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Dances with black widow spiders: Dysregulation of glutamate signalling enters centre stage in ADHD

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Abstract
Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with impairments across the lifespan. The persistence of ADHD is associated with considerable liability to neuropsychiatric co-morbidity such as depression, anxiety and substance use disorder. The substantial heritability of ADHD is well documented and recent genome-wide analyses for risk genes revealed synaptic adhesion molecules (e.g. latrophilin-3, *LPHN3*; fibronectin leucine-rich repeat transmembrane protein-3, *FLRT3*), glutamate receptors (e.g. metabotropic glutamate receptor-5, *GRM5*) and mediators of intracellular signalling pathways (e.g. nitric oxide synthase-1, *NOS1*). These genes encode principal components of the molecular machinery that connects pre- and postsynaptic neurons, facilitates glutamatergic transmission, controls synaptic plasticity and empowers intersecting neural circuits to process and refine information. Thus, identification of genetic variation affecting molecules essential for the formation, specification and function of excitatory synapses is refocusing research efforts on ADHD pathogenesis to include the long-neglected glutamate system.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD; MIM #143465) is a common, early onset and enduring neuropsychiatric disorder characterised by developmentally inappropriate inattention, hyperactivity, increased impulsivity and motivational/emotional dysregulation with similar prevalence rates throughout different cultural settings, resulting in impairments of learning performance in scholastic settings as well as in multiple other domains of personal and professional life. ADHD has long been considered a disorder of childhood that resolves gradually with maturation during adolescence but this view was contested by systematic follow-up studies documenting remarkable persistence of ADHD into adulthood (adult ADHD, aADHD) associated with considerable risk for psychiatric co-morbidity such as depression, anxiety and substance use disorder as well as

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failure in psychosocial adaptation (for review e.g. Geissler and Lesch, 2011).

Insight from pharmacological approaches, candidate gene association studies and animal models consistently implicate altered neurotransmission and dysfunctional network connectivity in the neurobiology underlying ADHD. Effectiveness of ADHD treatment with psychostimulants (e.g. methylphenidate, MPH) and norepinephrine reuptake inhibitors (e.g. atomoxetine, ATX), influencing dopamine (DA) and norepinephrine (NE) systems, and the capacity of antidepressant drugs (e.g. selective serotonin reuptake inhibitors, SSRIs) to moderate ADHD symptoms in the DA transporter-deficient mouse directed past research to both catecholamine and serotonin (5-HT) signalling.

Although the substantial heritability of ADHD is documented in numerous family, twin and adoption studies, with estimates up to 80%, genome-wide linkage (Romanos et al., 2008; Zhou et al., 2008 and references therein) as well as single nucleotide polymorphism (SNP) and copy number variant (CNV) association analyses are just recently beginning to reliably identify ADHD-associated genes. With the discovery of variation affecting genes encoding glutamate (GLU) receptors (e.g. metabotropic GLU receptor-5, GRM5) and mediators of their intracellular signalling pathways (e.g. nitric oxide synthase-1, NOS1) as well as interacting molecules in the formation and plasticity of glutamatergic synapses (e.g. latrophilin-3, LPHN3) as relevant causative factors, research on ADHD pathogenesis is increasingly shifting focus to the long-neglected GLU system.

2. Latrophilin 3: of spider dances and tarantella genes

In 2010 Arcos-Burgos and colleagues (Arcos-Burgos et al., 2010) reported evidence of a risk haplotype in the gene coding for latrophilin-3 (*LPHN3*), revealed by classic linkage analysis using a set of microsatellite markers of a South American genetic isolate and subsequent fine-mapping of the chromosome 4q13.2 locus in several North American and European populations. Functionality of the risk haplotype at the level of neuronal activity and viability was demonstrated by an inverse correlation between the risk haplotype dosage and N-acetylaspartate (NAA)/creatine (Cr) ratio particularly in the thalamus using proton magnetic resonance spectroscopy (^{1}H MRS). Replication in a Spanish cohort of patients with aADHD further supports a role for *LPHN3* in the persistence of ADHD across the lifespan (Ribases et al., 2011). Moreover, *LPHN3* confers its risk upon ADHD in interaction with maternal stress during pregnancy (Choudhry et al., 2012). In a genome-wide association (GWA) study of patients with substance use disorders, Liu and coworkers also identified *LPHN3* and several others (e.g. CDH13, Rivero et al., in press) among 86 potential risk genes (Liu et al., 2006), supporting the clinical observation that both ADHD and substance dependence share a high degree of comorbidity. Of related interest, *LPHN3* variants have also been associated with cognitive abilities (crystallised-type intelligence) (Davies et al., 2011).

