agonist guanfacine and for ACh-esterase inhibitors. As said, a similar strategy could be beneficial for a subgroup within the ADHD population. Personalizing or biomarking this subgroup could perhaps be effectuated using specific assessments for cerebellar dysfunction.

For ASD, especially drugs targeting the cholinergic system have been under-examined, while accumulating neurobiological evidence suggests that these drugs can potentially help treatment (Lippiello 2006; Mukaetova-Ladinska et al. 2010). Additionally, future pharmacological trials should consider the core deficits of ASD, as these deficits are currently not often assessed. Future studies should also investigate the neurobiological effects of these agents in ASD patients, as preliminarily done for propranolol and tianeptine (Narayanan et al. 2010; Hegarty et al. 2017; Wichers et al. 2021). For example, the intraindividual variability of connectivity can be assessed to see how pharmacological agents may influence this potential underlying mechanism of ASD pathology (Falahpour et al. 2016).

As to stimulants, MPH is a generally effective medication in ADHD, but only few studies have assessed its effects on core ASD deficits. The efficacy and tolerability of MPH are mediated by genetic factors in both ASD and ADHD patients (McCracken et al. 2014; Myer et al. 2018). As mentioned, while some MPH trials show some improvements in ASD symptomatology, a meta-analysis showed that MPH does not significantly influence the core deficits of ASD (Sturman et al. 2017). However, as supported by the genetic mediation studies (McCracken et al. 2014; Myer et al. 2018), MPH may only be effective in specific ASD subgroups. One clue is the association between MPH effectiveness and varieties of the *DRD3* and *SLC6A2* genes, in both ASD and ADHD populations. Other biomarkers in ASD patients may also be predictive. For example, pupillometry measures have been used in ASD to identify abnormalities in the LC-NE and NBM-ACh systems (Lynch 2018; Artoni et al. 2019). In addition, future research could investigate the value of spontaneous eye blink rate (sEBR) to assess DA functioning in ASD (Jongkees and Colzato 2016). Pupillometry and sEBR,

in combination with gene studies, may help identify which pharmacological treatment may be most effective in a specific ASD patient.

The current review has some limitations. First, not all potentially important neuromodulatory substances have been examined. Although not considered here, the histaminergic, serotonergic and opioid systems have been implicated in ASD pathology (Eissa et al. 2018; Pellissier et al. 2018). Also, the current review has examined the neuromodulatory systems as more or less independent, while these systems interact. For example, the dorsal raphe nuclei project to VTA and VTA projects to the LC (Beier et al. 2015; Morales and Margolis 2017). Moreover, NE reuptake transporters also clear DA from synapses in frontal areas (Madras et al. 2005). This illustrates how these systems are connected to one another and that the interactions between these systems should be investigated further (Marder 2012).

Altogether, DA, NE and ACh are important systems in ASD and ADHD symptomatology. Although the dysfunction of these systems show overlap between the disorders, there are also differences such as PC/cerebellar abnormalities and the involvement of specific genes (*DRD3*, *SLC6A2*). Current medications prescribed for ADHD are effective in ADHD patients, but there is currently not enough evidence to suggest that these medications can consistently and effectively alleviate ASD symptoms in ASD patients. NErgic agents, MPH, and cholinergic agents should be investigated further using double-blind placebo-controlled trials to confirm the potential therapeutic value of these agents and to assess their neurobiological effects in ASD patients. Lastly, biomarkers such as pupillometry and sEBR in combination with genetics should be investigated in relation to ASD to identify which medications may be most effective in certain patients.

Declarations of Interest

None.

References

- Aboitiz F, Ossandon T, Zamorano F, et al (2014) Irrelevant stimulus processing in ADHD: catecholamine dynamics and attentional networks. *Front Psychol* 5:183. <https://doi.org/10.3389/fpsyg.2014.00183>
- Aitta-aho T, Hay YA, Phillips BU, et al (2018) Basal Forebrain and Brainstem Cholinergic Neurons Differentially Impact Amygdala Circuits and Learning-Related Behavior. *Curr Biol* 28:2557-2569.e4. <https://doi.org/10.1016/j.cub.2018.06.064>
- Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 9:357–381. <https://doi.org/10.1146/annurev.ne.09.030186.002041>

- Allen EA, Damaraju E, Plis SM, et al (2014) Tracking Whole-Brain Connectivity Dynamics in the Resting State. *Cereb Cortex* 24:663–676. <https://doi.org/10.1093/cercor/bhs352>
- Aman MG, Kasper W, Manos G, et al (2010) Line-Item Analysis of the Aberrant Behavior Checklist: Results from Two Studies of Aripiprazole in the Treatment of Irritability Associated with Autistic Disorder. *J Child Adolesc Psychopharmacol* 20:415–422. <https://doi.org/10.1089/cap.2009.0120>
- Amaral DG, Schumann CM, Nordahl CW (2008) Neuroanatomy of autism. *Trends Neurosci* 31:137–145. <https://doi.org/10.1016/j.tins.2007.12.005>
- American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders (DSM-5®). American Psychiatric Pub
- Andén N-E, Dahlström A, Fuxe K, et al (1966) Ascending Monoamine Neurons to the Telencephalon and Diencephalon. *Acta Physiol Scand* 67:313–326. <https://doi.org/10.1111/j.1748-1716.1966.tb03318.x>
- Anderson JS, Druzgal TJ, Froehlich A, et al (2011) Decreased Interhemispheric Functional Connectivity in Autism. *Cereb Cortex* 21:1134–1146. <https://doi.org/10.1093/cercor/bhq190>
- Anderson LT, Campbell M, Adams P, et al (1989) The effects of haloperidol on discrimination learning and behavioral symptoms in autistic children. *J Autism Dev Disord* 19:227–239. <https://doi.org/10.1007/BF02211843>
- Anderson LT, Campbell M, Grega DM, et al (1984) Haloperidol in the treatment of infantile autism: effects on learning and behavioral symptoms. *Am J Psychiatry* 141:1195–1202. <https://doi.org/10.1176/ajp.141.10.1195>
- Antshel KM, Zhang-James Y, Faraone SV (2013) The comorbidity of ADHD and autism spectrum disorder. *Expert Rev Neurother* 13:1117–1128. <https://doi.org/10.1586/14737175.2013.840417>
- Arnold HM, Burk JA, Hodgson EM, et al (2002) Differential cortical acetylcholine release in rats performing a sustained attention task versus behavioral control tasks that do not explicitly tax attention. *Neuroscience* 114:451–460. [https://doi.org/10.1016/S0306-4522\(02\)00292-0](https://doi.org/10.1016/S0306-4522(02)00292-0)
- Arnold LE, Aman MG, Cook AM, et al (2006) Atomoxetine for Hyperactivity in Autism Spectrum Disorders: Placebo-Controlled Crossover Pilot Trial. *J Am Acad Child Adolesc Psychiatry* 45:1196–1205. <https://doi.org/10.1097/01.chi.0000231976.28719.2a>
- Arnold LE, Aman MG, Hollway J, et al (2012) Placebo-Controlled Pilot Trial of Mecamylamine for Treatment of Autism Spectrum Disorders. *J Child Adolesc Psychopharmacol* 22:198–205. <https://doi.org/10.1089/cap.2011.0056>
- Artani P, Piffer A, Vinci V, et al (2019) Deep learning of spontaneous arousal fluctuations detects early cholinergic defects across neurodevelopmental mouse models and patients. *Proc Natl Acad Sci* 117:23298–23303. <https://doi.org/10.1073/pnas.1820847116>
- Aston-Jones G, Cohen JD (2005a) An Integrative Theory of Locus Coeruleus-Norpeinephrine Function: Adaptive Gain and Optimal Performance. *Annu Rev Neurosci* 28:403–450. <https://doi.org/10.1146/annurev.neuro.28.061604.135709>
- Aston-Jones G, Cohen JD (2005b) Adaptive gain and the role of the locus coeruleus–norepinephrine system in optimal performance. *J Comp Neurol* 493:99–110. <https://doi.org/10.1002/cne.20723>
- Aston-Jones G, Waterhouse B (2016) Locus coeruleus: From global projection system to adaptive regulation of behavior. *Brain Res* 1645:75–78. <https://doi.org/10.1016/j.brainres.2016.03.001>

- Baccarin M, Picinelli C, Tomaiuolo P, et al (2020) Appropriateness of array-CGH in the ADHD clinics: A comparative study. *Genes Brain Behav* 19:e12651. <https://doi.org/10.1111/gbb.12651>
- Bacchelli E, Battaglia A, Cameli C, et al (2015) Analysis of CHRNA7 rare variants in autism spectrum disorder susceptibility. *Am J Med Genet A* 167:715–723. <https://doi.org/10.1002/ajmg.a.36847>
- Baghdadli A, Assouline B, Sonié S, et al (2012) Developmental Trajectories of Adaptive Behaviors from Early Childhood to Adolescence in a Cohort of 152 Children with Autism Spectrum Disorders. *J Autism Dev Disord* 42:1314–1325. <https://doi.org/10.1007/s10803-011-1357-z>
- Bargmann CI, Marder E (2013) From the connectome to brain function. *Nat Methods* 10:483–490. <https://doi.org/10.1038/nmeth.2451>
- Barkley RA (2006) Attention-Deficit/Hyperactivity Disorder. In: Behavioral and emotional disorders in adolescents: Nature, assessment, and treatment. Guilford Publications, New York, NY, US, pp 91–152
- Baron-Cohen S, Ring HA, Bullmore ET, et al (2000) The amygdala theory of autism. *Neurosci Biobehav Rev* 24:355–364. [https://doi.org/10.1016/S0149-7634\(00\)00011-7](https://doi.org/10.1016/S0149-7634(00)00011-7)
- Barrie ES, Pinsonneault JK, Sadee W, et al (2018) Testing genetic modifiers of behavior and response to atomoxetine in autism spectrum disorder with ADHD. *J Dev Phys Disabil* 30:355–371. <https://doi.org/10.1007/s10882-018-9590-4>
- Becker EBE, Stoodley CJ (2013) Autism Spectrum Disorder and the Cerebellum. In: Konopka G (ed) International Review of Neurobiology. Academic Press, pp 1–34
- Beier KT, Gao XJ, Xie S, et al (2019) Topological Organization of Ventral Tegmental Area Connectivity Revealed by Viral-Genetic Dissection of Input-Output Relations. *Cell Rep* 26:159–167.e6. <https://doi.org/10.1016/j.celrep.2018.12.040>
- Beier KT, Steinberg EE, DeLoach KE, et al (2015) Circuit Architecture of VTA Dopamine Neurons Revealed by Systematic Input-Output Mapping. *Cell* 162:622–634. <https://doi.org/10.1016/j.cell.2015.07.015>
- Berridge CW, Waterhouse BD (2003) The locus coeruleus–noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Res Rev* 42:33–84. [https://doi.org/10.1016/S0165-0173\(03\)00143-7](https://doi.org/10.1016/S0165-0173(03)00143-7)
- Beversdorf DQ, Ferguson B, Reznicek E, et al (2013) Effects of Propranolol on Social Functioning in Autism Spectrum Disorder. *Neurology* 80:S18.002
- Beversdorf DQ, Zamzow R, Ferguson B, et al (2014) Predictors of Response to Propranolol for Social Functioning in Autism Spectrum Disorder. *Neurology* 82:I4-1.002.
- Beversdorf DQ, Carpenter AL, Miller RF, et al (2008) Effect of propranolol on verbal problem solving in autism spectrum disorder. *Neurocase* 14:378–383. <https://doi.org/10.1080/13554790802368661>
- Beversdorf DQ, Saklayen S, Higgins KF, et al (2011) Effect of Propranolol on Word Fluency in Autism. *Cogn Behav Neurol* 24:11–17. <https://doi.org/10.1097/WNN.0b013e318204d20e>
- Bobb AJ, Addington AM, Sidransky E, et al (2005) Support for association between ADHD and two candidate genes: NET1 and DRD1. *Am J Med Genet B Neuropsychiatr Genet* 134B:67–72. <https://doi.org/10.1002/ajmg.b.30142>
- Bodner KE, Beversdorf DQ, Saklayen SS, Christ SE (2012) Noradrenergic Moderation of Working Memory Impairments in Adults with Autism Spectrum Disorder. *J Int Neuropsychol Soc* 18:556–564. <https://doi.org/10.1017/S1355617712000070>

