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www.elsevier.com/locate/developmentalbiology

PII: S0012-1606(17)30688-7
DOI: https://doi.org/10.1016/j.ydbio.2018.03.023
Reference: YDBIO7727

To appear in: *Developmental Biology*

Received date: 23 October 2017
Revised date: 4 March 2018
Accepted date: 27 March 2018

Cite this article as: Callum Dark, Jihane Homman-Ludiye and Robert J Bryson-Richardson, The Role of ADHD Associated Genes in Neurodevelopment, *Developmental Biology,* https://doi.org/10.1016/j.ydbio.2018.03.023

The Role of ADHD Associated Genes in Neurodevelopment

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is a highly heritable neurodevelopmental disorder of childhood. It is primarily characterised by high levels of activity, inattention, and impulsivity, and has strong negative impacts on academic functioning. Children with ADHD show a reduction in volume, and hypoactivity, in a range of brain regions. The underlying mechanisms behind these phenotypes are unknown, however, variants in several genes with known roles in neurodevelopment are associated with ADHD. In this review we discuss how these ADHD associated genes contribute to neurodevelopment, and how variants in these genes could give rise to the neurological phenotypes seen in ADHD.

Keywords: ADHD, neurodevelopment, synaptogenesis, psychiatric disorder

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a common neuropsychiatric disorder of childhood, affecting 5% of school-aged children worldwide (Polanczyk et al., 2007), and persisting into adulthood in 30-50% of cases (Faraone and Biederman, 2005; Polanczyk et al., 2007). The disorder, characterised by high levels of inattention, uncontrollable hyperactivity, and impulsivity, is classified into three clinical subtypes: predominantly inattentive, predominantly hyperactive, and combined (American Psychiatric Association, 2013). ADHD is reported more often in males than females, with population and clinical studies showing male:female ratios of 4:1 and 9:1 respectively (Biederman et al., 2002; Cuffe et al., 2005). The disorder has been shown to have negative impacts on family relations and academic functioning (Mannuzza et al., 1993), and is associated with a greater likelihood of risk taking behaviours and drug use (Konstenius et al., 2015).

The aetiology of ADHD remains poorly understood, although both environmental and genetic factors are known to contribute to the onset of the disorder. Environmental factors such as prenatal exposure to alcohol, cigarettes, and illicit drugs have all been associated with an increased risk of ADHD (Banerjee et al., 2007; Langley et al., 2005; Sagiv et al., 2013). Low birth weight and adverse life experiences have also demonstrated associations (Banerjee et al., 2007; Heinonen et al., 2010). Despite this, only a small portion of the aetiology of ADHD can be explained by environmental factors. Family and twin studies provide estimates of heritability at around 76% (Faraone et al., 2005). Furthermore, concordance rates in monozygotic (MZ) twins are consistently higher than those in dizygotic (DZ) twins (~80% and ~40%, respectively; Levy et al., 1997). There is, therefore, a significant genetic contribution to ADHD risk.

Research into the genetic basis of ADHD initially focussed on candidate genes identified from animal models or knowledge of drug targets. In particular, genes involved in catecholamine (dopamine, noradrenaline) and serotonin transmission have been thought to be important to the aetiology of ADHD, and several of these have demonstrated replicable evidence of association (Faraone and Biederman, 2002; Gizer et al., 2009). More recently, hypothesis free genome wide association studies (GWAS) have been used to identify single nucleotide polymorphisms (SNPs), and copy number variations (CNVs) associated with the disorder. These approaches scan the genomes of cases and control individuals for thousands of SNPs to determine if any SNPs or CNVs (as identified by consecutive sets of SNPs) are associated with the disorder. For the detection of associated SNPs, this approach has, until recently, mostly been unsuccessful (Akutagava-Martins et al., 2016), with only one quantitative trait loci GWAS, examining six traits derived from ADHD clinical and symptom measures, identifying two significant associations (Lasky-Su et al., 2008). However, in what is the biggest ADHD GWAS to date, (Demontis et al., 2017) utilised 20,183 ADHD cases and 35,191 controls to identify 12 hits significant at the GWAS level ($p \leq 5 \times 10^{-8}$). With regards to CNVs, there has been success in identifying significant associations between ADHD and several genes mapped to these CNVs (Hawi et al., 2015). There are several limitations with this however, noting in particular low penetrance of variants, minimal overlap with previously reported ADHD common variants, and an inconsistency of individual variants being carried by different ADHD patients (Hawi et al., 2015). Despite this, the evidence from candidate gene, GWA-SNP and GWA-CNV studies has suggested many genetic associations with ADHD. A database of ADHD genetic associations and the study which identified them is available at (Zhang et al., 2012).

ADHD often co-exists alongside other psychiatric disorders such as oppositional defiant disorder, conduct disorder, anxiety disorder, depression, tic disorder, bipolar disorder, Tourette's syndrome, and substance use disorder (in adult cases) (Jensen and Steinhausen, 2015; Kessler et al., 2006;

Steinhausen et al., 2006), suggesting a common aetiology. In addition, ADHD has been shown to share a significant genetic component with other neurodevelopmental cognitive disorders including schizophrenia, autism spectrum disorder (ASD), and X-linked intellectual disability (Cristino et al., 2013). Therefore, genes associated with these conditions may also play a role in ADHD.

ADHD is associated with macroanatomical changes in multiple brain regions, resulting from disrupted neurodevelopmental mechanisms. In the largest imaging meta-analysis to date, Hoogman et al., (2017) demonstrated significantly smaller volumes in ADHD cases for the accumbens, caudate, putamen, amygdala, hippocampus, as well as reduced intracranial volume as a whole, adding to previously identified changes. While these studies identify regions affected in ADHD (Table 1, Fig.1), how these changes manifest has not yet been elucidated. In addition to changes in volume, cortical thickening in the prefrontal areas is delayed in ADHD, taking around 2.5-5 years longer than matched controls to achieve normal cortical thickness (Almeida et al., 2010; Montes et al., 2013; Shaw et al., 2007). Alongside the morphological changes in these structures, functions associated with these regions are disrupted. Studies have demonstrated hypoactivation during response inhibition tasks in frontal and parietal regions, as well as the thalamus, basal ganglia, and cingulate cortex (Dickstein et al., 2006; Hart et al., 2013). Furthermore, in attention demanding tasks, decreased activity in frontal regions, as well as the basal ganglia, thalamus (pulvinar), and the parietal and temporal lobes was identified (Dickstein et al., 2006; Hart et al., 2013). In addition to decreased activity in attention demanding tasks and response inhibition, both directly related to the ADHD phenotype, an array of other functions is disrupted in ADHD. These include reduced activity in the striatum in reward anticipation tasks (Scheres et al., 2007), and in the cerebellum in cognitive tasks, motor timing, and in the resting state (Suskauer et al., 2007; Tian et al., 2006; Vloet et al., 2010). Overall, consistently decreased brain volumes and hypoactivation of regions known for their roles in inhibition and attention are consistent with the behavioural ADHD phenotype. Given the neurodevelopmental phenotype, we might expect a developmental role for ADHD associated genes, and genes known to be involved in neurodevelopment may provide candidates for ADHD.

The changes observed in the brains of ADHD cases result from impaired development during pregnancy and/or early postnatal life. The formation of a functioning brain occurs in a conserved sequence. Initially, pools of neural progenitors distributed across multiple neurogenic zones proliferate and give rise to the different classes of neurons. The newly formed neurons migrate across the developing brain and, upon reaching their final destination, establish a network of connections. These include short-range connections with neighbouring neurons in the same region and long-range projections to other regions, for example between thalamic nuclei and the neocortex, which encompasses the motor and sensory cortices and areas responsible for higher-order cognitive functions. This initial pattern of connectivity is later refined through activity-driven pruning, selecting for the strongest synaptic contacts, and reducing the number of neurons. Here we discuss the role of ADHD associated genes (Table 2) in each of these phases of neurodevelopment.

Table 1. Changes in brain volumes seen in ADHD

Region	Function	Volume change	Reference
Accumbens	Reward processing	Reduced	(Hoogman et al., 2017)
Amygdala	Memory, emotional regulation	Reduced	(Hoogman et al., 2017)
Anterior cingulate cortex	Executive functioning	Reduced	(Pliszka et al., 2006)
Caudate	Learning and motor control	Reduced	(Hoogman et al., 2017)
Cerebellum	Motor coordination, inhibition, executive functioning	Reduced	(Valera et al., 2007)
Cortex	Sensory processing and cognition	Reduced Thickness	(Narr et al., 2009)
Hippocampus	Short to long term memory transfer, emotion regulation	Reduced	(Hoogman et al., 2017)
Occipital lobe	Visual processing	Reduced	(Durston et al., 2004)
Parietal lobe	Visuo-spatial, selective attention	Conflicting evidence: both reduced and increased volumes reported	(Castellanos et al., 2002; Sowell et al., 2003)
Prefrontal cortex	DLPFC: attention, working memory VLPFC: inhibition OFC: social behaviour, balance of inhibition and disinhibition, emotional regulation	Reduced	(Mostofsky et al., 2002) (Sowell et al., 2003)
Putamen	Learning	Reduced	(Hoogman et al., 2017)
Temporal lobe	Visual and auditory association, memory, emotional regulation	Conflicting evidence: both reduced and increased volumes reported	(Castellanos et al., 2002; Sowell et al., 2003)
Thalamus (pulvinar)	Attention	Reduced	(Ivanov et al., 2010)

Abbreviations: DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; OFC, orbitofrontal cortex.