LPHN3, a putative adhesion-G protein-coupled receptor (adhesion-GPCR) with the structural propensity to moderate cell–cell interactions, is implicated in axon guidance, synaptogenesis and synaptic plasticity (Silva et al., 2011; Sudhof, 2001) (Figure 1). It contains a large extracellular portion linked to seven transmembrane domains by a proteolytic site. Among various other possible functions, LPHN3 may act as one of the receptors for α-latrotoxin (αLTX), a component of the black widow spider (*Latrodectus mactans*) venom, causing acute and massive exocytosis of various neurotransmitters (e.g. GLU, γ-aminobutyric acid/GABA, biogenic amines) from presynaptic vesicles (Grishin, 1998) leading to an alternating state of lethargia (depression, accompanied by fear of death) with hyperexcitability (extreme pain, muscle spasms, agitated confusion and occationally hallucinations). In the Italian city Taranto in Apulia, the poisonous bite was erroneously attributed to a locally common spider, named tarantula (*Lycosa tarentula*, a wolf spider), whereas the bite of another creature lurking nearby, the Mediterranean black widow spider (*Latrodectus tredecim guttatus*), is actually leading to the venom's intoxication symptoms (Latrodectism). As a treatment for Latrodectism the dance Tarantella is thought to be rooted in the traditional folk medicine. The legend tells that the stated belief in the 16–17th centuries regarding the only remedy was that victims had to engage in vigorous, sometimes frensied dancing to very rhythmic music with an upbeat tempo, hence sweating out the spider's poison and preventing death: *Antidotum tarantulae* (Fernandino, 1621; Kircher, 1641). State-of-the-art treatment however is the rapid application of antisera.

Despite converging evidence for a potential role in ADHD pathogenesis, genetic screenings have so far failed to identify disease-causing variants or to address the question of whether a gain- or loss-of-function of LPHN3 is driving the risk for ADHD and related disorders. The lack of information about the physiological function of LPHN3 and its participation in the pathogenesis of disease is presently prompting further studies in cell and animal model systems.

For efficient probing of the genetic and neurodevelopmental bases of behaviour the zebrafish has been established as a valid animal model (Norton et al., 2012). As an initial attempt to characterise the participation of LPHN3 in ADHD pathogenesis, larval zebrafish were used to assess the developmental and behavioural function of Lphn3.1 activity, one of the zebrafish orthologs of LPHN3. Morpholino-induced knockdown of Lphn3.1 activity triggers hyperactive/impulsive locomotion and selectively disrupts DA system development (Lange et al., 2012). The behavioural phenotype is rescued by MPH and ATX, drugs that are effective in treating ADHD. The specificity of Lphn3.1 for the formation of the DA system in zebrafish is intriguing in the face of an ubiquitous expression pattern of Lphn3 in murine brain, although preferential expression is evident in catecholaminergic and serotonergic cell clusters and their targets, including GABA and GLU neurons, in hippocampus, amygdala and cortex. Therefore, subtle alterations at the level of synapse formation and neuronal connectivity are likely to exist across sevaral transmitter systems, modifying for example GLU and 5-HT signalling. The complex interactions between the GLU and 5-HT systems are reviewed elsewhere (Waider et al., 2011).

Initial characterisation of Lphn3 null mutant mice revealed a hyperactive phenotype independent of sex, increased levels of DA and 5-HT in the dorsal striatum, changes in DA and 5-HT receptor expression and increased sensitivity to the locomotor stimulant effects of cocaine (Wallis et al., 2012). In addition to the identification of