- Bonnot O, Holzer L (2012) Use of antipsychotics in child and adolescent. *Neuropsychiatr Enfance Adolesc* 60:12–19. <https://doi.org/10.1016/j.neurenf.2011.07.003>
- Bora E, Pantelis C (2016) Meta-analysis of social cognition in attention-deficit/hyperactivity disorder (ADHD): comparison with healthy controls and autistic spectrum disorder. *Psychol Med* 46:699–716. <https://doi.org/10.1017/S0033291715002573>
- Brezina V (2010) Beyond the wiring diagram: signalling through complex neuromodulator networks. *Philos Trans R Soc B Biol Sci* 365:2363–2374. <https://doi.org/10.1098/rstb.2010.0105>
- Brooks DJ (2016) Molecular imaging of dopamine transporters. *Ageing Res Rev* 30:114–121. <https://doi.org/10.1016/j.arr.2015.12.009>
- Bruce B, Thernlund G, Nettelbladt U (2006) ADHD and language impairment. *Eur Child Adolesc Psychiatry* 15:52–60. <https://doi.org/10.1007/s00787-006-0508-9>
- Bruchmüller K, Margraf J, Schneider S (2012) Is ADHD diagnosed in accord with diagnostic criteria? Overdiagnosis and influence of client gender on diagnosis. *J Consult Clin Psychol* 80:128–138. <https://doi.org/10.1037/a0026582>
- Caillies S, Bertot V, Motte J, et al (2014) Social cognition in ADHD: Irony understanding and recursive theory of mind. *Res Dev Disabil* 35:3191–3198. <https://doi.org/10.1016/j.ridd.2014.08.002>
- Campbell M, Anderson LT, Small AM, et al (1982) The effects of haloperidol on learning and behavior in autistic children. *J Autism Dev Disord* 12:167–175. <https://doi.org/10.1007/BF01531306>
- Candy M, Jones L, Williams R, et al (2008) Psychostimulants for depression. *Cochrane Database Syst Rev* CD006722. <https://doi.org/10.1002/14651858.CD006722.pub2>
- Cardinal RN, Parkinson JA, Hall J, Everitt BJ (2002) Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. *Neurosci Biobehav Rev* 26:321–352. [https://doi.org/10.1016/S0149-7634\(02\)00007-6](https://doi.org/10.1016/S0149-7634(02)00007-6)
- Carey MR, Regehr WG (2009) Noradrenergic Control of Associative Synaptic Plasticity by Selective Modulation of Instructive Signals. *Neuron* 62:112–122. <https://doi.org/10.1016/j.neuron.2009.02.022>
- Carper RA, Courchesne E (2005) Localized enlargement of the frontal cortex in early autism. *Biol Psychiatry* 57:126–133. <https://doi.org/10.1016/j.biopsych.2004.11.005>
- Casey JP, Magalhaes T, Conroy JM, et al (2012) A novel approach of homozygous haplotype sharing identifies candidate genes in autism spectrum disorder. *Hum Genet* 131:565–579. <https://doi.org/10.1007/s00439-011-1094-6>
- Chandler DJ, Gao W-J, Waterhouse BD (2014) Heterogeneous organization of the locus coeruleus projections to prefrontal and motor cortices. *Proc Natl Acad Sci U S A* 111:6816–6821. <https://doi.org/10.1073/pnas.1320827111>
- Chandler DJ, Jensen P, McCall JG, et al (2019) Redefining Noradrenergic Neuromodulation of Behavior: Impacts of a Modular Locus Coeruleus Architecture. *J Neurosci* 39:8239–8249. <https://doi.org/10.1523/JNEUROSCI.1164-19.2019>
- Chandler DJ, Lamperski CS, Waterhouse BD (2013) Identification and distribution of projections from monoaminergic and cholinergic nuclei to functionally differentiated subregions of prefrontal cortex. *Brain Res* 1522:38–58. <https://doi.org/10.1016/j.brainres.2013.04.057>
- Chen T, Cai W, Ryali S, et al (2016) Distinct Global Brain Dynamics and Spatiotemporal Organization of the Salience Network. *PLoS Biol* 14:e100249. <https://doi.org/10.1371/journal.pbio.1002469>

- Chevallier C, Kohls G, Troiani V, et al (2012) The social motivation theory of autism. *Trends Cogn Sci* 16:231–239. <https://doi.org/10.1016/j.tics.2012.02.007>
- Chevrier A, Bhaijiwala M, Lipszyc J, et al (2019) Disrupted reinforcement learning during post-error slowing in ADHD. *PLoS ONE* 14:e0206780. <https://doi.org/10.1371/journal.pone.0206780>
- Chez MG, Aimonovitch M, Buchanan T, et al (2004) Treating autistic spectrum disorders in children: utility of the cholinesterase inhibitor rivastigmine tartrate. *J Child Neurol* 19:165–169
- Chez MG, Buchanan TM, Becker M, et al (2003) Donepezil hydrochloride: a double-blind study in autistic children. *J Pediatr Neurol* 1:83–88. <https://doi.org/10.1055/s-0035-1557175>
- Clark T, Feehan C, Tinline C, Vostanis P (1999) Autistic symptoms in children with attention deficit-hyperactivity disorder. *Eur Child Adolesc Psychiatry* 8:50–55. <https://doi.org/10.1007/s007870050083>
- Cohen D, Raffin M, Canitano R, et al (2013) Risperidone or aripiprazole in children and adolescents with autism and/or intellectual disability: A Bayesian meta-analysis of efficacy and secondary effects. *Res Autism Spectr Disord* 7:167–175. <https://doi.org/10.1016/j.rasd.2012.08.001>
- Cohen NJ, Vallance DD, Barwick M, et al (2000) The Interface between ADHD and Language Impairment: An Examination of Language, Achievement, and Cognitive Processing. *J Child Psychol Psychiatry* 41:353–362. <https://doi.org/10.1111/1469-7610.00619>
- Corp SA, Gitlin MJ, Altshuler LL (2014) A review of the use of stimulants and stimulant alternatives in treating bipolar depression and major depressive disorder. *J Clin Psychiatry* 75:1010–1018. <https://doi.org/10.4088/JCP.13r08851>
- Coury D (2010) Medical treatment of autism spectrum disorders. *Curr Opin Neurol* 23:131–136. <https://doi.org/10.1097/WCO.0b013e32833722fa>
- Craig F, Margari F, Legrottaglie AR, et al (2016) A review of executive function deficits in autism spectrum disorder and attention-deficit/hyperactivity disorder. *Neuropsychiatr Dis Treat* 12:1191–1202. <https://doi.org/10.2147/NDT.S104620>
- Darcq E, Kieffer BL (2015) PI3K signaling in the locus coeruleus: a new molecular pathway for ADHD research. *EMBO Mol Med* 7:859–861. <https://doi.org/10.15252/emmm.201505266>
- Dawson G, Webb SJ, McPartland J (2005) Understanding the Nature of Face Processing Impairment in Autism: Insights From Behavioral and Electrophysiological Studies. *Dev Neuropsychol* 27:403–424. https://doi.org/10.1207/s15326942dn2703_6
- de la Torre-Ubieta L, Won H, Stein JL, Geschwind DH (2016) Advancing the understanding of autism disease mechanisms through genetics. *Nat Med* 22:345–361. <https://doi.org/10.1038/nm.4071>
- de Lacy N, Calhoun VD (2018) Dynamic connectivity and the effects of maturation in youth with attention deficit hyperactivity disorder. *Netw Neurosci* 3:195–216. https://doi.org/10.1162/netn_a_00063
- de Luca V, Muglia P, Jain U, Kennedy JL (2004) No evidence of linkage or association between the norepinephrine transporter (NET) gene MnlI polymorphism and adult ADHD. *Am J Med Genet B Neuropsychiatr Genet* 124B:38–40. <https://doi.org/10.1002/ajmg.b.20075>
- del Campo N, Chamberlain SR, Sahakian BJ, Robbins TW (2011) The Roles of Dopamine and Noradrenaline in the Pathophysiology and Treatment of Attention-Deficit/Hyperactivity Disorder. *Biol Psychiatry* 69:e145–e157. <https://doi.org/10.1016/j.biopsych.2011.02.036>
- Deserno MK, Borsboom D, Begeer S, et al (2019) Sleep determines quality of life in autistic adults: A longitudinal study. *Autism Res* 12:794–801. <https://doi.org/10.1002/aur.2103>

- Deutsch SI, Urbano MR, Neumann SA, et al (2010) Cholinergic Abnormalities in Autism: Is There a Rationale for Selective Nicotinic Agonist Interventions? *Clin Neuropharmacol* 33:114–120. <https://doi.org/10.1097/WNF.0b013e3181d6f7ad>
- di Michele F, Prichep L, John ER, Chabot RJ (2005) The neurophysiology of attention-deficit/hyperactivity disorder. *Int J Psychophysiol* 58:81–93. <https://doi.org/10.1016/j.ijpsycho.2005.03.011>
- Dichter GS, Damiano CA, Allen JA (2012a) Reward circuitry dysfunction in psychiatric and neurodevelopmental disorders and genetic syndromes: animal models and clinical findings. *J Neurodev Disord* 4:19. <https://doi.org/10.1186/1866-1955-4-19>
- Dichter GS, Felder JN, Green SR, et al (2012b) Reward circuitry function in autism spectrum disorders. *Soc Cogn Affect Neurosci* 7:160–172. <https://doi.org/10.1093/scan/nsq095>
- Duan X, Chen H, He C, et al (2017) Resting-state functional under-connectivity within and between large-scale cortical networks across three low-frequency bands in adolescents with autism. *Prog Neuropsychopharmacol Biol Psychiatry* 79:434–441. <https://doi.org/10.1016/j.pnpbp.2017.07.027>
- Durstun S, van Belle J, de Zeeuw P (2011) Differentiating Frontostriatal and Fronto-Cerebellar Circuits in Attention-Deficit/Hyperactivity Disorder. *Biol Psychiatry* 69:1178–1184. <https://doi.org/10.1016/j.biopsych.2010.07.037>
- Ebisch SJH, Gallese V, Willems RM, et al (2011) Altered intrinsic functional connectivity of anterior and posterior insula regions in high-functioning participants with autism spectrum disorder. *Hum Brain Mapp* 32:1013–1028. <https://doi.org/10.1002/hbm.21085>
- Edgar JC, Khan SY, Blaskey L, et al (2015) Neuromagnetic Oscillations Predict Evoked-Response Latency Delays and Core Language Deficits in Autism Spectrum Disorders. *J Autism Dev Disord* 45:395–405. <https://doi.org/10.1007/s10803-013-1904-x>
- Eissa N, Al-Houqani M, Sadeq A, et al (2018) Current Enlightenment About Etiology and Pharmacological Treatment of Autism Spectrum Disorder. *Front Neurosci* 12:304. <https://doi.org/10.3389/fnins.2018.00304>
- Falahpour M, Thompson WK, Abbott AE, et al (2016) Underconnected, But Not Broken? Dynamic Functional Connectivity MRI Shows Underconnectivity in Autism Is Linked to Increased Intra-Individual Variability Across Time. *Brain Connect* 6:403–414. <https://doi.org/10.1089/brain.2015.0389>
- Fankhauser MP, Karumanchi VC, German ML, et al (1992) A double-blind, placebo-controlled study of the efficacy of transdermal clonidine in autism. *J Clin Psychiatry* 53:77–82
- Faraone SV (2018) The pharmacology of amphetamine and methylphenidate: Relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. *Neurosci Biobehav Rev* 87:255–270. <https://doi.org/10.1016/j.neubiorev.2018.02.001>
- Faraone SV, Larsson H (2019) Genetics of attention deficit hyperactivity disorder. *Mol Psychiatry* 24:562–575. <https://doi.org/10.1038/s41380-018-0070-0>
- Faraone SV, Mick E (2010) Molecular Genetics of Attention Deficit Hyperactivity Disorder. *Psychiatr Clin* 33:159–180. <https://doi.org/10.1016/j.psc.2009.12.004>
- Faraone SV, Perlis RH, Doyle AE, et al (2005) Molecular Genetics of Attention-Deficit/Hyperactivity Disorder. *Biol Psychiatry* 57:1313–1323. <https://doi.org/10.1016/j.biopsych.2004.11.024>
- Faraone SV, Spencer TJ, Madras BK, et al (2014) Functional effects of dopamine transporter gene genotypes on in vivo dopamine transporter functioning: a meta-analysis. *Mol Psychiatry* 19:880–889. <https://doi.org/10.1038/mp.2013.126>