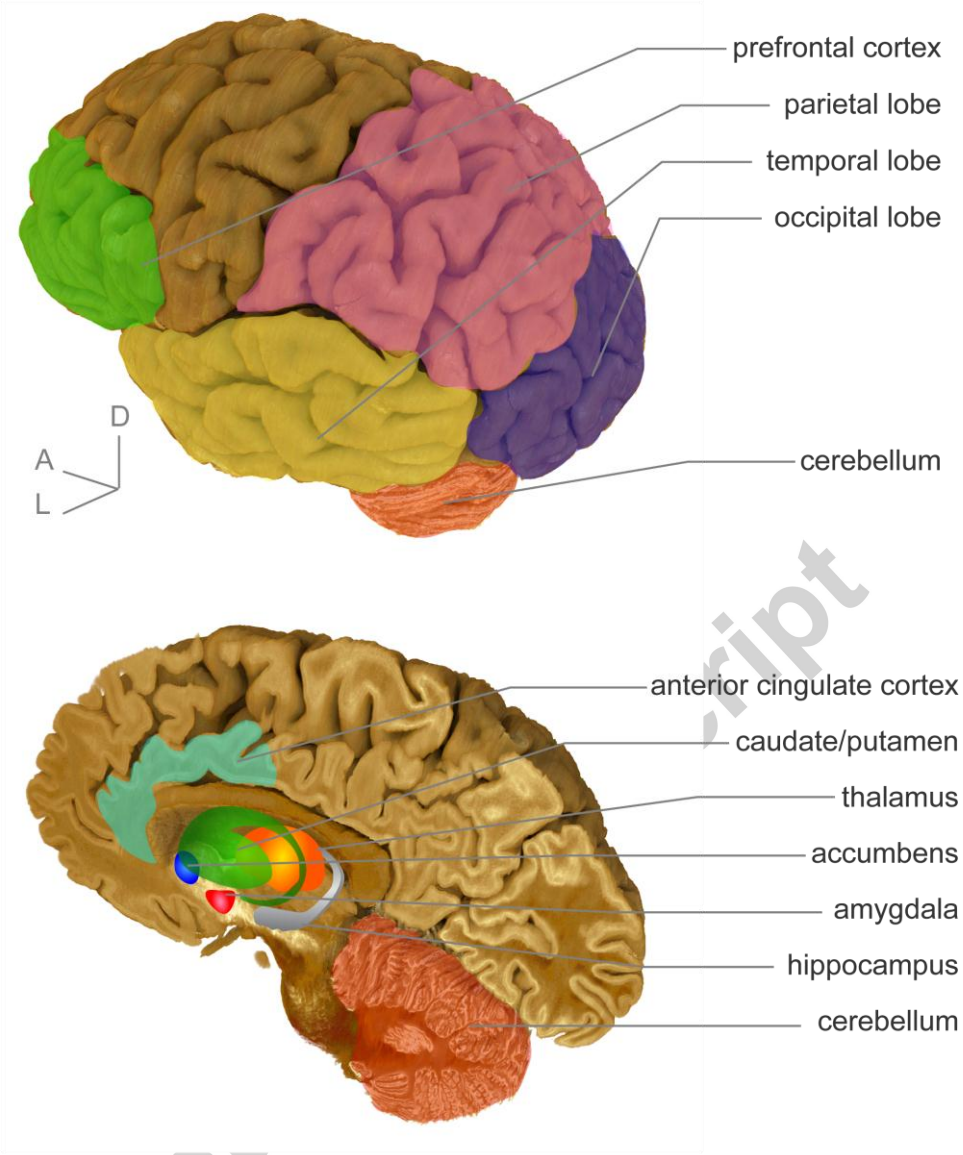


Fig.1. Brain regions affected in ADHD. 3D rendering of an adult male brain obtained from the Big Brain project (Amunts et al., 2013) and rendered using Drishti (Limaye 2012). **A** anterior, **D** dorsal, **L** lateral.

Table 2. ADHD associated genes that play a role in neurodevelopment.

Gene	Study type	Reference	Neurodevelopmental process
BDNF	Candidate Gene	(Hawi et al., 2017; Kent et al., 2005)	Synaptogenesis, Selective cell death, Glia and Microglia

CDH13	GWAS-SNP	(Lasky-Su et al., 2008)	Neurogenesis, Connectivity, Synaptogenesis
CHRNA7	GWAS-CNV	(Williams et al., 2012)	Synaptogenesis, Glia and Microglia
DRD5	Candidate Gene	(Daly et al., 1999; Gizer et al., 2009)	Glia and Microglia
FOXP2	GWAS-SNP	(Demontis et al., 2017)	Neurogenesis, Migration, Synaptogenesis
GIT1	Candidate Gene	(Won et al., 2011)	Glia and Microglia
GRM1	GWAS-CNV	(Elia et al., 2012)	Neurogenesis, Synaptic Plasticity, Selective cell death
GRM5	GWAS-CNV	(Elia et al., 2012)	Neurogenesis, Synaptogenesis, Selective cell death
GRM7	GWAS-CNV	(Elia et al., 2012)	Neurogenesis, Synaptic Plasticity, Selective cell death
5-HT1B	Candidate Gene	(Gizer et al., 2009; Hawi et al., 2002)	Synaptic Plasticity
LPHN3/*ADRGL3*	Candidate Gene	(Arcos-Burgos et al., 2010; Ribases et al., 2011)	Connectivity, Synaptogenesis
MEF2C	GWAS-SNP	(Demontis et al., 2017)	Neurogenesis, Synaptogenesis
NOS1	Candidate Gene	(Reif et al., 2009)	Neurogenesis, Synaptic Plasticity, Selective cell death, Glia and Microglia
PARK2	GWAS-CNV	(Jarick et al., 2014)	Neurogenesis, Selective cell death
PCDH7	GWAS-SNP	(Demontis et al., 2017)	Connectivity
PTPRF	GWAS-SNP	(Demontis et al., 2017)	Synaptogenesis, Selective Cell Death
SEMA6D	GWAS-SNP	(Demontis et al., 2017)	Connectivity
SLC6A2	GWAS-SNP	(Lasky-Su et al., 2008)	Glia and Microglia
SLC6A3	Candidate Gene	(Cook et al., 1995; Gizer et al., 2009)	Synaptic Activity, Synaptic Plasticity
SLC6A4	Candidate Gene	(Gizer et al., 2009; Manor et al., 2001)	Neurogenesis, Migration, Synaptic Plasticity, Selective Cell Death
SLC9A9	Candidate Gene, GWAS-SNP	(de Silva et al., 2003; Lasky-Su et al., 2008)	Synaptic Activity
SNAP25	Candidate Gene	(Brophy et al., 2002; Gizer et al., 2009)	Synaptic Activity, Selective Cell Death
SORCS3	GWAS-SNP	(Demontis et al., 2017)	Synaptic Plasticity
ST3GAL3	GWAS-SNP	(Demontis et al., 2017)	Synaptogenesis, Glia and Microglia

NEUROGENESIS

Neural progenitors in the developing brain undergo different modes of proliferation; symmetrical division to generate two progenitor cells and amplify the progenitor pool, or asymmetrical division; giving rise to a single progenitor cell and a neuron. In the later phases of development, progenitors undergo terminal symmetrical division, generating two neurons and depleting the neurogenic pool. Brain formation depends on a suitable balance between the different division modes to maintain sufficient progenitors whilst generating the appropriate number of neurons. This equilibrium is mediated through cell-cell interactions, for example, the Notch-Delta pathway, which promotes proliferation and inhibits differentiation (Egger et al., 2010). Alteration of this proliferation-differentiation balance has dramatic consequences for brain development and has been implicated in neurodevelopmental cognitive disorders including ASD (Kaushik and Zarbalis, 2016).

The numerous brain structures affected in ADHD, as revealed by MRI studies, (Table 1 and Fig. 1) have distinct developmental origins with the neurons populating them arising from separate neurogenic niches, each with a characteristic pattern of gene expression. Amongst the most studied of the brain structures affected in ADHD (see Table 1) is the neocortex, comprised of a heterogeneous population of locally born glutamatergic excitatory neurons, emerging from the neurogenic zones lining the lateral ventricles, and GABA (gamma aminobutyric acid)-ergic inhibitory interneurons, arising from the subcortical ganglionic eminences and preoptic area. The mechanisms regulating the development of the thalamus, caudate, putamen, and striatum are not as well defined as that of the neocortex but, the neurons populating these regions emerge from neurogenic zones lining the 3rd ventricle (Marin et al., 2000).

Several signalling molecules, such as glutamate, participate in neurogenesis. Given glutamate's role as a positive regulator of neurogenesis (reviewed in Schlett, 2006), it is unsurprising that members of the metabotropic glutamate receptor (*GRM, mGluR*) family also play roles in this process. *GRM-1*, *-5*, *-7*, and *-8*, demonstrated association with ADHD in a GWA-CNV study (duplications: *GRM1*, deletions: *GRM-5*, *-7* and *-8*; Elia et al., 2012). GRM1 and GRM5 can both induce neurogenesis (Baskys et al., 2005; Zhao et al., 2011), and activation of GRM5 in neural progenitor cells (NPCs) increases expression of *cyclinD1*, known to induce neural proliferation (Sundberg et al., 2006). Knockdown of GRM7 in mouse NPCs increases proliferation by relieving inhibition of cyclic AMP response element-binding protein (CREB) phosphorylation and Yes-associated protein (*Yap*) expression, thereby increasing expression of *cyclinD1* (Xia et al., 2015). This data provides the connection between ADHD-associated glutamate receptor signalling and the control of cell proliferation.