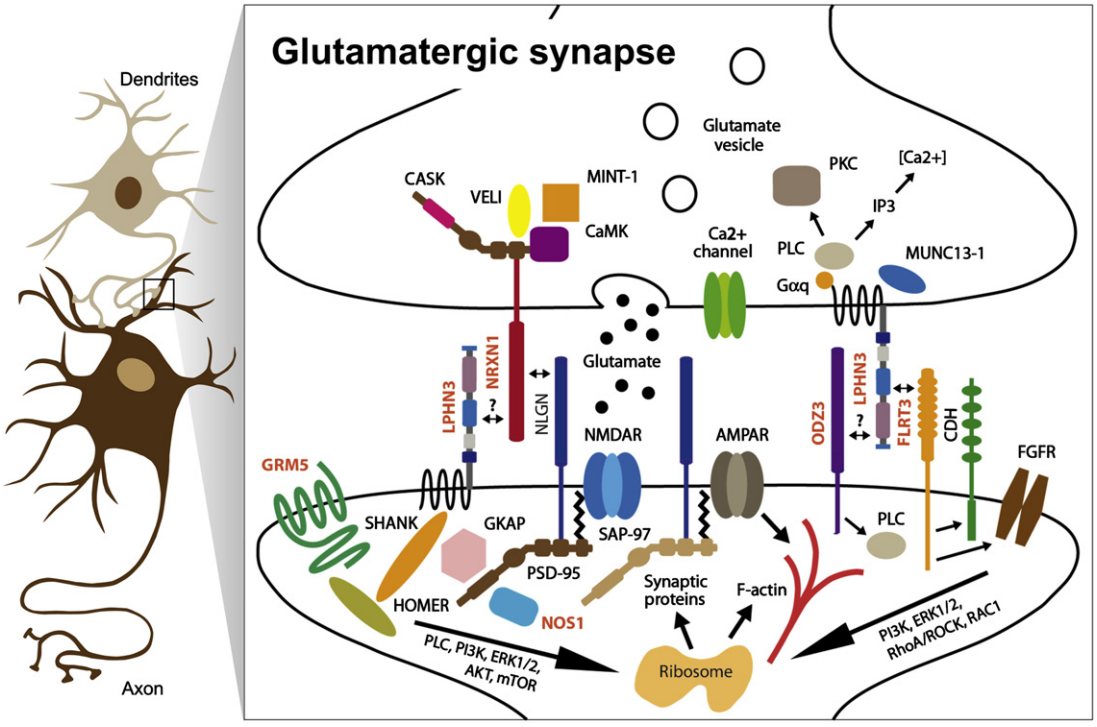

Figure 1 Schematic diagram of a glutamatergic synapse displaying involvement of synaptic proteins in attention-deficit/hyperactivity disorder (ADHD). The proteins identified as associated with ADHD risk are indicated in red. AKT, v-akt murine thymoma viral oncogene homolog (protein kinase B); AMPAR, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor; Ca^{2+} channel, calcium channel; CASK, membrane-associated guanylate-kinase protein (MAGUK); CaMK, calcium/calmodulin-dependent serine protein; CDH, cadherins; ERK1/2, extracellular-signal-regulated kinases 1/2 (classical MAP kinases); FGFR, fibroblast growth factor receptor; FLRT3, fibronectin leucine rich transmembrane protein 3; GKAP, G kinase anchoring protein; Gαq; G protein α-subunit q; GRM5, metabotropic glutamate receptor 5; IP3, inositol triphosphate; HOMER, homer homolog 1 (*Drosophila*); LPHN3, latrophilin-3; Mint-1, amyloid beta A4 precursor protein-binding; mTOR, mechanistic target of rapamycin (serine/threonine kinase); MUNC13-1 (UNC13A), unc-13 homolog (*Caenorhabditis elegans*); NLGN, neuroligin; NOS1, nitric oxide synthase-1; NRXN1, neurexin-1; NMDAR, NMDA (N-methyl-D-aspartate) receptor; ODZ3, odd Oz/ten-m homolog 3 (teneurin-3); PKC, phosphokinase C; PI3K, phosphatidylinositol 3-kinase; Rho/ROCK, RAC1, small GTPases PSD-95, postsynaptic density protein 95; PLC, phospholipase C; SAP-97, synapse-associated protein 97; SHANK, SH3 and multiple ankyrin repeat domains protein.

LPHN3 as such, an interaction of *LPHN3* risk SNPs with a region on chromosome 11q containing the DA receptor-2 (*DRD2*) and the neural cell adhesion molecule-1 (*NCAM1*) genes were identified by linkage analysis of multigenerational pedigrees (Jain et al., 2012). Taken together, these results conclusively implicate LPHN3 loss-of-function in interaction with other risk genes as one of the factors involved in the locomotor phenotype of ADHD and points to its critical role in DA system development. Future work will have to focus on the role of LPHN3-interacting molecules in ADHD pathophysiology (see below), on the Lphn3.2 homolog in zebrafish and on the behavioural and neurobiological features of a conditional Lphn3 knockout mouse model.