- Farrant K, Uddin LQ (2016) Atypical developmental of dorsal and ventral attention networks in autism. *Dev Sci* 19:550–563. <https://doi.org/10.1111/desc.12359>
- Fatemi SH, Halt AR, Realmuto G, et al (2002) Purkinje Cell Size Is Reduced in Cerebellum of Patients with Autism. *Cell Mol Neurobiol* 22:171–175. <https://doi.org/10.1023/A:1019861721160>
- Findling RL, Mankoski R, Timko K, et al (2014) A randomized controlled trial investigating the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with autistic disorder. *J Clin Psychiatry* 75:22–30. <https://doi.org/10.4088/jcp.13m08500>
- Foote SL, Morrison JH (1987) Extrathalamic Modulation of Cortical Function. *Annu Rev Neurosci* 10:67–95. <https://doi.org/10.1146/annurev.ne.10.030187.000435>
- Franke B, Vasquez AA, Johansson S, et al (2010) Multicenter Analysis of the SLC6A3/DAT1 VNTR Haplotype in Persistent ADHD Suggests Differential Involvement of the Gene in Childhood and Persistent ADHD. *Neuropsychopharmacology* 35:656–664. <https://doi.org/10.1038/npp.2009.170>
- Friedman SD, Shaw DWW, Artru AA, et al (2006) Gray and White Matter Brain Chemistry in Young Children With Autism. *Arch Gen Psychiatry* 63:786–794. <https://doi.org/10.1001/archpsyc.63.7.786>
- Fuenzalida M, Pérez M, R. Arias H (2016) Role of Nicotinic and Muscarinic Receptors on Synaptic Plasticity and Neurological Diseases. *Curr Pharm Des* 22:2004–2014
- Furey ML, Pietrini P, Haxby JV (2000) Cholinergic Enhancement and Increased Selectivity of Perceptual Processing During Working Memory. *Science* 290:2315–2319. <https://doi.org/10.1126/science.290.5500.2315>
- Furey ML, Pietrini P, Haxby JV, Drevets WC (2008) Selective Effects of Cholinergic Modulation on Task Performance during Selective Attention. *Neuropsychopharmacology* 33:913–923. <https://doi.org/10.1038/sj.npp.1301461>
- Gadow KD, DeVincent CJ, Olvet DM, et al (2010) Association of DRD4 polymorphism with severity of oppositional defiant disorder, separation anxiety disorder and repetitive behaviors in children with autism spectrum disorder. *Eur J Neurosci* 32:1058–1065. <https://doi.org/10.1111/j.1460-9568.2010.07382.x>
- Gallezot J-D, Bottlaender M, Grégoire M-C, et al (2005) In Vivo Imaging of Human Cerebral Nicotinic Acetylcholine Receptors with 2-18F-Fluoro-A-85380 and PET. *J Nucl Med* 46:240–247
- Gault J, Robinson M, Berger R, et al (1998) Genomic Organization and Partial Duplication of the Human $\alpha 7$ Neuronal Nicotinic Acetylcholine Receptor Gene (CHRNA7). *Genomics* 52:173–85. <https://doi.org/10.1006/geno.1998.5363>
- Genro JP, Kieling C, Rohde LA, Hutz MH (2010) Attention-deficit/hyperactivity disorder and the dopaminergic hypotheses. *Expert Rev Neurother* 10:587–601. <https://doi.org/10.1586/ern.10.17>
- Geschwind DH (2011) Genetics of Autism Spectrum Disorders. *Trends Cogn Sci* 15:409–416. <https://doi.org/10.1016/j.tics.2011.07.003>
- Geurts HM, Embrechts M (2008) Language Profiles in ASD, SLI, and ADHD. *J Autism Dev Disord* 38:1931. <https://doi.org/10.1007/s10803-008-0587-1>
- Ghaleiha A, Ghyasvand M, Mohammadi M-R, et al (2014) Galantamine efficacy and tolerability as an augmentative therapy in autistic children: A randomized, double-blind, placebo-controlled trial. *J Psychopharmacol (Oxf)* 28:677–685. <https://doi.org/10.1177/0269881113508830>

- Ghanizadeh A (2011) Sensory Processing Problems in Children with ADHD, a Systematic Review. *Psychiatry Investig* 8:89–94. <https://doi.org/10.4306/pi.2011.8.2.89>
- Ghanizadeh A, Sahraeizadeh A, Berk M (2014) A Head-to-Head Comparison of Aripiprazole and Risperidone for Safety and Treating Autistic Disorders, a Randomized Double Blind Clinical Trial. *Child Psychiatry Hum Dev* 45:185–192. <https://doi.org/10.1007/s10578-013-0390-x>
- Gillentine M, Berry L, Goin-Kochel R, et al (2017) The cognitive and behavioral phenotypes of individuals with CHRNA7 duplications. *J Autism Dev Disord* 47:549–562. <https://doi.org/10.1007/s10803-016-2961-8>
- Gillentine M, Schaaf CP (2015) The Human Clinical Phenotypes of Altered CHRNA7 Copy Number. *Biochem Pharmacol* 97:352–362. <https://doi.org/10.1016/j.bcp.2015.06.012>
- Gizer IR, Ficks C, Waldman ID (2009) Candidate gene studies of ADHD: a meta-analytic review. *Hum Genet* 126:51–90. <https://doi.org/10.1007/s00439-009-0694-x>
- Gordon CT, Rapoport JL, Hamburger SD, et al (1992) Differential response of seven subjects with autistic disorder to clomipramine and desipramine. *Am J Psychiatry* 149:363–366. <https://doi.org/10.1176/ajp.149.3.363>
- Gordon CT, State RC, Nelson JE, et al (1993) A double-blind comparison of clomipramine, desipramine, and placebo in the treatment of autistic disorder. *Arch Gen Psychiatry* 50:441–447. <https://doi.org/10.1001/archpsyc.1993.01820180039004>
- Gregory AM, Agnew-Blais JC, Matthews T, et al (2017a) Associations between ADHD and sleep quality: Longitudinal analyses from a nationally-representative cohort of twins. *J Clin Child Adolesc Psychol Off J Soc Clin Child Adolesc Psychol Am Psychol Assoc Div 53* 46:284–294. <https://doi.org/10.1080/15374416.2016.1183499>
- Gregory AM, Agnew-Blais JC, Matthews T, et al (2017b) ADHD and Sleep Quality: Longitudinal Analyses From Childhood to Early Adulthood in a Twin Cohort. *J Clin Child Adolesc Psychol* 46:284–294. <https://doi.org/10.1080/15374416.2016.1183499>
- Guo X, Duan X, Suckling J, et al (2019) Partially impaired functional connectivity states between right anterior insula and default mode network in autism spectrum disorder. *Hum Brain Mapp* 40:1264–1275. <https://doi.org/10.1002/hbm.24447>
- Haber SN (2016) Corticostriatal circuitry. *Dialogues Clin Neurosci* 18:7–21
- Hamilton PJ, Campbell NG, Sharma S, et al (2013) De novo mutation in the dopamine transporter gene associates dopamine dysfunction with autism spectrum disorder. *Mol Psychiatry* 18:1315–1323. <https://doi.org/10.1038/mp.2013.102>
- Hampson DR, Blatt GJ (2015) Autism spectrum disorders and neuropathology of the cerebellum. *Front Neurosci* 9:420. <https://doi.org/10.3389/fnins.2015.00420>
- Handen BL, Johnson CR, Lubetsky M (2000) Efficacy of methylphenidate among children with autism and symptoms of attention-deficit hyperactivity disorder. *J Autism Dev Disord* 30:245–255. <https://doi.org/10.1023/a:1005548619694>
- Handen BL, Johnson CR, McAuliffe-Bellin S, et al (2011) Safety and Efficacy of Donepezil in Children and Adolescents with Autism: Neuropsychological Measures. *J Child Adolesc Psychopharmacol* 21:43–50. <https://doi.org/10.1089/cap.2010.0024>
- Handen BL, Sahl R, Hardan AY (2008) Guanfacine in Children with Autism and/or Intellectual Disabilities. *J Dev Behav Pediatr* 29:303–308. <https://doi.org/10.1097/DBP.0b013e3181739b9d>

- Harfterkamp M, Buitelaar JK, Minderaa RB, et al (2013) Long-Term Treatment with Atomoxetine for Attention-Deficit/Hyperactivity Disorder Symptoms in Children and Adolescents with Autism Spectrum Disorder: An Open-Label Extension Study. *J Child Adolesc Psychopharmacol* 23:194–199. <https://doi.org/10.1089/cap.2012.0012>
- Harfterkamp M, Buitelaar JK, Minderaa RB, et al (2014) Atomoxetine in Autism Spectrum Disorder: No Effects on Social Functioning; Some Beneficial Effects on Stereotyped Behaviors, Inappropriate Speech, and Fear of Change. *J Child Adolesc Psychopharmacol* 24:481–485. <https://doi.org/10.1089/cap.2014.0026>
- Harfterkamp M, van de Loo-Neus G, Minderaa RB, et al (2012) A Randomized Double-Blind Study of Atomoxetine Versus Placebo for Attention-Deficit/Hyperactivity Disorder Symptoms in Children With Autism Spectrum Disorder. *J Am Acad Child Adolesc Psychiatry* 51:733–741. <https://doi.org/10.1016/j.jaac.2012.04.011>
- Hawi Z, Matthews N, Barry E, et al (2013) A high density linkage disequilibrium mapping in 14 noradrenergic genes: evidence of association between SLC6A2, ADRA1B and ADHD. *Psychopharmacology (Berl)* 225:895–902. <https://doi.org/10.1007/s00213-012-2875-x>
- Hegarty JP, Ferguson BJ, Zamzow RM, et al (2017) Beta-adrenergic antagonism modulates functional connectivity in the default mode network of individuals with and without autism spectrum disorder. *Brain Imaging Behav* 11:1278–1289. <https://doi.org/10.1007/s11682-016-9604-8>
- Hettinger JA (2009) The role of dopamine-related genes in autism spectrum disorders: Evidence for specific genes and risk for ASD in families with affected males. Doctoral Thesis
- Hollander E, Wasserman S, Swanson EN, et al (2006) A Double-Blind Placebo-Controlled Pilot Study of Olanzapine in Childhood/Adolescent Pervasive Developmental Disorder. *J Child Adolesc Psychopharmacol* 16:541–548. <https://doi.org/10.1089/cap.2006.16.541>
- Horev G, Ellegood J, Lerch JP, et al (2011) Dosage-dependent phenotypes in models of 16p11.2 lesions found in autism. *Proc Natl Acad Sci* 108:17076–17081. <https://doi.org/10.1073/pnas.1114042108>
- Horvitz JC (2000) Mesolimbocortical and nigrostriatal dopamine responses to salient non-reward events. *Neuroscience* 96:651–656. [https://doi.org/10.1016/S0306-4522\(00\)00019-1](https://doi.org/10.1016/S0306-4522(00)00019-1)
- Howe M, Dombeck D (2016) Rapid signaling in distinct dopaminergic axons during locomotion and reward. *Nature* 535:505–510. <https://doi.org/10.1038/nature18942>
- Huguet G, Ey E, Bourgeron T (2013) The Genetic Landscapes of Autism Spectrum Disorders. *Annu Rev Genomics Hum Genet* 14:191–213. <https://doi.org/10.1146/annurev-genom-091212-153431>
- Huppé-Gourgues F, Jegouic K, Vaucher E (2018) Topographic Organization of Cholinergic Innervation From the Basal Forebrain to the Visual Cortex in the Rat. *Front Neural Circuits* 12:19. <https://doi.org/10.3389/fncir.2018.00019>
- Huss M, Duhan P, Gandhi P, et al (2017) Methylphenidate dose optimization for ADHD treatment: review of safety, efficacy, and clinical necessity. *Neuropsychiatr Dis Treat* 13:1741–1751. <https://doi.org/10.2147/NDT.S130444>
- Ichikawa H, Mikami K, Okada T, et al (2017) Aripiprazole in the Treatment of Irritability in Children and Adolescents with Autism Spectrum Disorder in Japan: A Randomized, Double-blind, Placebo-controlled Study. *Child Psychiatry Hum Dev* 48:796–806. <https://doi.org/10.1007/s10578-016-0704-x>
- Ilango A, Kesner AJ, Keller KL, et al (2014) Similar Roles of Substantia Nigra and Ventral Tegmental Dopamine Neurons in Reward and Aversion. *J Neurosci* 34:817–822. <https://doi.org/10.1523/JNEUROSCI.1703-13.2014>