In addition to the neurotransmitter glutamate influencing proliferation, serotonin, and nitrous oxide (NO) may also play a role. NO is a non-synaptic signalling molecule that inhibits dopamine, noradrenaline, and serotonin reuptake by inhibiting transporter function (Asano et al., 1997; Kaye et al., 1997; Lonart and Johnson, 1995, 1994; Pogun et al., 1994). Nitrous oxide synthase 1 (NOS1) is responsible for producing NO (Nathan, 1992) and has demonstrated association with ADHD in a candidate gene study (Reif et al., 2009). Application of NO to developing *Xenopus* embryos decreases neuronal proliferation in the optic tectum, and, conversely, loss of NO increases proliferation (Peunova et al., 2001), which is also seen in *Nos1* knockout mice (Packer et al., 2003). In addition, inhibition of NOS1 increases proliferation in neurogenic regions of the adult mouse brain, such as the subventricular zone and the dentate gyrus, (Matarredona et al., 2004; Zhu et al., 2006). Of particular interest is the interaction between NOS1 and the serotonin transporter (SLC6A4, 5-HTT, SERT; Chanrion et al., 2007). *SLC6A4* is associated with ADHD (Gizer et al., 2009; Manor et al., 2001), and

regulates the uptake of serotonin from the synaptic cleft into the pre-synaptic neuron (Lesch and Waider, 2012). The physical interaction between NOS1 and SLC6A4 reduces SLC6A4's cell-surface localisation in HEK293 cells and decreases serotonin uptake in these cells (Chanrion et al., 2007). In addition, application of serotonin to NOS1 and SLC6A4 expressing cells increases NO production (Chanrion et al., 2007). This could then result in decreased neural proliferation, consistent with decreased brain volume.

Members of the cadherin family are known to play important roles in axon outgrowth, guidance, synaptogenesis, and synapse maintenance (Redies et al., 2012). *CDH13* showed association with ADHD in a quantitative trait GWAS (Lasky-Su et al., 2008), and its expression is consistent with a role in neurodevelopment; peaking at postnatal day 7 in the developing mouse brain, before steadily decreasing into adulthood (Rivero et al., 2015). From GWAS studies it is not possible to determine if an increase or decrease of CDH13 function is associated with ADHD, but neuroblastoma cells expressing CDH13 lose their mitogenic proliferative response when treated with epidermal growth factor, suggesting that CDH13 acts as a negative regulator of proliferation (Takeuchi et al., 2000). In addition, CDH13 is suppressed by DNA methyltransferase 3b (DNMT3b), and release of this suppression, due to *DNMT3b* loss in PC12 cells, prevents nerve growth factor induced neuronal differentiation (Bai et al., 2006), suggesting that CDH13 negatively regulates both proliferation and differentiation.

The E3 ubiquitin ligase parkin (*PARK2*) is another example of an ADHD associated gene that influences both neural proliferation and differentiation. A GWA-CNV study demonstrated an enrichment of *PARK2* CNVs (deletions and duplications) in ADHD (Jarick et al., 2014). E3 ubiquitin ligases are important for the ubiquitination of proteins destined for the 26S proteasome (Goldberg, 2003), and PARK2 has demonstrated roles in mitophagy, cell survival, and vesicle trafficking (Imai et al., 2002; Kawahara et al., 2008; Staropoli et al., 2003). Park et al., (2017) demonstrated that PARK2 is directly involved in the ubiquitination of p21, a negative regulator of cell-cycle progression. Knockout of *Park2* results in accumulation of p21 in neural stem cells, blocking differentiation. The exact role of PARK2 in the aetiology of ADHD is not yet known, however, *in vitro* evidence suggests that PARK2 is important for forming dopaminergic neurons (Shaltouki et al., 2015). Given the well-established role for the dopamine system (Kirley, 2002) and reduction in volume of dopaminergic-rich brain regions in ADHD (Schneider et al., 2006), the requirement for PARK2 in dopamine neurogenesis strongly supports its association with the disorder.

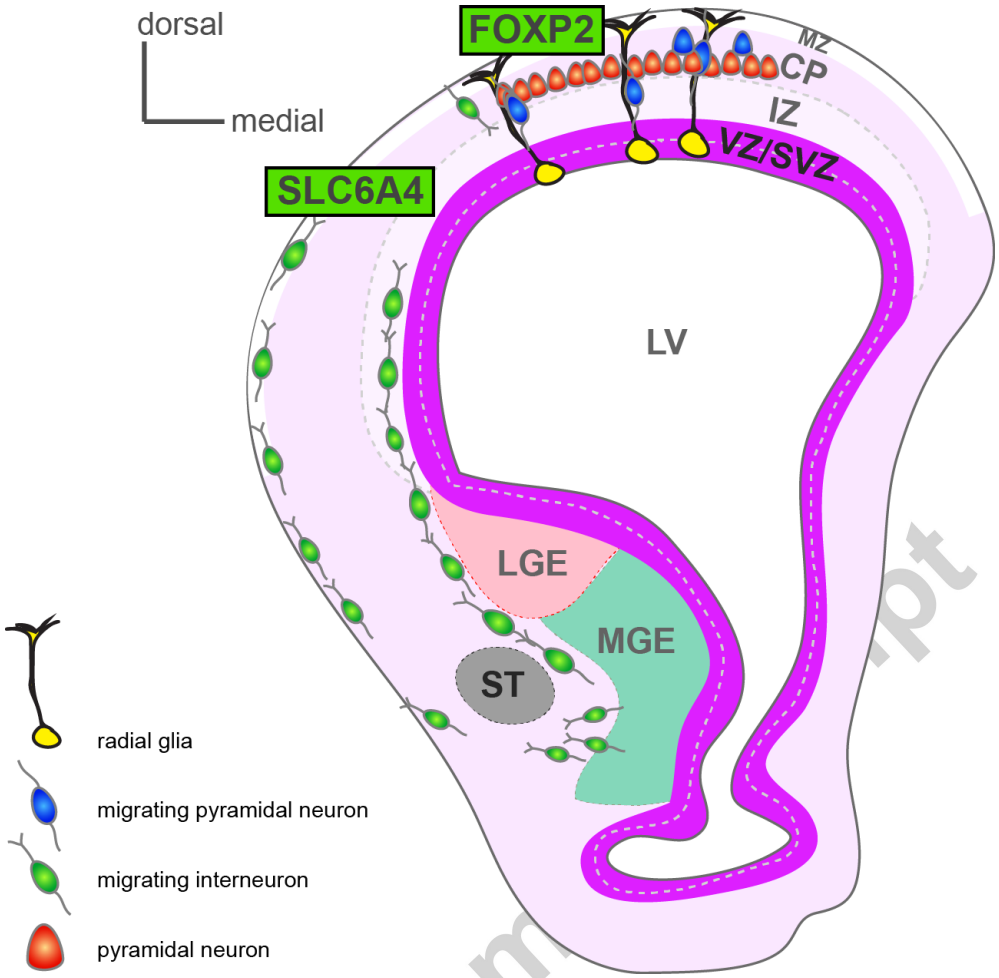
Two transcription factors, Myocyte Enhancer Factor 2C (*MEF2C*), and Forkhead box transcription factor P2 (*FOXP2*) also have roles in neural differentiation and have recently been associated with ADHD via GWAS (Demontis et al., 2017). CNVs encompassing *MEF2C* have also been associated with ASD (Yingjun et al., 2017), and conditional brain specific *Mef2c* knockout mice are hyperactive (Adachi et al., 2016). Expression of *Mef2c* in murine embryonic stem cells induces differentiation into neuronal progenitors *in vitro*, (Z. Li et al., 2008) and conditional brain specific *Mef2c* null mice show impaired neural differentiation, without deficits in proliferation or survival (H. Li et al., 2008). Knockout of *Foxp2* in mice leads to severe motor impairment and premature death (Shu et al., 2005), while knockdown of FOXP2 in mice embryonic stem cells leads to decreased neurogenesis, and expression of human FOXP2 promotes neurogenesis (Tsui et al., 2013). Whilst *MEF2C* haploinsufficiency and knockout of *Foxp2* result in severe mental retardation (Rocha et al., 2016; Zweier and Rauch, 2011) and premature death (Shu et al., 2005) respectively, it is possible that the subtle changes in the function or expression of these genes as a result of ADHD gene variants would result in decreased differentiation, and hence contribute to the decreased brain volume seen in ADHD.

MIGRATION

Following the initial proliferative phase, newborn neurons exit the neurogenic zone to populate the developing brain. They are guided along "molecular corridors" consisting of unique combinations of migration cues. The migrating neuron's ability to sense the appropriate cue, and therefore follow the correct path to its predestined location, is determined by the set of receptors it expresses at its surface, which is in turn specified by its lineage. Neural progenitors are characterised by the differential expression of morphogens and transcription factors, which regulate the genes expressed by their neuronal progeny, determining their functional and molecular identities and, ultimately, their fate. Therefore, neurons originating from the same pool of progenitors migrate together, forming large migratory streams across the developing brain. These neurons migrate according to two distinct modes, radial or tangential to the surface of the brain, often switching from one to the other. For example, the glutamatergic excitatory neurons populating the cortex are born locally and migrate radially in the developing cortical plate, along the glial fibres (Fig. 2). Their GABAergic inhibitory counterparts are born ectopically, in the subcortical ganglionic eminences and the preoptic area, and migrate first tangentially along the ventral surface of the brain and switch to a radial migratory mode upon entering the cortical plate, at the level of the marginal zone or the intermediate zone (reviewed in Marín and Rubenstein, 2003). The neurons of the caudate, putamen, and striatum originate from the neurogenic zones lining the 3rd ventricle and migrate laterally to cluster into discrete nuclei. Cell adhesion molecules, including the cadherin family, are critically involved in this process, segregating subpopulations of cells based on their expression. Disruptions to migratory pathways can lead to abnormal brain development, either by delaying the migration of neurons to their final positions, or mislocalisation of neuronal subsets.