3. Latrophilin-induced signal transduction: convergence on glutamatergic synapse

Several intracellular signalling pathways may be activated by LPHNs at both the pre- and postsynaptic level. α-LTX targets the presynaptic terminal of neurons by inducing receptor-mediated vesicle exocytosis via both Ca^{2+}-dependent and -independent pathways (Figure 1). The Ca^{2+}-independent effects are likely transduced by G proteins. The subunit Gαq activates both phospholipase C and inositol-3-phosphate (IP3) resulting in Ca^{2+} mobilisation from intracellular Ca^{2+} stores (Davletov et al., 1998; Ichtchenko et al., 1998) for review (Sudhof, 2001), eventually followed by release of neurotransmitter, such as norepinephrine (Rahman et al., 1999). LPHNs are constitutively cleaved into two subunits (Krasnoperov et al., 2002; Silva et al., 2009) and the association between subunits may be dynamically regulated by ligand binding to modulate LPHN-induced G protein signalling. Moreover, the presynaptic diacylglycerol (DAG) receptor UNC13A (MUNC13-1), essential for synaptic vesicle-mediated neurotransmitter release, also participates in LPHN-dependent regulation of exocytosis (Augustin et al., 2001) and links LPHN signalling to the DAG pathway implicated in the mechanism of action of the mood stabiliser lithium and hence bipolar disorder, whereas recent evidence points towards a contribution of DAG kinase ε also in ADHD (Weber et al., 2011).

Postsynaptically, LPHNs' C-terminal region interacts with proteins of the SHANK family (Kreienkamp et al., 2000). SHANK proteins are synaptic multidomain scaffold proteins of the postsynaptic density (PSD) that connect neurotransmitter receptors, ion channels, and other membrane proteins to the

actin cytoskeleton and G protein-coupled signalling pathways and also play a role in synapse formation and dendritic spine maturation. Mutations in SHANK3 confer risk for autism spectrum disorders (ASD) which are characterised by impairments in social interaction and communication as well as restricted behavioural patterns and interests and which display syndromic overlap with ADHD (Durand et al., 2007; Moessner et al., 2007) for review: (Grabrucker et al., 2011). Of related relevance, SHANK3 mutations trigger modification of dendritic spine morphology via an actin-dependent mechanism (Durand et al., 2012), likely to result in defects at striatal synapses and cortico-striatal circuits that were reported in Shank3 mutant mice (Peca et al., 2011).

At the glutamatergic postsynapse, SHANK3 also couples to GKAP (Naisbitt et al., 1999; Romorini et al., 2004) and via this adaptor protein to the NMDA receptor–PSD-95–nitric oxide (NO) synthase-1 (NOS1) complex. While GKAP is thought to be a PSD-95 associated scaffolding protein maintaining synaptic junctions and synaptic stability, the PSD complex also operates as a functional link as it tightly couples the NMDA receptor to NOS1. The latter is able to bind to PSD-95 by an unique PDZ–PDZ domain interaction, allowing for attachment of NOS1 to the NMDA receptor complex (Christopherson et al., 1999). Thus, NOS1 is spatially close to where Ca^{2+} influx occurs, which activates NOS1 as a consequence of CaM binding. Again by binding to PSD-95, which features three PDZ domains, the NO receptor soluble guanylyl cyclase (sGC) can bind to the NDMA–PSD-95–NOS1 complex (Russwurm et al., 2001; Zabel et al., 2002), which links the site of NO production to its immediate effector site. The gene encoding NOS1 (*NOS1*) was shown to be linked to aADHD (Reif et al., 2009; see below) and impulsive behaviours (Hoogman et al., 2011) further implicating the glutamatergic postsynaptic machinery in ADHD.

Lastly, SHANKs bind to HOMER proteins, another group of postsynaptic density scaffolding protein (Tu et al., 1999; Xiao et al., 2000), which, in turn, are able to interact with metabotropic GLU receptor subtypes 1 and 5. SHANK and HOMER proteins cross-link metabotropic GLU receptors with LPHN, which hence, in addition to its interaction with FLRT proteins and subsequent G protein signalling, impacts glutamatergic (and possibly other transmitter-specific) signalling in a dual mode (see below).