- Inkster B, Muglia P, Jain U, Kennedy JL (2004) Linkage disequilibrium analysis of the dopamine beta-hydroxylase gene in persistent attention deficit hyperactivity disorder. *Psychiatr Genet* 14:117–120. <https://doi.org/10.1097/01.ypg.0000107932.32051.1c>
- Jaselskis CA, Cook EH, Fletcher KE (1992) Clonidine treatment of hyperactive and impulsive children with autistic disorder. *J Clin Psychopharmacol* 12:322–327. <https://doi.org/10.1097/00004714-199210000-00005>
- Jensen AA, Frølund B, Liljefors T, Krogsgaard-Larsen P (2005) Neuronal Nicotinic Acetylcholine Receptors: Structural Revelations, Target Identifications, and Therapeutic Inspirations. *J Med Chem* 48:4705–4745. <https://doi.org/10.1021/jm040219e>
- Johansson J, Landgren M, Fernell E, et al (2013) Decreased binding capacity (Bmax) of muscarinic acetylcholine receptors in fibroblasts from boys with attention-deficit/hyperactivity disorder (ADHD). *ADHD Atten Deficit Hyperact Disord* 5:267–271. <https://doi.org/10.1007/s12402-013-0103-0>
- Johnston BA, Mwangi B, Matthews K, et al (2014) Brainstem abnormalities in attention deficit hyperactivity disorder support high accuracy individual diagnostic classification. *Hum Brain Mapp* 35:5179–5189. <https://doi.org/10.1002/hbm.22542>
- Jones MB, Palmour RM, Zwaigenbaum L, Szatmari P (2004) Modifier effects in autism at the MAO-A and DBH loci. *Am J Med Genet Part B Neuropsychiatr Genet Off Publ Int Soc Psychiatr Genet* 126B:58–65. <https://doi.org/10.1002/ajmg.b.20172>
- Jongkees BJ, Colzato LS (2016) Spontaneous eye blink rate as predictor of dopamine-related cognitive function—A review. *Neurosci Biobehav Rev* 71:58–82. <https://doi.org/10.1016/j.neubiorev.2016.08.020>
- Jou RJ, Handen BL, Hardan AY (2005) Retrospective Assessment of Atomoxetine in Children and Adolescents with Pervasive Developmental Disorders. *J Child Adolesc Psychopharmacol* 15:325–330. <https://doi.org/10.1089/cap.2005.15.325>
- Jouvet M (1969) Biogenic amines and the states of sleep. *Science* 163:32–41. <https://doi.org/10.1126/science.163.3862.32>
- Jwaid AH, Muslem ZH, Dawood EB (2020) Measurement the Level of Dopamine Beta Hydroxylase Enzyme in Autistic Iraqi Children. *Prensa Med Argent* 106:1–7
- Kana RK, Uddin LQ, Kenet T, et al (2014) Brain connectivity in autism. *Front Hum Neurosci* 8:349. <https://doi.org/10.3389/fnhum.2014.00349>
- Kanne SM, Mazurek MO (2011) Aggression in children and adolescents with ASD: prevalence and risk factors. *J Autism Dev Disord* 41:926–937. <https://doi.org/10.1007/s10803-010-1118-4>
- Karvat G, Kimchi T (2014) Acetylcholine Elevation Relieves Cognitive Rigidity and Social Deficiency in a Mouse Model of Autism. *Neuropsychopharmacology* 39:831–840. <https://doi.org/10.1038/npp.2013.274>
- Kaufman S, Friedman S (1965) Dopamine-Beta-Hydroxylase. *Pharmacol Rev* 17:71–100
- Kebschull JM, Garcia da Silva P, Reid AP, et al (2016) High-Throughput Mapping of Single-Neuron Projections by Sequencing of Barcoded RNA. *Neuron* 91:975–987. <https://doi.org/10.1016/j.neuron.2016.07.036>
- Kemper TL, Bauman M (1998) Neuropathology of infantile autism. *J Neuropathol Exp Neurol* 57:645–652. <https://doi.org/10.1097/00005072-199807000-00001>

- Kenemans JL (2015) Specific proactive and generic reactive inhibition. *Neurosci Biobehav Rev* 56:115–126. <https://doi.org/10.1016/j.neubiorev.2015.06.011>
- Kenemans L, Ramsey N (2013) *Psychology in the Brain: Integrative Cognitive Neuroscience*. Macmillan International Higher Education
- Kent L, Green E, Holmes J, et al (2001) No association between CHRNA7 microsatellite markers and attention-deficit hyperactivity disorder. *Am J Med Genet* 105:686–689. <https://doi.org/10.1002/ajmg.1553>
- Kleinhans NM, Richards T, Sterling L, et al (2008) Abnormal functional connectivity in autism spectrum disorders during face processing. *Brain* 131:1000–1012. <https://doi.org/10.1093/brain/awm334>
- Klinger LG, Klinger MR, Pohlig RL (2007) Implicit Learning Impairments in Autism Spectrum Disorders: Implications for Treatment. In: Vizcaino CN, Perez JM, Comi ML, Gonzalez PM (eds) *New Developments in Autism: The Future is Today*, 1st edn. Jessica Kingsley Publishers, London and Philadelphia, pp 76–103
- Konofal E, Lecendreux M, Cortese S (2010) Sleep and ADHD. *Sleep Med* 11:652–658. <https://doi.org/10.1016/j.sleep.2010.02.012>
- Koob GF, Volkow ND (2010) Neurocircuitry of Addiction. *Neuropsychopharmacology* 35:217–238. <https://doi.org/10.1038/npp.2009.110>
- Kosaka H, Omori M, Munosue T, et al (2010) Smaller insula and inferior frontal volumes in young adults with pervasive developmental disorders. *NeuroImage* 50:1357–1363. <https://doi.org/10.1016/j.neuroimage.2010.01.085>
- Krames ES, Hunter Peckham P, Rezai A, Aboelsaad F (2009) What Is Neuromodulation? In: Krames ES, Peckham PH, Rezai AR (eds) *Neuromodulation*. Academic Press, San Diego, pp 3–8
- Krames ES, Peckham PH, Rezai AR (2018) *Neuromodulation: Comprehensive Textbook of Principles, Technologies, and Therapies*. Academic Press
- Kroemer NB, Guevara A, Ciocanea Teodorescu I, et al (2014) Balancing reward and work: Anticipatory brain activation in NAcc and VTA predict effort differentially. *NeuroImage* 102:510–519. <https://doi.org/10.1016/j.neuroimage.2014.07.060>
- Kumari V, Postma P (2005) Nicotine use in schizophrenia: The self medication hypotheses. *Neurosci Biobehav Rev* 29:1021–1034. <https://doi.org/10.1016/j.neubiorev.2005.02.006>
- Lakens D (2013) Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Front Psychol* 4:863. <https://doi.org/10.3389/fpsyg.2013.00863>
- Lawrence KE, Hernandez LM, Bookheimer SY, Dapretto M (2019) Atypical longitudinal development of functional connectivity in adolescents with autism spectrum disorder. *Autism Research* 12:53–65. <https://doi.org/10.1002/aur.1971>
- Lecavalier L (2006) Behavioral and Emotional Problems in Young People with Pervasive Developmental Disorders: Relative Prevalence, Effects of Subject Characteristics, and Empirical Classification. *J Autism Dev Disord* 36:1101–1114. <https://doi.org/10.1007/s10803-006-0147-5>
- Lee J, Laurin N, Crosbie J, et al (2008) Association study of the nicotinic acetylcholine receptor $\alpha 4$ subunit gene, CHRNA4, in attention-deficit hyperactivity disorder. *Genes Brain Behav* 7:53–60. <https://doi.org/10.1111/j.1601-183X.2007.00325.x>
- Lee M, Martin-Ruiz C, Graham A, et al (2002) Nicotinic receptor abnormalities in the cerebellar cortex in autism. *Brain* 125:1483–1495. <https://doi.org/10.1093/brain/awf160>