The association between variants in neurotransmitter receptors, including glutamate and GABA receptors, and ADHD (Chang et al., 2014; Lasky-Su et al., 2008; Yuan et al., 2017) is particularly interesting as neurotransmitters have been demonstrated to modulate neuronal migration (reviewed in Heng et al., 2007). For example, activation of the glutamate receptors stimulates the migration of glutamatergic excitatory cortical neurons during development, promoting radial migration from the neurogenic zones to the appropriate cortical layer. Similarly, activation of GABA receptors expressed by inhibitory interneurons is able to modulate both their tangential and radial migration. Therefore, variants affecting GABA and glutamate receptors in ADHD might not only affect neuronal communication but also disrupt the migration of excitatory and inhibitory neurons during development.

In addition to glutamate, the neurotransmitter serotonin also has a role in neuronal migration. The migration of GABAergic interneurons is delayed, and more neurons are found, in the supragranular cortical layers in mice lacking the serotonin transporter gene, *Slc6a4* (Riccio et al., 2009). Knockout mice have increased levels of extracellular serotonin, due to the inability of the serotonin transporter to appropriately reuptake serotonin from the extracellular space into the presynaptic neuron. This increase in extracellular serotonin would lead to elevated activity of the 5HT6 serotonin receptor, which decreases the rate of migration in radially migrating pyramidal neurons (Riccio et al., 2011) and in interneurons (Riccio et al., 2009). Altogether, this evidence suggests that serotonin acts to regulate the rate of neuronal migration to provide correct developmental timing and positioning.



Interestingly, *FOXP2* may play a role in radial neuron migration through the modification of neural progenitor morphology (Garcia-Calero et al., 2016). A gradient of *Foxp2* expression in the developing mouse striatum, with low FOXP2 levels in the SVZ through to high levels in the mantle layer, promotes a change from multipolar (many neurites) to bipolar (two neurites) morphology (Garcia-Calero et al., 2016). Ectopic expression of *Foxp2* in the SVZ induces a change to bipolar morphology (Garcia-Calero et al., 2016), and impairs the radial migration of multipolar cells (Clovis et al., 2012; Garcia-Calero et al., 2016). Migration of radial glial cells is also disrupted in the knockout (Shu et al., 2005). Variants affecting the level of function of FOXP2 could therefore disrupt neuronal morphology and subsequently migration in ADHD.

Fig. 2. Neurogenesis in the human embryonic neocortex. Coronal section through a human embryonic brain at 12 weeks post conception illustrating newly born pyramidal neurons (blue), generated locally, migrating radially along glial processes, through preceding generations of neurons (red) and settling over them. Inhibitory interneurons (green) are born ectopically, in subcortical regions and migrate tangentially, forming a deep and a superficial stream to avoid the striatum (ST), which secretes repulsive signals. The interneurons later switch to a radial migratory mode to reach the appropriate cortical layer. ADHD associated genes (boxed) involved in neurotransmitter regulation, participate in the both radial and tangential neuronal migration. **CP** cortical plate; **IZ** intermediate zone; **LGE** lateral ganglionic eminence; **LV** lateral ventricle; **MGE** medial ganglionic eminence; **MZ** marginal zone; **ST** striatum; **VZ/SVZ** ventricular/subventricular zones.

The evidence for a role of neurotransmitters in neurodevelopment prior to synaptogenesis is building. Considering that neurotransmitters, such as glutamate, can regulate the levels of intracellular Ca^{2+} that are vital for the reorganisation of the cytoskeleton during migration (Doherty et al., 2000; Gordon-Weeks, 2004), it is possible that neurotransmitters influence early stages of neuronal development. Further characterisation of the role of neurotransmitters in development could therefore greatly add to our knowledge of ADHD.

CONNECTIVITY

The guidance cues and adhesion molecules dispersed across the developing brain not only coordinate neuronal migration, they also direct the pathfinding of neuronal processes (neurites), and the formation of connections. The growth cone located at the tip of extending neurites is enriched in guidance cue receptors and adhesion molecules, which allow it to probe the environment. Interactions between the molecules at the surface of the navigating growth cone and their specific ligands in the extracellular matrix, or on neighbouring cells, triggers intracellular cascades resulting in cytoskeletal rearrangements. These morphological changes promote growth towards the source of the guidance cue (attraction) or away from it (repulsion; Fig. 3). Similar to migration, dysregulation of guidance cues can lead to abnormal distribution of neurons in the developing brain. Delayed establishment of neural connections would result in an underdeveloped brain, consistent with the developmental delay seen in individuals with ADHD.

Short-range cues are membrane bound, acting as guide posts for branching axons. Upon contact with these molecules, growth cones will either continue to extend in the same direction or will be repelled. Two members of the cadherin family, *CDH13* and protocadherin 7 (*PCDH7*, also known as neural fold protocadherin, *NFPC*), act as short-range guidance cues. CDH13 is a negative regulator of neuronal axon projections that acts on spinal motor neurons (Fredette et al., 1996; Fredette and

Ranscht, 1994), and infragranular (cortical layers 5&6) neurons of the cortex (Hayano et al., 2014). CDH13 knockdown in infragranular neurons, which send contralateral projections through the corpus callosum and ipsilateral projections through the intermediate zone, results in abnormal projections to the subcortical plate (Hayano et al., 2014). In addition, ectopic expression of CDH13 in the supragranular (layers 2&3) neurons results in some neurons projecting into the internal capsule, rather than the corpus callosum as expected, and delays extension (Hayano et al., 2014). Therefore alteration of *Cdh1*3 expression has dramatic consequences for cortical axonal pathfinding.

PCDH7 was recently identified as a significant GWAS hit (Demontis et al., 2017), and is known to be expressed in the developing rat brain (Kim et al., 2007). Leung et al., (2013) demonstrated that knockdown of Pcdh7 in developing *Xenopus* embryos leads to stalled axonal projection in the optic tract, showing that Pcdh7 acts as a positive cue for axonal guidance. While it is not yet fully understood whether CDH13 acts as a short or long range cue, or both (Ciatto et al., 2010); (Denzel et al., 2010; Hug et al., 2004), both CDH13 and PCDH7 show evidence of homophilic binding (Ciatto et al., 2010; Leung et al., 2013), suggesting that both of these genes can act as short range guidance cues. Overall, *CDH13* and *PCDH7* have important roles in axonal guidance, most likely through roles in cell-cell adhesion and short range signalling, and variants in these genes could lead to disruptions in neuronal localisation, and, as a result, brain structure.

Long range guidance cues are secreted in the neural environment and diffuse to form a gradient to guide growth cones expressing the corresponding receptors. One such guidance cue is formed by the cleavage of the extracellular domain from fibronectin and leucine-rich transmembrane protein-3 (FLRT3), which then acts as a chemo-repellent when bound to the uncoordinated-5B (UNC5B) membrane bound protein (Yamagishi et al., 2011). FLRT3 can also form a trans-membrane connection with Adhesion G protein coupled receptor L3 (ADGRL3), previously known as latrophilin 3 (LPHN3) (O'Sullivan et al., 2012). Interestingly, studies examining the structure of ADGRL3-FLRT3 binding have demonstrated that FLRT3 can bind to UNC5B and ADGRL3 proteins simultaneously (Lu et al., 2015; Ranaivoson et al., 2015). *ADRGL3* demonstrates association with ADHD (Arcos-Burgos et al., 2010; Ribases et al., 2011), and is a member of a family of secretin G protein coupled receptors (Matsushita et al., 1999) that localise to the presynaptic terminal (Grishin, 1998). Increased locomotor activity is seen in *Adrgl3* mutant mice (Orsini et al., 2016; Wallis et al., 2012), *Drosophila melanogaster* (van der Voet et al., 2016), and zebrafish (Lange et al., 2012), with the fish phenotype rescued by the most common ADHD medication, methylphenidate (Ritalin). It is important to note that the combination of receptors present on individual axons affects the response to the guidance cues in the environment, therefore it is difficult to ascertain what the effect of this trimeric complex is on axonal guidance. However, variants in *ADGRL3* could potentially modulate growth cone extension and neural connectivity through modulation of the trimeric ADGRL3/FLRT3/UNC5B complex.

Semaphorin 6D (*SEMA6D*), recently associated with ADHD via GWAS (Demontis et al., 2017), is a chemo-repellent during axonal pathfinding (Qu et al., 2002), acting as both a short range transmembrane cue and, when the extracellular domain is cleaved, a long range cue (Toyofuku et al., 2004a, 2004b). *Sema6d* mutant mice show abnormal proprioceptive axon positioning in the spinal cord (Leslie et al., 2011) and recombinant secreted SEMA6D inhibits axon extension and induces growth cone collapse (Qu et al., 2002). In addition, SEMA6D repels retinal ganglion cell axons at the optic chiasm, thereby promoting the crossing of contralateral fibres, however, when SEMA6D is coupled with PLXNA1 and Ng-CAM-related cell adhesion molecule (Nr-CAM), this becomes a growth promotion effect (Kuwajima et al., 2012). *SEMA6D* is an example of how complex even

singular guidance cues can be, and how disruptions to such a gene could result in a wide array of neuronal localisation abnormalities.

Considering that axonal branching and extension occurs from early life through to adulthood, an inability to efficiently guide projecting neurites to their targets could potentially delay the establishment of effective neuronal connections. Over time, it is possible that these detrimental effects could become less profound as neuronal pathways are established, consistent with the decline in ADHD symptoms with age.

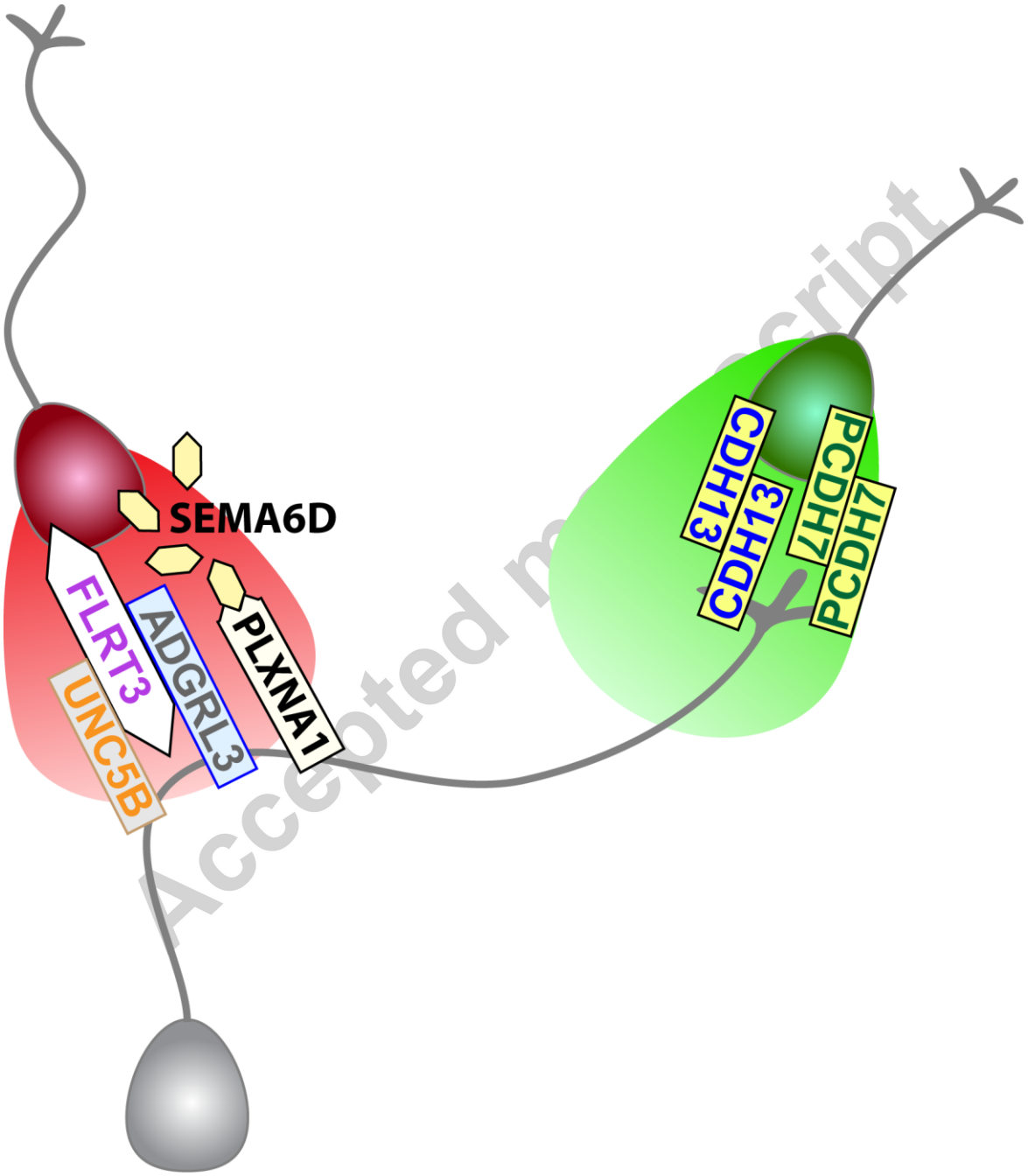


Fig. 3. Axonal outgrowth is directed by short and long range guidance cues. Membrane bound FLRT3 and UNC5B are repulsive cues (red), forming a trimeric complex with ADGRL3. SEMA6D acts as a repulsive cue either as a short range transmembrane cue, or when the extracellular domain is cleaved, over long range. Cleaved FLRT3 could act as a long range repulsion cue. CDH13 and PCDH7 homophilic interactions are short range attractants (green).

SYNAPTOGENESIS

The significant volume reduction in multiple regions of ADHD brains is often attributed to loss of synaptic density rather than actual loss of neurons. The mechanisms controlling neuronal migration and pathfinding are also recruited during the establishment of synaptic contacts between axons and the dendrites of postsynaptic neurons, with local attractive cues determining the sites of synapse formation. The accumulation of guidance cues at a specific location along the dendrites suggests that synapses are pre-patterned. However, the underlying mechanisms remain unknown, although some studies in *C. elegans* suggest control by glial-like cells (reviewed in Shen and Cowan, 2010). In order for synaptic contacts to mature into a functional synapse, the transient contacts require stabilisation through cell-cell interactions mediated by surface proteins, for example ephrin type-B receptor 2 (EPHB2, Kayser et al., 2008) and Cadherins 11 and 13 (Paradis et al., 2007). Surface proteins are also involved in recruiting the machinery necessary for the maturation of a functional synapse, including clustering neurotransmitter receptors (Takasu et al., 2002). A wide array of ADHD associated genes are involved in synaptogenesis, with a reduction in synaptic density potentially contributing to the reduced brain volumes seen in individuals with ADHD.

In addition to their roles in axonal connectivity, intercellular signalling proteins CDH13 and ADRGL3 have a role in synapse formation. Knockdown of CDH13 leads to a reduction in GABAergic and glutamatergic synaptic density (Paradis et al., 2007). In addition, *CDH13* expression overlaps with regions that show volume reductions in ADHD, such as the prefrontal cortex (Takeuchi et al., 2000). It is likely that these volume reductions are a consequence of decreased synaptic densities resulting from disruption of CDH13's role in cell-cell signalling. Knockdown of ADRGL3 in rodents decreases glutamatergic synaptic density in the hippocampus (O'Sullivan et al., 2012) and the cortex (O'Sullivan et al., 2014), and in zebrafish, loss of the ADRGL3 orthologue Lphn3.1 results in a decrease in dopaminergic neurons in the ventral diencephalon (Lange et al., 2012). Given the close relationship between axonal connectivity and synaptogenesis it would be beneficial to determine how variants in *CDH13* and *ADGRL3* affect both of these processes in the same model.

Other ADHD associated genes have roles in synaptogenesis via modulation of glutamate transmission, including *CHRNA7*, *GRM5*, and *BDNF*. Duplications at the 15q13.3 locus, which includes *CHRNA7*, are enriched in ADHD (Williams et al., 2012) and individuals with a deletion encompassing *CHRNA7* and the first exon of *OTUD7A* demonstrate consistent neurological phenotypes such as mental retardation and global developmental delay (Shinawi et al., 2009). *CHRNA7* codes for the α7 subunit of the neuronal nicotinic acetylcholine receptor (α7nAChR), and mice null for the *CHRNA7* orthologue have decreased cortical glutamatergic and GABAergic synapse development, with a decrease in synaptic N-methyl-D-aspartate receptor (*Nmdar*) expression, suggesting dysfunction in glutamate transmission (Lin et al., 2014a, 2014b). Disruption of glutamate transmission by knockout of the postsynaptic receptor *Grm5*, decreases dendritic spine density in younger mice (P21-23; Wijetunge et al., 2008), and increases densities in older mice (P45; Chen et al., 2012). Chen et al., (2012) suggest that this could be due to glutamate's ability to induce *de novo* spine formation (Kwon and Sabatini, 2011), so it is possible that without correct postsynaptic modulation of glutamate signalling, an increased number of spines could form. At the least, the lower dendritic levels seen in younger mice is consistent with a developmental delay, and loss of α7nAChR and GRM5 disrupt synaptogenesis, likely through irregular glutamate signalling. Further examination, particularly into α7nAChR, is needed to elucidate the mechanism behind this phenotype. In addition, BDNF has been shown to stimulate both GABAergic synapse formation (Palizvan et al., 2004; Vicario-Abejón et al., 1998), which is supported by a reduction in GABAergic synapse development in *Bdnf* knockout mice (Kohara et al., 2007), and formation of glutamatergic synapses (Alsina et al., 2001; Hu et al., 2005;

Vicario-Abejón et al., 1998). However, in contrast to GABAergic neurons, glutamatergic synapses are not reduced in density in *Bdnf* knockout mice, but their maturation into functional synapses is impaired (Itami et al., 2003; Korte et al., 1995). The loss of inhibitory synapses would be consistent with the impulsive/loss of inhibitions phenotype seen in ADHD.