- Lee T-L, Raygada MJ, Rennert OM (2012) Integrative gene network analysis provides novel regulatory relationships, genetic contributions and susceptible targets in autism spectrum disorders. *Gene* 496:88–96. <https://doi.org/10.1016/j.gene.2012.01.020>
- Lee Y, Kim H, Kim J-E, et al (2018) Excessive D1 Dopamine Receptor Activation in the Dorsal Striatum Promotes Autistic-Like Behaviors. *Mol Neurobiol* 55:5658–5671. <https://doi.org/10.1007/s12035-017-0770-5>
- Lerner TN, Shilyansky C, Davidson TJ, et al (2015) Intact-Brain Analyses Reveal Distinct Information Carried by SNc Dopamine Subcircuits. *Cell* 162:635–647. <https://doi.org/10.1016/j.cell.2015.07.014>
- Levin ED, Rezvani AH (2002) Nicotinic Treatment for Cognitive Dysfunction. *Curr Drug Targets - CNS Neurol Disord* 1:423–431. <https://doi.org/10.2174/1568007023339102>
- Levy F, Swanson J (2001) Timing, space and ADHD: The dopamine theory revisited. *Aust N Z J Psychiatry* 35:504–11. <https://doi.org/10.1046/j.1440-1614.2001.00923.x>
- Lewis AS, van Schalkwyk GI, Lopez MO, et al (2018) An Exploratory Trial of Transdermal Nicotine for Aggression and Irritability in Adults with Autism Spectrum Disorder. *J Autism Dev Disord* 48:2748–2757. <https://doi.org/10.1007/s10803-018-3536-7>
- Lewis MH, Tanimura Y, Lee LW, Bodfish JW (2007) Animal models of restricted repetitive behavior in autism. *Behav Brain Res* 176:66–74. <https://doi.org/10.1016/j.bbr.2006.08.023>
- Lippiello PM (2006) Nicotinic cholinergic antagonists: A novel approach for the treatment of autism. *Med Hypotheses* 66:985–990. <https://doi.org/10.1016/j.mehy.2005.11.015>
- Liu AKL, Chang RC-C, Pearce RKB, Gentleman SM (2015) Nucleus basalis of Meynert revisited: anatomy, history and differential involvement in Alzheimer's and Parkinson's disease. *Acta Neuropathol (Berl)* 129:527–540. <https://doi.org/10.1007/s00401-015-1392-5>
- Liu R, Crawford J, Callahan PM, et al (2018) Intermittent stimulation in the nucleus basalis of Meynert improves sustained attention in rhesus monkeys. *Neuropharmacology* 137:202–210. <https://doi.org/10.1016/j.neuropharm.2018.04.026>
- Logemann HNA, Böcker KBE, Deschamps PKH, et al (2014) The effect of enhancing cholinergic neurotransmission by nicotine on EEG indices of inhibition in the human brain. *Pharmacol Biochem Behav* 122:89–96. <https://doi.org/10.1016/j.pbb.2014.03.019>
- London EB (2018) Neuromodulation and a Reconceptualization of Autism Spectrum Disorders: Using the Locus Coeruleus Functioning as an Exemplar. *Front Neurol* 9:1120. <https://doi.org/10.3389/fneur.2018.01120>
- London EB, Yoo JH, Fethke ED, Zimmerman-Bier B (2020) The Safety and Effectiveness of High-Dose Propranolol as a Treatment for Challenging Behaviors in Individuals With Autism Spectrum Disorders. *J Clin Psychopharmacol* 40:122–129. <https://doi.org/10.1097/JCP.0000000000001175>
- Loomes R, Hull L, Mandy WPL (2017) What Is the Male-to-Female Ratio in Autism Spectrum Disorder? A Systematic Review and Meta-Analysis. *J Am Acad Child Adolesc Psychiatry* 56:466–474. <https://doi.org/10.1016/j.jaac.2017.03.013>
- Lord C, Risi S, Pickles A (2004) Trajectory of Language Development in Autistic Spectrum Disorders. In: *Developmental language disorders: From phenotypes to etiologies*. Lawrence Erlbaum Associates Publishers, Mahwah, NJ, US, pp 7–29

- Luby J, Mrakotsky C, Stalets MM, et al (2006) Risperidone in Preschool Children with Autistic Spectrum Disorders: An Investigation of Safety and Efficacy. *J Child Adolesc Psychopharmacol* 16:575–587. <https://doi.org/10.1089/cap.2006.16.575>
- Lynch G (2018) Using Pupillometry to Assess the Atypical Pupillary Light Reflex and LC-NE System in ASD. *Behav Sci*. <https://doi.org/10.3390/bs8110108>
- MacDonald SWS, Cervenka S, Farde L, et al (2009) Extrastriatal dopamine D2 receptor binding modulates intraindividual variability in episodic recognition and executive functioning. *Neuropsychologia* 47:2299–2304. <https://doi.org/10.1016/j.neuropsychologia.2009.01.016>
- MacDonald SWS, Nyberg L, Bäckman L (2006) Intra-individual variability in behavior: links to brain structure, neurotransmission and neuronal activity. *Trends Neurosci* 29:474–480. <https://doi.org/10.1016/j.tins.2006.06.011>
- Madras BK, Miller GM, Fischman AJ (2005) The Dopamine Transporter and Attention-Deficit/Hyperactivity Disorder. *Biol Psychiatry* 57:1397–1409. <https://doi.org/10.1016/j.biopsych.2004.10.011>
- Maia CRM, Cortese S, Caye A, et al (2017) Long-Term Efficacy of Methylphenidate Immediate-Release for the Treatment of Childhood ADHD: A Systematic Review and Meta-Analysis. *J Atten Disord* 21:3–13. <https://doi.org/10.1177/1087054714559643>
- Makkonen I, Riikonen R, Kokki H, et al (2008) Serotonin and dopamine transporter binding in children with autism determined by SPECT. *Dev Med Child Neurol* 50:593–597. <https://doi.org/10.1111/j.1469-8749.2008.03027.x>
- Malow BA, Marzec ML, McGrew SG, et al (2006) Characterizing Sleep in Children with Autism Spectrum Disorders: A Multidimensional Approach. *Sleep* 29:1563–1571. <https://doi.org/10.1093/sleep/29.12.1563>
- Mansur AP, Avakian SD, Paula RS, et al (1998) Pharmacokinetics and pharmacodynamics of propranolol in hypertensive patients after sublingual administration: systemic availability. *Braz J Med Biol Res* 31:691–696. <https://doi.org/10.1590/S0100-879X1998000500014>
- Marco EJ, Hinkley LBN, Hill SS, Nagarajan SS (2011) Sensory Processing in Autism: A Review of Neurophysiologic Findings. *Pediatr Res* 69:48–54. <https://doi.org/10.1203/PDR.0b013e3182130c54>
- Marcus RN, Owen R, Kamen L, et al (2009) A Placebo-Controlled, Fixed-Dose Study of Aripiprazole in Children and Adolescents With Irritability Associated With Autistic Disorder. *J Am Acad Child Adolesc Psychiatry* 48:1110–1119. <https://doi.org/10.1097/CHI.0b013e3181b76658>
- Marder E (2012) Neuromodulation of Neuronal Circuits: Back to the Future. *Neuron* 76:1–11. <https://doi.org/10.1016/j.neuron.2012.09.010>
- Marotta R, Risoleo MC, Messina G, et al (2020) The Neurochemistry of Autism. *Brain Sci* 10:163. <https://doi.org/10.3390/brainsci10030163>
- Martin-Ruiz CM, Lee M, Perry RH, et al (2004) Molecular analysis of nicotinic receptor expression in autism. *Mol Brain Res* 123:81–90. <https://doi.org/10.1016/j.molbrainres.2004.01.003>
- Masi A, DeMayo MM, Glozier N, Guastella AJ (2017) An Overview of Autism Spectrum Disorder, Heterogeneity and Treatment Options. *Neurosci Bull* 33:183–193. <https://doi.org/10.1007/s12264-017-0100-y>
- Mastronardi CA, Pillai E, Pineda DA, et al (2016) Linkage and association analysis of ADHD endophenotypes in extended and multigenerational pedigrees from a genetic isolate. *Mol Psychiatry* 21:1434–1440. <https://doi.org/10.1038/mp.2015.172>

- Mazza M, Pino MC, Mariano M, et al (2014) Affective and cognitive empathy in adolescents with autism spectrum disorder. *Front Hum Neurosci* 8:791. <https://doi.org/10.3389/fnhum.2014.00791>
- McCormick DA (1989) Cholinergic and noradrenergic modulation of thalamocortical processing. *Trends Neurosci* 12:215–221. [https://doi.org/10.1016/0166-2236\(89\)90125-2](https://doi.org/10.1016/0166-2236(89)90125-2)
- McCormick DA (1992) Neurotransmitter actions in the thalamus and cerebral cortex and their role in neuromodulation of thalamocortical activity. *Prog Neurobiol* 39:337–388. [https://doi.org/10.1016/0301-0082\(92\)90012-4](https://doi.org/10.1016/0301-0082(92)90012-4)
- McCracken JT, Badashova KK, Posey DJ, et al (2014) Positive effects of methylphenidate on hyperactivity are moderated by monoaminergic gene variants in children with autism spectrum disorders. *Pharmacogenomics J* 14:295–302. <https://doi.org/10.1038/tpj.2013.23>
- McCracken JT, McGough J, Shah B, et al (2002) Risperidone in children with autism and serious behavioral problems. *N Engl J Med* 347:314–321. <https://doi.org/10.1056/NEJMoa013171>
- McCutcheon RA, Nour MM, Dahoun T, et al (2019) Mesolimbic Dopamine Function Is Related to Salience Network Connectivity: An Integrative Positron Emission Tomography and Magnetic Resonance Study. *Biol Psychiatry* 85:368–378. <https://doi.org/10.1016/j.biopsych.2018.09.010>
- McDougle CJ, Holmes JP, Carlson DC, et al (1998) A Double-blind, Placebo-Controlled Study of Risperidone in Adults With Autistic Disorder and Other Pervasive Developmental Disorders. *Arch Gen Psychiatry* 55:633–641. <https://doi.org/10.1001/archpsyc.55.7.633>
- McDougle CJ, Scahill L, Aman MG, et al (2005) Risperidone for the Core Symptom Domains of Autism: Results From the Study by the Autism Network of the Research Units on Pediatric Psychopharmacology. *Am J Psychiatry* 162:1142–1148. <https://doi.org/10.1176/appi.ajp.162.6.1142>
- McEvoy B, Hawi Z, Fitzgerald M, Gill M (2002) No evidence of linkage or association between the norepinephrine transporter (NET) gene polymorphisms and ADHD in the Irish population. *Am J Med Genet* 114:665–666. <https://doi.org/10.1002/ajmg.10416>
- Menon V, Uddin LQ (2010) Saliency, switching, attention and control: a network model of insula function. *Brain Struct Funct* 214:655–667. <https://doi.org/10.1007/s00429-010-0262-0>
- Mesulam MM (2000) Behavioral Neuroanatomy: Large-Scale Networks, Association Cortex, Frontal Syndromes, the Limbic System, and Hemispheric Specializations. In: Mesulam MM (ed) *Principles of Behavioral and Cognitive Neurology*, 2nd edn. Oxford University Press, New York, NY, pp 1–120
- Mesulam MM, Geula C (1988) Nucleus basalis (Ch4) and cortical cholinergic innervation in the human brain: Observations based on the distribution of acetylcholinesterase and choline acetyltransferase. *J Comp Neurol* 275:216–240. <https://doi.org/10.1002/cne.902750205>
- Mesulam MM, Mufson EJ, Levey AI, Wainer BH (1983) Cholinergic innervation of cortex by the basal forebrain: Cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (Substantia innominata), and hypothalamus in the rhesus monkey. *J Comp Neurol* 214:170–197. <https://doi.org/10.1002/cne.902140206>
- Meyza KZ, Blanchard DC (2017) The BTBR mouse model of idiopathic autism – current view on mechanisms. *Neurosci Biobehav Rev* 76:99–110. <https://doi.org/10.1016/j.neubiorev.2016.12.037>
- Misra V (2014) The Social Brain Network and Autism. *Ann Neurosci* 21:69–73. <https://doi.org/10.5214/ans.0972.7531.210208>