Roles in synaptogenesis have also been suggested for the newly associated GWA genes, *ST3GAL3*, *PTPRF*, *MEF2C*, and *FOXP2* (Demontis et al., 2017). ST3GAL3 plays a role in the sialylation of glycosphingolipids (also known as gangliosides), a subset of cell-surface glycans which play an important role in cell-cell and cell-environment signalling. Proteoglycans are particularly important in brain maturation as they enwrap neurons, forming a perineuronal net that stabilises mature synapses. Deficits in sialylation due to mutations in *ST3GAL3* lead to intellectual disability and reduced cognitive function (Edvardson et al., 2013; Hu et al., 2011). *St3gal3* null mice also show significantly increased motor activity, and decreased synaptic densities (Yoo et al., 2015). *PTPRF*, encodes the Leukocyte Antigen-Related Protein Tyrosine Phosphatase receptor (LAR-RPTP) and loss of excitatory synapses and dendritic spines is seen following overexpression of dominant-negative mutations or knockdown of LAR (Dunah et al., 2005). Presynaptic LAR expression has also been shown to induce clustering of excitatory postsynaptic proteins (Woo et al., 2009). This is potentially related to a role in axon guidance, as demonstrated for the *Drosophila* orthologue (Johnson and Van Vactor, 2003), however, experiments in *Xenopus* suggest LAR does not play the same role in vertebrates (Johnson et al., 2001). Lastly, *MEF2C* also negatively regulates excitatory synapse formation, with brain specific loss of *Mef2c* in mice leading to increased synapse and dendritic spine formation in the hippocampus (Adachi et al., 2016; Barbosa et al., 2008). In addition, overexpression of MEF2C-VP16, to create a transcriptional enhancer, decreases excitatory synapse formation (Barbosa et al., 2008). In the cortex, the opposite is seen, with conditional loss of *Mef2c* resulting in decreased excitatory synapses densities and increased inhibitory synapses densities (Harrington et al., 2016), however, this is potentially due to cell-specific effects of *Mef2c* loss. *Mef2c* has also been shown to be repressed by FOXP2 through direct DNA binding, *Foxp2* knockouts having decreased synaptic density as a result of the de-repression of *Mef2c* (Chen et al., 2016). FOXP2 also negatively regulates the sushi repeat-containing protein X-linked 2 (*Srpx2*) gene (Sia et al., 2013). *Srpx2* positively regulates excitatory synapse formation, and transfection of *Foxp2* into rat cortical neurons decreases SRPX2 levels, and as such, decreases excitatory synapse densities (Sia et al., 2013). Together, this evidence supports the associations between these genes and an ADHD phenotype, and while a full loss of these genes is not seen in individuals with ADHD, a subtle phenotype caused by a gene variant could well be contributing to alterations in synaptic densities.

SYNAPTIC ACTIVITY

Other than a small fraction of electrical synapses, which directly transmit the nerve impulse to the post-synaptic neuron, synapses are predominantly chemical with the action potential carried along the axon triggering the release of neurotransmitters. Vesicles containing the neurotransmitter fuse with the membrane of the pre-synaptic element to release their contents into the synaptic cleft enabling neurotransmitter molecules to bind to receptors located at the surface of the post-synaptic element. Therefore, vesicular trafficking, fusion and recycling are critical for neurotransmission, and mutations affecting these processes have deleterious effects on brain function, and as a consequence disrupt development (Fig. 4).

Synaptosomal associated protein 25 (SNAP25) is a member of the family of proteins that make up the soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNARE) complex. This

complex is involved in intracellular vesicular trafficking, facilitating neurotransmitter release, and is also important for the maintenance of cell membranes during cell fusion and division (Cupertino et al., 2016). Variants in genes encoding components of the SNARE complex have been implicated in ADHD, ASD, schizophrenia, depression, and bipolar disorder, and defects in this complex disrupt neurodevelopment at multiple stages including axonal growth, synaptic plasticity, and neuronal survival (Cupertino et al., 2016).

SNAP25 makes up two of the four helices that comprise the SNARE complex (Sutton et al., 1998), and variants in *SNAP25* are associated with ADHD (Brophy et al., 2002; Gizer et al., 2009). Deletion of *Snap25* is found in the *Coloboma* mouse, in which homozygotes die embryonically (Theiler et al., 1979), and heterozygotes display hyperactive phenotypes and fail to meet neurodevelopmental milestones (Hess et al., 1992; Heyser et al., 1995). SNAP25A and SNAP25B, are the primary splice isoforms expressed during pre- and post-natal development, respectively (Bark et al., 1995). Adult mice expressing SNAP25A, but not SNAP25B, have decreased spatial learning, higher anxiety, and swollen hippocampal mossy fibres, with some areas showing almost complete loss of synaptophysin immunoreactivity, suggesting a loss of functional presynaptic elements (Johansson et al., 2008). This is most likely due to the disruption of the SNARE complex and hence failure of synaptic membrane maintenance.

The solute carrier family 9 member A9 gene (*SLC9A9*) encodes a sodium/proton exchanger (NHE9), and has shown strong association with both ADHD (de Silva et al., 2003; Kondapalli et al., 2014; Lasky-Su et al., 2008) and ASD (Kondapalli et al., 2014). NHE9 is localised to late recycling endosome membranes, where it acts as a trans-membrane transporter for Na^+ and H^+ ions, controlling endosomal pH (Casey et al., 2010). Mutations in *Slc9a9* have been found in the WKY/NCrl rat strain that primarily displays an inattentive phenotype (Zhang-James et al., 2011), as well as in ADHD cases displaying impulsivity and intellectual disability (de Silva et al., 2003). Downregulation of *Slc9a9* expression is also seen in the spontaneously hypertensive rat (SHR), which is known to display the combined phenotype of ADHD (Zhang-James et al., 2011). The limited work using knockout models of *Slc9a9* has mostly identified traits related to ASD rather than ADHD (Yang et al., 2016). Considering that SLC9A9 has been shown to interact with proteins such as CHP and RACK1 (Lin and Barber, 1996; Ohgaki et al., 2008), known to be involved in Ca^{2+} signalling which is important for the phosphorylation of plasma membrane receptors such as solute carrier family 6 member 3 (SLC6A3, also known as DAT1) and NMDA (Belmeguenai and Hansel, 2005; Lee et al., 2004; Mansuy et al., 1998), this may be how *SLC9A9* variants contribute to ADHD. However, more research into SLC9A9 knockdown animal models is needed to determine if this is the case.