- Mitoma H, Ishida K, Shizuka-Ikeda M, Mizusawa H (2003) Dual impairment of GABAA- and GABAB-receptor-mediated synaptic responses by autoantibodies to glutamic acid decarboxylase. *J Neurol Sci* 208:51–56. [https://doi.org/10.1016/S0022-510X\(02\)00423-9](https://doi.org/10.1016/S0022-510X(02)00423-9)
- Mizuno A, Villalobos ME, Davies MM, et al (2006) Partially enhanced thalamocortical functional connectivity in autism. *Brain Res* 1104:160–174. <https://doi.org/10.1016/j.brainres.2006.05.064>
- Moessner R, Marshall CR, Sutcliffe JS, et al (2007) Contribution of SHANK3 Mutations to Autism Spectrum Disorder. *Am J Hum Genet* 81:1289–1297. <https://doi.org/10.1086/522590>
- Monk CS, Peltier SJ, Wiggins JL, et al (2009) Abnormalities of intrinsic functional connectivity in autism spectrum disorders. *NeuroImage* 47:764–772. <https://doi.org/10.1016/j.neuroimage.2009.04.069>
- Moolchan ET, Ernst M, Henningfield JE (2000) A review of tobacco smoking in adolescents: treatment implications. *J Am Acad Child Adolesc Psychiatry* 39:682–693. <https://doi.org/10.1097/00004583-200006000-00006>
- Morales M, Margolis E (2017) Ventral tegmental area: Cellular heterogeneity, connectivity and behaviour. *Nat Rev Neurosci* 18:73–85. <https://doi.org/10.1038/nrn.2016.165>
- Moseley RL, Ypma RJF, Holt RJ, et al (2015) Whole-brain functional hypoconnectivity as an endophenotype of autism in adolescents. *NeuroImage Clin* 9:140–152. <https://doi.org/10.1016/j.nicl.2015.07.015>
- Mouton PR, Pakkenberg B, Gundersen HJG, Price DL (1994) Absolute number and size of pigmented locus coeruleus neurons in young and aged individuals. *J Chem Neuroanat* 7:185–190. [https://doi.org/10.1016/0891-0618\(94\)90028-0](https://doi.org/10.1016/0891-0618(94)90028-0)
- Mueller A, Hong DS, Shepard S, Moore T (2017) Linking ADHD to the Neural Circuitry of Attention. *Trends Cogn Sci* 21:474–488. <https://doi.org/10.1016/j.tics.2017.03.009>
- Mukaetova-Ladinska EB, Westwood J, Perry EK (2010) Cholinergic Component of Autism Spectrum Disorder. In: Blatt GJ (ed) *The Neurochemical Basis of Autism: From Molecules to Minicolumns*. Springer US, Boston, MA, pp 129–161
- Müller R-A (2007) The study of autism as a distributed disorder. *Ment Retard Dev Disabil Res Rev* 13:85–95. <https://doi.org/10.1002/mrdd.20141>
- Müller R-A, Shih P, Keehn B, et al (2011) Underconnected, but how? A survey of functional connectivity MRI studies in autism spectrum disorders. *Cereb Cortex N Y N 1991* 21:2233–2243. <https://doi.org/10.1093/cercor/bhq296>
- Murdaugh DL, Shinkareva SV, Deshpande HR, et al (2012) Differential Deactivation during Mentalizing and Classification of Autism Based on Default Mode Network Connectivity. *PLoS ONE* 7:e50064. <https://doi.org/10.1371/journal.pone.0050064>
- Murray ML, Hsia Y, Glaser K, et al (2014) Pharmacological treatments prescribed to people with autism spectrum disorder (ASD) in primary health care. *Psychopharmacology (Berl)* 231:1011–1021. <https://doi.org/10.1007/s00213-013-3140-7>
- Musser ED, Backs RW, Schmitt CF, et al (2011) Emotion Regulation via the Autonomic Nervous System in Children with Attention-Deficit/Hyperactivity Disorder (ADHD). *J Abnorm Child Psychol* 39:841–852. <https://doi.org/10.1007/s10802-011-9499-1>
- Myer NM, Boland JR, Faraone SV (2018) Pharmacogenetics predictors of methylphenidate efficacy in childhood ADHD. *Mol Psychiatry* 23:1929–1936. <https://doi.org/10.1038/mp.2017.234>

- Nagaraj R, Singhi P, Malhi P (2006) Risperidone in Children With Autism: Randomized, Placebo-Controlled, Double-Blind Study. *J Child Neurol* 21:450–455. <https://doi.org/10.1177/08830738060210060801>
- Nagasaka K, Watanabe Y, Takashima I (2017) Topographical projections from the nucleus basalis magnocellularis (Meynert) to the frontal cortex: A voltage-sensitive dye imaging study in rats. *Brain Stimulat* 10:977–980. <https://doi.org/10.1016/j.brs.2017.06.008>
- Nair A, Treiber JM, Shukla DK, et al (2013) Impaired thalamocortical connectivity in autism spectrum disorder: a study of functional and anatomical connectivity. *Brain* 136:1942–1955. <https://doi.org/10.1093/brain/awt079>
- Narayanan A, White CA, Saklayen S, et al (2010) Effect of Propranolol on Functional Connectivity in Autism Spectrum Disorder—A Pilot Study. *Brain Imaging Behav* 4:189–197. <https://doi.org/10.1007/s11682-010-9098-8>
- Nayate A, Bradshaw JL, Rinehart NJ (2005) Autism and Asperger's disorder: Are they movement disorders involving the cerebellum and/or basal ganglia? *Brain Res Bull* 67:327–334. <https://doi.org/10.1016/j.brainresbull.2005.07.011>
- Nguyen M, Roth A, Kyzar EJ, et al (2014) Decoding the contribution of dopaminergic genes and pathways to autism spectrum disorder (ASD). *Neurochem Int* 66:15–26. <https://doi.org/10.1016/j.neuint.2014.01.002>
- Niederhofer H, Staffen W, Mair A (2002) Galantamine May Be Effective In Treating Autistic Disorder. *BMJ* 325:1422–1422
- Niederhofer H, Staffen W, Mair A (2003) Tianeptine: a novel strategy of psychopharmacological treatment of children with autistic disorder. *Hum Psychopharmacol* 18:389–393. <https://doi.org/10.1002/hup.491>
- Niklasson L, Rasmussen P, Oskarsdóttir S, Gillberg C (2009) Autism, ADHD, mental retardation and behavior problems in 100 individuals with 22q11 deletion syndrome. *Res Dev Disabil* 30:763–773. <https://doi.org/10.1016/j.ridd.2008.10.007>
- Nobusako S, Nishi Y, Nishi Y, et al (2017) Transcranial Direct Current Stimulation of the Temporoparietal Junction and Inferior Frontal Cortex Improves Imitation-Inhibition and Perspective-Taking with no Effect on the Autism-Spectrum Quotient Score. *Front Behav Neurosci* 11:84. <https://doi.org/10.3389/fnbeh.2017.00084>
- Nomi JS, Uddin LQ (2015) Developmental changes in large-scale network connectivity in autism. *NeuroImage Clin* 7:732–741. <https://doi.org/10.1016/j.nicl.2015.02.024>
- Ohmura Y, Tsutsui-Kimura I, Yoshioka M (2012) Impulsive Behavior and Nicotinic Acetylcholine Receptors. *J Pharmacol Sci* 118:413–422. <https://doi.org/10.1254/jphs.11R06CR>
- Oikonomakis V, Kosma K, Mitrakos A, et al (2016) Recurrent copy number variations as risk factors for autism spectrum disorders: analysis of the clinical implications. *Clin Genet* 89:708–718. <https://doi.org/10.1111/cge.12740>
- Olinicy A, Blakeley-Smith A, Johnson L, et al (2016) Brief Report: Initial Trial of Alpha7-Nicotinic Receptor Stimulation in Two Adult Patients with Autism Spectrum Disorder. *J Autism Dev Disord* 46:3812–3817. <https://doi.org/10.1007/s10803-016-2890-6>
- Olinicy A, Harris JG, Johnson LL, et al (2006) Proof-of-concept trial of an alpha7 nicotinic agonist in schizophrenia. *Arch Gen Psychiatry* 63:630–638. <https://doi.org/10.1001/archpsyc.63.6.630>
- Orsolini L, Tomasetti C, Valchera A, et al (2016) An update of safety of clinically used atypical antipsychotics. *Expert Opin Drug Saf* 15:1329–1347. <https://doi.org/10.1080/14740338.2016.1201475>

- Owen R, Sikich L, Marcus RN, et al (2009) Aripiprazole in the Treatment of Irritability in Children and Adolescents With Autistic Disorder. *Pediatrics* 124:1533–1540. <https://doi.org/10.1542/peds.2008-3782>
- Park S, Park J-E, Cho S-C, et al (2014) No association of the norepinephrine transporter gene (SLC6A2) and cognitive and behavioural phenotypes of patients with autism spectrum disorder. *Eur Arch Psychiatry Clin Neurosci* 264:507–515. <https://doi.org/10.1007/s00406-013-0480-6>
- Passarelli F, Donfrancesco R, Nativio P, et al (2013) Anti-Purkinje cell antibody as a biological marker in attention deficit/hyperactivity disorder: a pilot study. *J Neuroimmunol* 258:67–70. <https://doi.org/10.1016/j.jneuroim.2013.02.018>
- Pavál D (2017) A Dopamine Hypothesis of Autism Spectrum Disorder. *Dev Neurosci* 39:355–360. <https://doi.org/10.1159/000478725>
- Pearson DA, Santos CW, Aman MG, et al (2013) Effects of Extended Release Methylphenidate Treatment on Ratings of Attention-Deficit/Hyperactivity Disorder (ADHD) and Associated Behavior in Children with Autism Spectrum Disorders and ADHD Symptoms. *J Child Adolesc Psychopharmacol* 23:337–351. <https://doi.org/10.1089/cap.2012.0096>
- Pellissier LP, Gandía J, Laboute T, et al (2018) μ opioid receptor, social behaviour and autism spectrum disorder: reward matters. *Br J Pharmacol* 175:2750–2769. <https://doi.org/10.1111/bph.13808>
- Perry EK, Lee MLW, Martin-Ruiz CM, et al (2001) Cholinergic Activity in Autism: Abnormalities in the Cerebral Cortex and Basal Forebrain. *Am J Psychiatry* 158:1058–1066. <https://doi.org/10.1176/appi.ajp.158.7.1058>
- Peters SK, Dunlop K, Downar J (2016) Cortico-Striatal-Thalamic Loop Circuits of the Salience Network: A Central Pathway in Psychiatric Disease and Treatment. *Front Syst Neurosci* 10:104. <https://doi.org/10.3389/fnsys.2016.00104>
- Phillis JW (1968) Acetylcholine release from the cerebral cortex: Its role in cortical arousal. *Brain Res* 7:378–389. [https://doi.org/10.1016/0006-8993\(68\)90004-8](https://doi.org/10.1016/0006-8993(68)90004-8)
- Picard F, Sadaghiani S, Leroy C, et al (2013) High density of nicotinic receptors in the cingulo-insular network. *NeuroImage* 79:42–51. <https://doi.org/10.1016/j.neuroimage.2013.04.074>
- Pinto D, Pagnamenta AT, Klei L, et al (2010) Functional impact of global rare copy number variation in autism spectrum disorders. *Nature* 466:368–372. <https://doi.org/10.1038/nature09146>
- Politte LC, Scahill L, Figueroa J, et al (2018) A randomized, placebo-controlled trial of extended-release guanfacine in children with autism spectrum disorder and ADHD symptoms: an analysis of secondary outcome measures. *Neuropsychopharmacology* 43:1772–1778. <https://doi.org/10.1038/s41386-018-0039-3>
- Pomerleau OF, Downey KK, Stelson FW, Pomerleau CS (1995) Cigarette smoking in adult patients diagnosed with attention deficit hyperactivity disorder. *J Subst Abuse* 7:373–378. [https://doi.org/10.1016/0899-3289\(95\)90030-6](https://doi.org/10.1016/0899-3289(95)90030-6)
- Potter AS, Newhouse PA (2004) Effects of acute nicotine administration on behavioral inhibition in adolescents with attention-deficit/hyperactivity disorder. *Psychopharmacology (Berl)* 176:183–194. <https://doi.org/10.1007/s00213-004-1874-y>
- Potter AS, Newhouse PA, Bucci DJ (2006) Central nicotinic cholinergic systems: A role in the cognitive dysfunction in Attention-Deficit/Hyperactivity Disorder? *Behav Brain Res* 175:201–211. <https://doi.org/10.1016/j.bbr.2006.09.015>

- Potter AS, Schaubhut G, Shipman M (2014) Targeting the Nicotinic Cholinergic System to Treat Attention-Deficit/Hyperactivity Disorder: Rationale and Progress to Date. *CNS Drugs* 28:1103–1113. <https://doi.org/10.1007/s40263-014-0208-9>
- Purper-Ouakil D, Ramoz N, Lepagnol-Bestel A-M, et al (2011) Neurobiology of Attention Deficit/Hyperactivity Disorder. *Pediatr Res* 69:69–76. <https://doi.org/10.1203/PDR.0b013e318212b40f>
- Quintana H, Birmaher B, Stedje D, et al (1995) Use of methylphenidate in the treatment of children with autistic disorder. *J Autism Dev Disord* 25:283–294. <https://doi.org/10.1007/BF02179289>
- Ragozzino ME, Pal SN, Unick K, et al (1998) Modulation of Hippocampal Acetylcholine Release and Spontaneous Alternation Scores by Intrahippocampal Glucose Injections. *J Neurosci* 18:1595–1601. <https://doi.org/10.1523/JNEUROSCI.18-04-01595.1998>
- Raichle ME (2015) The Brain's Default Mode Network. *Annu Rev Neurosci* 38:433–447. <https://doi.org/10.1146/annurev-neuro-071013-014030>
- Ramachandran VS, Oberman LM (2006) Broken Mirrors. *Sci Am* 295:62–69
- Ray MA, Graham AJ, Lee M, et al (2005) Neuronal nicotinic acetylcholine receptor subunits in autism: an immunohistochemical investigation in the thalamus. *Neurobiol Dis* 19:366–377. <https://doi.org/10.1016/j.nbd.2005.01.017>
- Remington G, Sloman L, Konstantareas M, et al (2001) Clomipramine Versus Haloperidol in the Treatment of Autistic Disorder: A Double-Blind, Placebo-Controlled, Crossover Study. *J Clin Psychopharmacol* 21:440–444
- Research Units on Pediatric Psychopharmacology Autism Network (2005) Randomized, controlled, crossover trial of methylphenidate in pervasive developmental disorders with hyperactivity. *Arch Gen Psychiatry* 62:1266–1274. <https://doi.org/10.1001/archpsyc.62.11.1266>
- Rinne UK, Laihinien A, Rinne JO, et al (1990) Positron emission tomography demonstrates dopamine D2 receptor supersensitivity in the striatum of patients with early Parkinson's disease. *Mov Disord* 5:55–59. <https://doi.org/10.1002/mds.870050114>
- Robbins TW (2000) Chemical neuromodulation of frontal-executive functions in humans and other animals. *Exp Brain Res* 133:130–138. <https://doi.org/10.1007/s002210000407>
- Robbins TW, Arnsten AFT (2009) The Neuropsychopharmacology of Fronto-Executive Function: Monoaminergic Modulation. *Annu Rev Neurosci* 32:267–287. <https://doi.org/10.1146/annurev.neuro.051508.135535>
- Robertson SD, Plummer NW, de Marchena J, Jensen P (2013) Developmental origins of central norepinephrine neuron diversity. *Nat Neurosci* 16:1016–1023. <https://doi.org/10.1038/nn.3458>
- Robinson PD, Schutz CK, Macciardi F, et al (2001) Genetically determined low maternal serum dopamine β -hydroxylase levels and the etiology of autism spectrum disorders. *Am J Med Genet* 100:30–36. <https://doi.org/10.1002/ajmg.1187>
- Rommelse NNJ, Geurts HM, Franke B, et al (2011) A review on cognitive and brain endophenotypes that may be common in autism spectrum disorder and attention-deficit/hyperactivity disorder and facilitate the search for pleiotropic genes. *Neurosci Biobehav Rev* 35:1363–1396. <https://doi.org/10.1016/j.neubiorev.2011.02.015>
- Ronald A, Simonoff E, Kuntsi J, et al (2008) Evidence for overlapping genetic influences on autistic and ADHD behaviours in a community twin sample. *J Child Psychol Psychiatry* 49:535–542. <https://doi.org/10.1111/j.1469-7610.2007.01857.x>

- Ross RG (2012) Advances in the Genetics of ADHD. *Am J Psychiatry* 169:115–117. <https://doi.org/10.1176/appi.ajp.2011.11111647>
- Rossi MA, Sukharnikova T, Hayrapetyan VY, et al (2013) Operant Self-Stimulation of Dopamine Neurons in the Substantia Nigra. *PLoS ONE* 8:e65799. <https://doi.org/10.1371/journal.pone.0065799>
- Rout UK, Mungan NK, Dhossche DM (2012) Presence of GAD65 autoantibodies in the serum of children with autism or ADHD. *Eur Child Adolesc Psychiatry* 21:141–147. <https://doi.org/10.1007/s00787-012-0245-1>
- Sadaghiani S, Ng B, Altmann A, et al (2017) Overdominant Effect of a CHRNA4 Polymorphism on Cingulo-Opercular Network Activity and Cognitive Control. *J Neurosci* 37:9657–9666. <https://doi.org/10.1523/JNEUROSCI.0991-17.2017>
- Sagar-Ouriaghli I, Lievesley K, Santosh PJ (2018) Propranolol for treating emotional, behavioural, autonomic dysregulation in children and adolescents with autism spectrum disorders. *J Psychopharmacol (Oxf)* 32:641–653. <https://doi.org/10.1177/0269881118756245>
- Salatino-Oliveira A, Rohde LA, Hutz MH (2018) The dopamine transporter role in psychiatric phenotypes. *Am J Med Genet B Neuropsychiatr Genet* 177:211–231. <https://doi.org/10.1002/ajmg.b.32578>
- Salgado JV, Costa-Silva M, Malloy-Diniz LF, et al (2007) Prefrontal cognitive dysfunction following brainstem lesion. *Clin Neurol Neurosurg* 109:379–382. <https://doi.org/10.1016/j.clineuro.2007.01.002>
- Sanchez LE, Campbell M, Small AM, et al (1996) A pilot study of clomipramine in young autistic children. *J Am Acad Child Adolesc Psychiatry* 35:537–544. <https://doi.org/10.1097/00004583-199604000-00021>
- Sander D, Grafman J, Zalla T (2003) The human amygdala: an evolved system for relevance detection. *Rev Neurosci* 14:303–316. <https://doi.org/10.1515/revneuro.2003.14.4.303>
- Scahill L, McCracken JT, King BH, et al (2015) Extended-Release Guanfacine for Hyperactivity in Children With Autism Spectrum Disorder. *Am J Psychiatry* 172:1197–1206. <https://doi.org/10.1176/appi.ajp.2015.15010055>
- Schreibman L, Dawson G, Stahmer AC, et al (2015) Naturalistic Developmental Behavioral Interventions: Empirically Validated Treatments for Autism Spectrum Disorder. *J Autism Dev Disord* 45:2411–2428. <https://doi.org/10.1007/s10803-015-2407-8>
- Schutte I, Deschamps PKH, van Harten PN, Kenemans JL (2020) Dopaminergic and noradrenergic manipulation of anticipatory reward and probability event-related potentials. *Psychopharmacology (Berl)*. <https://doi.org/10.1007/s00213-020-05515-x>
- Schwarz LA, Miyamichi K, Gao XJ, et al (2015) Viral-genetic tracing of the input–output organization of a central noradrenaline circuit. *Nature* 524:88–92. <https://doi.org/10.1038/nature14600>
- Seeley WW, Menon V, Schatzberg AF, et al (2007) Dissociable Intrinsic Connectivity Networks for Salience Processing and Executive Control. *J Neurosci* 27:2349–2356. <https://doi.org/10.1523/JNEUROSCI.5587-06.2007>
- Sengupta SM, Grizenko N, Thakur GA, et al (2012) Differential association between the norepinephrine transporter gene and ADHD: role of sex and subtype. *J Psychiatry Neurosci* 37:129–137. <https://doi.org/10.1503/jpn.110073>
- Shea S, Turgay A, Carroll A, et al (2004) Risperidone in the Treatment of Disruptive Behavioral Symptoms in Children With Autistic and Other Pervasive Developmental Disorders. *Pediatrics* 114:e634–e641. <https://doi.org/10.1542/peds.2003-0264-F>

- Shu SY, Jiang G, Zheng Z, et al (2019) A New Neural Pathway from the Ventral Striatum to the Nucleus Basalis of Meynert with Functional Implication to Learning and Memory. *Mol Neurobiol* 56:7222–7233. <https://doi.org/10.1007/s12035-019-1588-0>
- Sidlauskaite J, Sonuga-Barke E, Roeyers H, Wiersma JR (2016) Altered intrinsic organisation of brain networks implicated in attentional processes in adult attention-deficit/hyperactivity disorder: a resting-state study of attention, default mode and salience network connectivity. *Eur Arch Psychiatry Clin Neurosci* 266:349–357. <https://doi.org/10.1007/s00406-015-0630-0>
- Silvetti M, Wiersma JR, Sonuga-Barke E, Verguts T (2013) Deficient reinforcement learning in medial frontal cortex as a model of dopamine-related motivational deficits in ADHD. *Neural Netw* 46:199–209. <https://doi.org/10.1016/j.neunet.2013.05.008>
- Simonoff E, Pickles A, Charman T, et al (2008) Psychiatric Disorders in Children With Autism Spectrum Disorders: Prevalence, Comorbidity, and Associated Factors in a Population-Derived Sample. *J Am Acad Child Adolesc Psychiatry* 47:921–929. <https://doi.org/10.1097/CHI.0b013e318179964f>
- Sinkus ML, Graw S, Freedman R, et al (2015) The Human CHRNA7 and CHRFAM7A Genes: A Review of the Genetics, Regulation, and Function. *Neuropharmacology* 96:274–288. <https://doi.org/10.1016/j.neuropharm.2015.02.006>
- Sinzig J, Bruning N, Morsch D, Lehmkuhl G (2008) Attention profiles in autistic children with and without comorbid hyperactivity and attention problems. *Acta Neuropsychiatr* 20:207–215. <https://doi.org/10.1111/j.1601-5215.2008.00292.x>
- Sokhadze EM, Casanova MF, El-Baz AS, et al (2016) TMS-based neuromodulation of evoked and induced gamma oscillations and event-related potentials in children with autism. *NeuroRegulation* 3:101. <https://doi.org/10.15540/nr.3.3.101>
- Sokol DK, Dunn DW, Edwards-Brown M, Feinberg J (2002) Hydrogen Proton Magnetic Resonance Spectroscopy in Autism: Preliminary Evidence of Elevated Choline/Creatine Ratio. *J Child Neurol* 17:245–249. <https://doi.org/10.1177/088307380201700401>
- Sousa NO, Grevet EH, Salgado CAI, et al (2011) Smoking and ADHD: An evaluation of self medication and behavioral disinhibition models based on comorbidity and personality patterns. *J Psychiatr Res* 45:829–834. <https://doi.org/10.1016/j.jpsychires.2010.10.012>
- Sridharan D, Levitin DJ, Menon V (2008) A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proc Natl Acad Sci* 105:12569–12574. <https://doi.org/10.1073/pnas.0800005105>
- Staal WG, de Krom M, de Jonge MV (2012) Brief Report: The Dopamine-3-Receptor Gene (DRD3) is Associated with Specific Repetitive Behavior in Autism Spectrum Disorder (ASD). *J Autism Dev Disord* 42:885–888. <https://doi.org/10.1007/s10803-011-1312-z>
- Stahl SM (2008) Circuits in Psychopharmacology. In: Stahl SM (ed) *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Application*, 3rd edn.
- Stahl SM (2013) *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*, 4th edn. Cambridge University Press
- Stark R, Bauer E, Merz CJ, et al (2011) ADHD related behaviors are associated with brain activation in the reward system. *Neuropsychologia* 49:426–434. <https://doi.org/10.1016/j.neuropsychologia.2010.12.012>
- Stevens T, Peng L, Barnard-Brak L (2016) The comorbidity of ADHD in children diagnosed with autism spectrum disorder. *Res Autism Spectr Disord* 31:11–18. <https://doi.org/10.1016/j.rasd.2016.07.003>