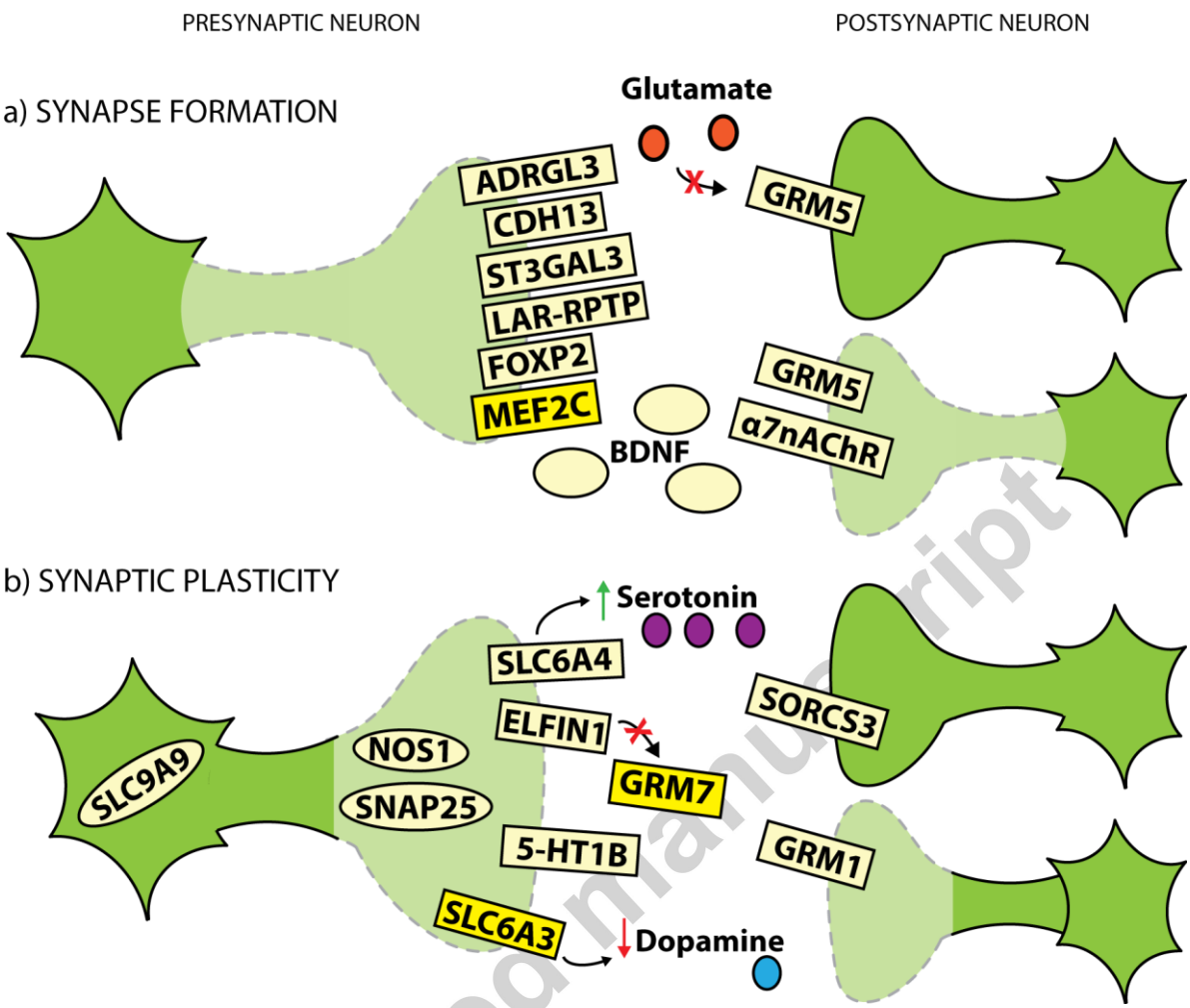


Fig. 4. Impacts of ADHD associated gene knockdowns on synaptogenesis. Gene knockdowns or knockouts are shown in faded yellow, while decreases in synaptic density or plasticity are depicted as faded green. a) Loss of ADGRL3, CDH13, ST3GAL3, LAR-RPTP, FOXP2, MEF2C, α7nAChR, and BDNF all result in decreased synaptic densities. *mGluR5* knockouts show decreased densities in young mice, and increased densities in older mice, potentially due to lack of postsynaptic glutamate regulation. b) Loss of NOS1, SNAP25, and GRM1 all result in decreased synaptic plasticity either through decreased long term potentiation or lack of synapse maintenance. An inability to recruit GRM7 to presynaptic membranes due to *Elfin1* knockout is thought to lead to a decrease in presynaptic plasticity, while SLC6A3 3'UTR 10R could potentially lead to a decrease in potentiation through increased dopamine reuptake. SLC6A4 and 5-HT1B, through modulation of serotonin signalling, and SLC9A9, through endosomal recycling, could also disrupt synaptic plasticity. SORCS3 acts as a negative regulator of synaptic plasticity.

SYNAPTIC PLASTICITY

Potentiation and depression of synapses reflect how synaptic activity can modulate neuronal pathways in the context of learning and memory. Potentiation and depression refer to the strengthening and weakening of synapses, respectively, which allow for neuronal pathways to be tuned in an activity dependent manner to improve efficiency. The inability to regulate neural connections can lead to decreased brain volumes and inefficient neural networks. A range of neurotransmitter systems, including dopamine, nitrous oxide, glutamate, and serotonin have been implicated in synaptic plasticity, and could therefore play a role in maintaining these neural connections.

The role of glutamate signalling in the long term depression and potentiation of synapses is demonstrated by members of the GRM family, as well as the newly identified ADHD gene, *SORCS3*. Members of the GRM family localise to pre- and postsynaptic elements, consistent with their role in long term depression and potentiation (Niswender and Conn, 2010). *Grm1* knockout mice exhibit decreased long term potentiation in hippocampal neurons when attempting to learn an associative classical conditioning task, which coincides with an inability to learn the task (Gil-Sanz et al., 2008). GRM7's regulation of both excitatory and inhibitory signalling systems makes it a candidate for the regulation of synapses (Palazzo et al., 2016). Its ability to inhibit excessive neurotransmitter release suggests that GRM7 is important for preventing over-excitation, and as such has a protective effect against neurological disorders, which is exemplified by the seizure susceptibility phenotype seen in *Grm7* null mice (Niswender and Conn, 2010; Sansig et al., 2001). Similarly, an epileptic phenotype is observed in mice lacking the extracellular-leucine-rich repeat (LRR) fibronectin domain 1 (ELFN1) protein, which interacts with, and recruits, GRM7 to synapses in somatostatin-containing interneurons in the hippocampus (Tomioka et al., 2014). *Elfn1* knockouts also show hyperactivity phenotypes and deficits in presynaptic plasticity (Tomioka et al., 2014). An inability to appropriately recruit GRM7 to synapses could be the cause of this phenotype, and the fact that *Grm7* null mice have deficits in working memory as well as short term potentiation supports GRM7's role in synaptic plasticity (Bushell et al., 2002; Goddyn et al., 2008; Hölscher et al., 2004). Given the strong evidence regarding the roles of GRM7 in neurodevelopment, and its interaction with ELFN1, *ELFN1* may also be a promising candidate for ADHD.

In addition to members of the GRM family, Sortilin Related VPS10 Domain Containing Receptor 3 (*SORCS3*), demonstrates a role in long term depression via glutamatergic signalling. *SORCS3* has been associated with ADHD both with rare overlapping CNVs (Lionel et al., 2011), and in a recent GWAS (Demontis et al., 2017). Loss of *Sorcs3* in mice leads to a loss of NMDA and mGluR dependent long-term depression in the hippocampus, as well as deficits in spatial learning ability

(Breiderhoff et al., 2013). Glutamate signalling thus plays a vital role in synaptic plasticity and variants in genes that are involved in glutamate pathways could lead to abnormal neural connections and inefficient brain networks.

Nitrous oxide, serotonin, and dopamine, also play roles in synaptic plasticity. *Nos1* knockout mice show increased impulsivity (Nelson et al., 1995), as well as deficits in spatial learning and memory (Wultsch et al., 2007). Memory deficits are suggestive of dysfunction in synaptic potentiation, as memory is the result of establishing lasting neuronal pathways. Serotonin has long been associated with alterations in synaptic plasticity, and the serotonin receptor 1B (*5-HT1B*) and *SLC6A4* are both associated with ADHD (Gizer et al., 2009; Hawi et al., 2002; Manor et al., 2001) and are known to play a role in this process (Lesch and Waider, 2012). Knockout of *Slc6a4* results in increased serotonin in the synaptic cleft (Lesch and Waider, 2012), and *5-Ht1b* knockout mice display increased activity (Brunner et al., 1999). Further, 5-HT1B activation by serotonin inhibits glutamate release in the thalmocortical somatosensory pathway in the developing rat (Rhoades et al., 1994; Salichon et al., 2001). The decrease in glutamate release following *Slc6a4* knockout would reduce long term potentiation of excitatory synapses, supported by decreased NMDAR-dependent long term potentiation following treatment of rat primary visual cortex slice with serotonin (Kim et al., 2006). It is however, important to note that the effect of serotonin may vary between developmental stages and regions due to difference in the expression of its receptors (Wirth et al., 2017).

SLC6A3 is potentially the best established ADHD-associated gene (Cook et al., 1995; Gizer et al., 2009), and is important for the reuptake of dopamine from the synaptic cleft into the pre-synaptic neuron. ADHD individuals homozygous for the ten repeat (10R) VNTR allele in the *SLC6A3* 3'UTR show significantly decreased cortical thickness in the right prefrontal cortex compared to heterozygotes and homozygotes for the 9 repeat (9R; Fernández-Jaén et al., 2015). In children, the 10R allele is associated with higher levels of the dopamine transporter (Brookes et al., 2007), which would lead to lower levels of dopamine in the synaptic cleft, consistent with a decrease in synaptic potentiation. This evidence further highlights the role of signalling molecules in synaptic plasticity, strengthening the association of neurotransmitter pathway genes with ADHD.

The combined evidence points to disruption of synapses being the most common effect of ADHD associated variants. In addition, decreases in brain volume through decreased synaptic potentiation and synaptic maintenance are consistent with the ADHD phenotype.

SELECTIVE CELL DEATH

In the nervous system, neurons are generated in excess and the brain undergoes a phase of selective cell death to eliminate redundant neurons. Connectivity is one of the main criteria determining if a neuron is to survive or not. This is achieved through the release of trophic factors at the level of the post-synaptic neuron, including nerve growth factor and brain derived neurotrophic factor (BDNF), to promote the survival of the presynaptic neuron. Therefore, the more active connections a neuron establishes, the more likely it is to survive. Nerve growth factor and BDNF bind with tropomyosin receptor kinase A (TrkA) and tropomyosin receptor kinase B (TrkB), respectively. Nerve growth factor binding to TrkA prevents an apoptosis cascade in the peripheral nervous system, but its role in the central nervous system is not clear (Dekkers et al., 2013), although cholinergic neurons in the basal forebrain follow this same form of neuronal survival (Sanchez-Ortiz et al., 2012). In the CNS TrkB does not activate apoptosis, and BDNF binding is not required to prevent apoptosis from occurring (Nikoletopoulou et al., 2010), suggesting BDNFs role in cell survival is not via TrkB.

However, most *Bdnf* null mice die at postnatal day 2 (Jones et al., 1994), and conditional *Bdnf* knockout in the cortex, (Baquet et al., 2004), which is the source of striatal BDNF, or the whole brain (Rauskolb et al., 2010), results in loss of dendritic complexity and neurons in the striatum, as well as loss of dopaminergic neurons in the midbrain-hindbrain region (Baquet et al., 2005). Conditional, forebrain restricted, knockouts also show progressive loss of cortical dendrite complexity (Gorski et al., 2003). There is therefore, substantial evidence that BDNF contributes to neuronal survival in the CNS, consistent with the ADHD phenotype.