- Stoner R, Chow ML, Boyle MP, et al (2014) Patches of Disorganization in the Neocortex of Children with Autism. *N Engl J Med* 370:1209–1219. <https://doi.org/10.1056/NEJMoa1307491>
- Strafella AP, Paus T, Barrett J, Dagher A (2001) Repetitive Transcranial Magnetic Stimulation of the Human Prefrontal Cortex Induces Dopamine Release in the Caudate Nucleus. *J Neurosci* 21:RC157–RC157. <https://doi.org/10.1523/JNEUROSCI.21-15-j0003.2001>
- Sturman N, Deckx L, Driel ML van (2017) Methylphenidate for children and adolescents with autism spectrum disorder. *Cochrane Database Syst Rev* 11:1465–1858. <https://doi.org/10.1002/14651858.CD011144.pub2>
- Svensson TH, Bunney BS, Aghajanian GK (1975) Inhibition of both noradrenergic and serotonergic neurons in brain by the α -adrenergic agonist clonidine. *Brain Research* 92:291–306. [https://doi.org/10.1016/0006-8993\(75\)90276-0](https://doi.org/10.1016/0006-8993(75)90276-0)
- Swanson JM (2003) Role of executive function in ADHD. *J Clin Psychiatry* 64 Suppl 14:35–39
- Szabadi E (2013) Functional neuroanatomy of the central noradrenergic system. *J Psychopharmacol (Oxf)* 27:659–693. <https://doi.org/10.1177/0269881113490326>
- Szerb JC (1967) Cortical acetylcholine release and electroencephalographic arousal. *J Physiol* 192:329–343. <https://doi.org/10.1113/jphysiol.1967.sp008303>
- Tager-Flusberg H (2006) Defining language phenotypes in autism. *Clin Neurosci Res* 6:219–224. <https://doi.org/10.1016/j.cnr.2006.06.007>
- Taurines R, Grünblatt E, Schecklmann M, et al (2011) Altered mRNA expression of monoaminergic candidate genes in the blood of children with attention deficit hyperactivity disorder and autism spectrum disorder. *World J Biol Psychiatry* 12:104–108. <https://doi.org/10.3109/15622975.2011.600297>
- Todd RD, Lobos EA, Sun L-W, Neuman RJ (2003) Mutational analysis of the nicotinic acetylcholine receptor alpha 4 subunit gene in attention deficit/hyperactivity disorder: evidence for association of an intronic polymorphism with attention problems. *Mol Psychiatry* 8:103–108. <https://doi.org/10.1038/sj.mp.4001257>
- Tomasi D, Volkow ND (2012) Abnormal Functional Connectivity in Children with Attention-Deficit/Hyperactivity Disorder. *Biol Psychiatry* 71:443–450. <https://doi.org/10.1016/j.biopsych.2011.11.003>
- Tong J, McKinley L-A, Cummins TDR, et al (2015) Identification and functional characterisation of a novel dopamine beta hydroxylase gene variant associated with attention deficit hyperactivity disorder. *World J Biol Psychiatry* 16:610–618. <https://doi.org/10.3109/15622975.2015.1036771>
- Tonhajzerova I, Ondrejka I, Adamik P, et al (2009) Changes in the cardiac autonomic regulation in children with attention deficit hyperactivity disorder (ADHD). *Indian J Med Res* 130:44–50
- Toro R, Fox PT, Paus T (2008) Functional Coactivation Map of the Human Brain. *Cereb Cortex* 18:2553–2559. <https://doi.org/10.1093/cercor/bhn014>
- Totah NK, Neves RM, Panzeri S, et al (2018) The Locus Coeruleus Is a Complex and Differentiated Neuromodulatory System. *Neuron* 99:1055–1068.e6. <https://doi.org/10.1016/j.neuron.2018.07.037>
- Tripp G, Wickens JR (2009) Neurobiology of ADHD. *Neuropharmacology* 57:579–589. <https://doi.org/10.1016/j.neuropharm.2009.07.026>

- Troost PW, Lahuis BE, Steenhuis M-P, et al (2005) Long-Term Effects of Risperidone in Children With Autism Spectrum Disorders: A Placebo Discontinuation Study. *J Am Acad Child Adolesc Psychiatry* 44:1137–1144. <https://doi.org/10.1097/01.chi.0000177055.11229.76>
- Uddin LQ, Menon V (2009) The anterior insula in autism: Under-connected and under-examined. *Neurosci Biobehav Rev* 33:1198–1203. <https://doi.org/10.1016/j.neubiorev.2009.06.002>
- Uddin LQ, Supekar K, Menon V (2013) Reconceptualizing functional brain connectivity in autism from a developmental perspective. *Front Hum Neurosci* 7:458. <https://doi.org/10.3389/fnhum.2013.00458>
- Valbonesi S, Magri C, Traversa M, et al (2015) Copy number variants in attention-deficit hyperactive disorder: identification of the 15q13 deletion and its functional role. *Psychiatr Genet* 25:59–70. <https://doi.org/10.1097/YPG.0000000000000056>
- van Steensel FJA, Bögels SM, de Bruin EI (2013) Psychiatric Comorbidity in Children with Autism Spectrum Disorders: A Comparison with Children with ADHD. *J Child Fam Stud* 22:368–376. <https://doi.org/10.1007/s10826-012-9587-z>
- Varni JW, Handen BL, Corey-Lisle PK, et al (2012) Effect of Aripiprazole 2 to 15 mg/d on Health-Related Quality of Life in the Treatment of Irritability Associated with Autistic Disorder in Children: A Post Hoc Analysis of Two Controlled Trials. *Clin Ther* 34:980–992. <https://doi.org/10.1016/j.clinthera.2012.02.023>
- Wall DP, Esteban FJ, DeLuca TF, et al (2009) Comparative analysis of neurological disorders focuses genome-wide search for autism genes. *Genomics* 93:120–129. <https://doi.org/10.1016/j.ygeno.2008.09.015>
- Wallis D, Arcos-Burgos M, Jain M, et al (2009) Polymorphisms in the neural nicotinic acetylcholine receptor $\alpha 4$ subunit (CHRNA4) are associated with ADHD in a genetic isolate. *ADHD Atten Deficit Hyperact Disord* 1:19–24. <https://doi.org/10.1007/s12402-009-0003-5>
- Wang L, Almeida LEF, Spornick NA, et al (2015a) Modulation of social deficits and repetitive behaviors in a mouse model of autism: the role of the nicotinic cholinergic system. *Psychopharmacology (Berl)* 232:4303–4316. <https://doi.org/10.1007/s00213-015-4058-z>
- Wang R, Lin P, Wu Y (2015b) Exploring Dynamic Temporal-Topological Structure of Brain Network Within ADHD. In: Liljenström H (ed) *Advances in Cognitive Neurodynamics (IV)*. Springer Netherlands, Dordrecht, pp 93–98
- Wang X-H, Jiao Y, Li L (2018) Identifying individuals with attention deficit hyperactivity disorder based on temporal variability of dynamic functional connectivity. *Sci Rep* 8:11789. <https://doi.org/10.1038/s41598-018-30308-w>
- Wass S (2011) Distortions and disconnections: Disrupted brain connectivity in autism. *Brain Cogn* 75:18–28. <https://doi.org/10.1016/j.bandc.2010.10.005>
- Watabe-Uchida M, Zhu L, Ogawa SK, et al (2012) Whole-Brain Mapping of Direct Inputs to Midbrain Dopamine Neurons. *Neuron* 74:858–873. <https://doi.org/10.1016/j.neuron.2012.03.017>
- Whitby PJS, Mancil GR (2009) Academic Achievement Profiles of Children with High Functioning Autism and Asperger Syndrome: A Review of the Literature. *Educ Train Dev Disabil* 44:551–560
- Whitney ER, Kemper TL, Rosene DL, et al (2009) Density of cerebellar basket and stellate cells in autism: Evidence for a late developmental loss of Purkinje cells. *J Neurosci Res* 87:2245–2254. <https://doi.org/10.1002/jnr.22056>

- Wichers RH, Findon JL, Jelsma A, et al (2021) Modulation of atypical brain activation during executive functioning in autism: a pharmacological MRI study of tianeptine. *Mol Autism* 12:14. <https://doi.org/10.1186/s13229-021-00422-0>
- Wigg K, Zai G, Schachar R, et al (2002) Attention Deficit Hyperactivity Disorder and the Gene for Dopamine Beta-Hydroxylase. *Am J Psychiatry* 159:1046–1048. <https://doi.org/10.1176/appi.ajp.159.6.1046>
- Wilens TE (2008) Effects of Methylphenidate on the Catecholaminergic System in Attention-Deficit/Hyperactivity Disorder. *J Clin Psychopharmacol* 28:S46. <https://doi.org/10.1097/JCP.0b013e318173312f>
- Williams NM, Franke B, Mick E, et al (2012) Genome-wide analysis of copy number variants in attention deficit hyperactivity disorder: the role of rare variants and duplications at 15q13.3. *Am J Psychiatry* 169:195–204. <https://doi.org/10.1176/appi.ajp.2011.11060822>
- Woolf NJ, Butcher LL (1982) Cholinergic projections to the basolateral amygdala: A combined Evans Blue and acetylcholinesterase analysis. *Brain Res Bull* 8:751–763. [https://doi.org/10.1016/0361-9230\(82\)90102-2](https://doi.org/10.1016/0361-9230(82)90102-2)
- Xing B, Li Y-C, Gao W-J (2016) Norepinephrine versus Dopamine and their Interaction in Modulating Synaptic Function in the Prefrontal Cortex. *Brain Res* 1641:217–233. <https://doi.org/10.1016/j.brainres.2016.01.005>
- Yang L, Wang Y-F, Li J, Faraone SV (2004) Association of Norepinephrine Transporter Gene With Methylphenidate Response. *J Am Acad Child Adolesc Psychiatry* 43:1154–1158. <https://doi.org/10.1097/01.chi.0000131134.63368.46>
- Yrigollen CM, Han SS, Kochetkova A, et al (2008) Genes Controlling Affiliative Behavior as Candidate Genes for Autism. *Biol Psychiatry* 63:911–916. <https://doi.org/10.1016/j.biopsych.2007.11.015>
- Zamzow RM, Christ SE, Saklayen SS, et al (2014) Effect of propranolol on facial scanning in autism spectrum disorder: A preliminary investigation. *J Clin Exp Neuropsychol* 36:431–445. <https://doi.org/10.1080/13803395.2014.904844>
- Zamzow RM, Ferguson BJ, Stichter JP, et al (2016) Effects of propranolol on conversational reciprocity in autism spectrum disorder: a pilot, double-blind, single-dose psychopharmacological challenge study. *Psychopharmacology (Berl)* 233:1171–1178. <https://doi.org/10.1007/s00213-015-4199-0>
- Zerbi V, Floriou-Servou A, Markicevic M, et al (2019) Rapid Reconfiguration of the Functional Connectome after Chemogenetic Locus Coeruleus Activation. *Neuron* 103:702-718.e5. <https://doi.org/10.1016/j.neuron.2019.05.034>
- Zhang HB, Wang YF, Li J, et al (2004) Association of dopamine beta-hydroxylase polymorphism with attention deficit hyperactivity disorder in children. *J Peking Univ Health Sci* 36:290–293
- Zhang Y, Larcher KM-H, Misic B, Dagher A (2017) Anatomical and functional organization of the human substantia nigra and its connections. *eLife* 6:e26653. <https://doi.org/10.7554/eLife.26653>
- Zhu H, Li J, Fan Y, et al (2015) Atypical prefrontal cortical responses to joint/non-joint attention in children with autism spectrum disorder (ASD): A functional near-infrared spectroscopy study. *Biomed Opt Express* 6:690–701. <https://doi.org/10.1364/BOE.6.000690>
- Zhu X, Zhang S, Kan D, Cooper R (2004) Haplotype block definition and its application. *Pac Symp Biocomput* 9:152–163. https://doi.org/10.1142/9789812704856_001