The regulation of neuronal survival is also influenced by the ADHD associated genes *SNAP25*, *PTPRF*, *PARK2*, *NOS1*, *SLC6A4*, and *GRMs*, via control of BDNF release, apoptosis, and oxidative stress. Loss of SNAP25 leads to neuronal degeneration, through an inability to maintain protein recycling at the plasma membrane (Peng et al., 2013). In addition to this, SNAP25 demonstrates an important role in neuronal survival through regulation of the exocytosis of BDNF in axons and dendrites of cortical neurons (Shimojo et al., 2015). Given that loss of BDNF results in neuronal loss in the CNS, appropriate regulation of its release would be essential for neuronal survival. Interestingly, BDNF strengthens the interaction of LAR-RPTP with TrkB in mice hippocampal neurons (Yang et al., 2006), and BDNF neurotrophic activity decreases in *Lar* knockouts and knockdowns, and increases following exogenous expression of *Lar* (Yang et al., 2006), connecting BDNF to another ADHD associated factor. PARK2 regulates apoptotic factors, with dopaminergic neurons formed from *PARK2* mutant iPSC lines showing lower pro-apoptotic factors and higher anti-apoptotic factors than controls (Konovalova et al., 2015). However, how this particular imbalance of apoptotic factors alters neuronal survival in ADHD requires further examination.

Signalling molecules such as nitrous oxide, serotonin, and glutamate demonstrate roles in neuronal programmed cell death. Administration of anaesthetics containing high levels of NO to postnatal infant rats causes severe hippocampal neurodegeneration (Head et al., 2009) and activation of the apoptotic proteins caspase-3 and -9 in the cerebral cortex and thalamus (Lu et al., 2006). *Slc6a4* knockout mice have decreased levels of apoptosis in the striatum, thalamus/hypothalamus, cerebral cortex, and hippocampus, suggesting that serotonin activity can trigger programmed cell death (Persico et al., 2003). In the case of glutamate, excess glutamate can lead to reduced glutathione levels, causing oxidative stress and cell death (Murphy et al., 1989). This glutamate cytotoxicity can be prevented through the activation of group 1 metabotropic glutamate receptors, GRM1 and GRM5, restoring glutathione levels and preventing oxidative stress (Sagara and Schubert, 1998). Considering other members of the GRM family such as GRM7 also regulate glutamate levels, they may also have a role in programmed cell death.

BDNF, NO, serotonin, glutamate, PARK2, SNAP25, and PTPRF, all play important roles in selective cell death. Increases in apoptosis would result in decreased neuronal number, consistent with decreased brain volumes seen in ADHD, while a decrease in apoptosis could result in an inability to clear inefficient neural connections, preventing the establishment of optimal neural networks.

GLIA AND MICROGLIA

Glial and microglial cells are essential to the development of a normal functioning brain and genetic variants affecting their organisation have been linked to neurodevelopmental cognitive disorders, including ASD (Zhan et al., 2014). Glial cells, comprising oligodendrocytes and astrocytes, arise from the same pools of progenitors as neurons, and disperse through the developing brain using the same guidance molecules as neurons. The supporting role of glial cells in neurodevelopment cannot be

overstated, as they are important in synaptic plasticity, maintaining neural environments, and allowing efficient neural networks through myelination. Disruptions to glial cell processes can therefore have wide reaching effects during neurodevelopment.

Oligodendrocytes are the myelinating cells of the brain, they wrap around segments of the axon, forming a sheath of insulating myelin to accelerate the conduction of action potentials. Myelinated fibres assemble in bundles, forming large white matter tracts easily detected by MRI and are reduced in ADHD (Liston et al., 2011; van Ewijk et al., 2012). The migration of oligodendrocyte precursor cells (OPCs) depends on cues expressed by neurons, including polysialylated neural adhesion molecule (PSA-NCAM), which promotes OPCs survival (Palser et al., 2009) and migration (Decker et al., 2000). PSA-NCAM also prevents the differentiation of OPCs into myelinating oligodendrocytes (Decker et al., 2000) with downregulation of PSA-NCAM on axons coinciding with the onset of myelination in the human fetal forebrain (Jakovcevski et al., 2007). Decreased levels of PSA-NCAM have also been shown in *St3gal3* null mice, which coincides with decreased myelination, myelin basic protein, and oligodendrocyte transcription factor 2 (Yoo et al., 2015). Variants in *NCAM* have demonstrated association with schizophrenia, which shows significant genetic overlap with ADHD (Cristino et al., 2013). In addition to this, NOS1 which promotes the growth and arborisation of oligodendrocytes (Garthwaite et al., 2015) also shows association with ADHD, suggesting that myelination defects might contribute to ADHD symptoms.

Genes implicated in the development and maturation of astrocytes have also been associated with ADHD. Astrocytic functions are essential for the brain's development and activity, providing supportive roles for neurons, clearing the environment of metabolic waste and cell debris following injury. The migration of astrocytes during brain development and maturation depends on GIT1, which promotes cell motility. *Git1* null mice exhibit abnormal astrocytosis in the basal ganglia pathway, altering synaptic transmission in the basal ganglia and, ultimately, impairing the inhibitory modulation of the thalamus (Lim and Mah, 2015). Alteration of these structures in ADHD (Table 1) and genetic studies revealing a correlation between *GIT1* and ADHD (Won et al., 2011), suggest that increased astrocytosis may play a role in the disorder. However, there is conflicting evidence with regards to *GIT1*'s role in ADHD (Klein et al., 2015), and this requires future investigation.

In addition to its neuronal expression, α7nAChR has also been detected on astrocytes, in the rat hippocampus (Shen and Yakel, 2012). Activation of astrocytic α7nAChR results in a greater increase in intracellular calcium in astrocytes compared to that recorded in neurons, suggesting that astrocytic α7nAChR participates in neuroprotection by reducing levels of extracellular calcium. Abnormal astrocytic expression of *CHRNA7* in ADHD could therefore result in increased neuronal cell death.

Astrocytes are responsible for clearing the neurotransmitter at the level of the synaptic space following neurotransmission to prepare the environment for a new release. Therefore neurotransmitter receptors and transporters are expressed in astrocytes, in particular the norepinephrine transporter SLC6A2 (Inazu et al., 2003), which is associated with ADHD (Lasky-Su et al., 2008). It is therefore possible that abnormal norepinephrine signalling by astrocytes may contribute to ADHD. Similarly, the dopamine receptor DRD5 is expressed in striatal astrocytes during development (Brito et al., 2004) and has also been associated with ADHD (Daly et al., 1999; Gizer et al., 2009). Astrocytic expression of *Drd5* is promoted by BDNF, which is pivotal in brain development, accelerating the maturation of newborn neurons and facilitating their survival (Brito et al., 2004). BDNF is expressed by oligodendrocytes and, to a lesser extent, astrocytes, which upregulate the trophic factor's expression following lesion (Dougherty et al., 2000). Altogether, the evidence indicates that abnormal

oligodendrogenesis would lead to a reduction of BDNF, impairing the astrocytic expression of *DRD5* and dopamine reuptake.

The brain also contains microglia, the resident myeloid cells found throughout the mammalian central nervous system. Microglia are critically involved in the immune response in the injured brain but also play essential roles during brain maturation. Microglia promote learning-dependent synapse formation in the juvenile brain through BDNF release at the level of the synapse (Parkhurst et al., 2013). Both spine elimination and formation, part of learning-dependent synaptic turnover, are significantly reduced following loss of microglial BDNF, resulting in severe learning deficits as seen in neurological disorders. Therefore, the symptoms associated with ADHD could result from abnormal secretion of BDNF from microglia. Similar to astrocytes, microglia express neurotransmitter receptors, including the serotonin receptor HTR2B (Kolodziejczak et al., 2015) and α7nAChR (Shytle et al., 2004; Suzuki et al., 2006). The cholinergic activation of α7nAChR that promotes the neuroprotective functions of microglia, and inhibits inflammation, may be another route by which variants in *CHRNA7* contribute to ADHD.

Therefore, whilst research has mainly focussed on the neuronal defects underlying ADHD symptoms, genes associated with ADHD are also involved in the development of the non-neuronal fraction of the brain and abnormal gliogenesis and microgliogenesis could contribute to the disorder.

CONCLUSIONS

ADHD associated genes participate in all stages of brain development, with those affecting neurotransmission potentially playing a role at every stage. Of course, neurotransmitters have been associated with ADHD for a long time, with the targeting of dopamine reuptake by methylphenidate being the most common medication. The beneficial effects of methylphenidate suggests that neurotransmitter dysregulation contributes to the disorder, but this does not preclude an additional contribution of neurotransmitters during neurodevelopment, and the dysregulation of the dopamine pathway in ADHD may have its origins in the early stages of brain development.

The majority of ADHD associated genes with a known developmental role are involved in the formation and activity of synapses, and disruption of this process is a likely cause of the reduced brain volume observed in ADHD. Furthermore, aberrations in neuronal and axonal migration are consistent with the developmental delay hypothesis. Whilst it is therefore possible to look at cell and animal studies to make a link to the symptoms observed, it is important to note that most of the studies reviewed here involve gene knockout or overexpression systems, while variants detected in ADHD are usually SNPs or variable number tandem repeats. The majority of these variants are found in non-coding regions and, individually, are likely to have very small effects on function. Looking forward, this presents a challenge in modelling ADHD-associated variants, as while it is getting easier to introduce single variants into animal models, we are lacking the necessary assays to detect the small changes in behaviour and physiology that these variants likely cause. Examining multiple variants simultaneously could provide us a way of examining the effects of these variants in a form naturally seen in ADHD, but would not allow dissection of their individual roles. The development of suitable animal models and, importantly, sensitive behavioural assays for these models, will allow further examination of the neurodevelopmental contribution to ADHD, and is a paramount to understanding the disorder as a whole.

Acknowledgements.

We would like to thank Ziarih Hawi and Brent Neumann for their comments on the manuscript.

Funding

Callum Dark is supported by an Australian Government Research Training Program (RTP) Scholarship.

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