4. The quest for latrophilin ligands

Endogenous ligands for LPHNs, which are characterised by multiple extracellular sequence domains (lectin, olfactomedin-like, serine/threonine-rich, hormone-binding, G protein-coupled receptor autoproteolysis-inducing domains) have been elusive-until very recently: three simutaneously published investigations began to shed light on LPHN action in brain development and synaptic plasticity (Boucard et al., 2012; O'Sullivan et al., 2012; Silva et al., 2011).

In addition to LPHNs, presynaptically located neurexins (NRXN1, -2, and -3 in vertebrates), are also targets of α-LTX (Figure 1). While both neuronal cell adhesion molecules are structurally distinct, they display binding interaction between their extracellular domains resulting in a stable intercellular adhesion complex (Boucard et al., 2012). This direct interaction between LPHN1, whose expression pattern overlaps with that of LPHN3, and NRXN was reported to be regulated by alternative splicing of NRXNs (longer β-NRXN and α-NRXN) and to compete with neuroligin-1 (NLGN1), a previously identified postsynaptic ligand of neurexins. While LPHN1 inactivation in 19p13.12 microdeletion syndrome may contribute to a wide spectrum of features, including deficits in brain develoment and function, such as intellectual disability, psychomotor and language delay and hyperactivity, variants in NLGNs and deletions in NRXN-1α are associated with ASD (Sudhof, 2008). In line with the pertinent view that impairment of synaptic plasticity is a fundamental pathogenetic mechanism which cuts across mental disease categories, variation in NRXN-1α was also reported in schizophrenia spectrum disorders (Kirov et al., 2009; Rujescu et al., 2009), amphetamine dependence (Uhl et al., 2008) and ADHD (Lesch et al., 2008; Neale et al., 2010) which displays syndromal overlap with ASD.

A splice-variant of the protein encoded by ODZ2 (odd Oz/ten-m homolog 2, teneurin-2) is also capable of interacting specifically with LPHN1 (Silva et al., 2011). Since their expression pattern in the hippocampus largely overlaps, ODZ3 and ODZ4 are potential candidates for an interaction with LPHN3. A deletion of ODZ3 was reported in an ADHD patient (Lionel et al., 2011), whereas GWA signals were detected for ODZ3 in childhood and adult ADHD (Lesch et al., 2008; Stergiakouli et al., 2012) and for ODZ4 in bipolar disorder (Sklar et al., 2011). A duplication on chromosome 11q14.1 affecting ODZ4 in a patient with ADHD was also reported (Williams et al., 2012). Taken together, the interaction of LPHN1 with both NRXNs and ODZ2 supports the view that LPHNs are critically involved in the formation and plasticity of glutamatergic synapses, although potential network specificity of LPHN3-mediated adhesion requires further scrutiny.

5. FLRT3 is interacting with LPHN3

The fibronectin leucine-rich repeat transmembrane protein-3 (FLRT3) was recently identified as a endogenous ligand specifically of LPHN3 and the transsynaptic LPHN3-FLRT3 interaction appears central to glutamatergic signalling (Figure 1) (O'Sullivan et al., 2012). *FLRT3* encodes a single-pass transmembrane protein with ten extracellular leucine-rich repeat domains and a juxtamembrane fibronectin type 3 domain. In addition to the previously reported function of proteolytically cleaved, soluble FLRT ectodomains in cell migration and axon guidance as repulsive molecules for Unc5 receptor-expressing neurons (Yamagishi et al., 2011), there is evidence that the extracellular domains of FLRT3 and LPHN3 interact as a ligand-receptor pair in the formation and regulation of excitatory synapses. The transsynaptic adhesion mediated by FLRT3-LPHN3 interaction is likely to trigger pre- and postsynaptic signal transduction events that activate synaptic function, and thus shape synaptic efficacy and plasticity. Since LPHNs have the propensity for auto-cleavage, FLRT binding to the LPHN may lead to reassociation of the LPHN subunits and generate subsequent G protein signalling. Notably, a similar dual function in axon pathfinding and synaptogenesis has also been demonstrated for other synaptic adhesion/signalling molecules, such as semaphorins and Ephs/Ephrins (Klein, 2009; Pasterkamp and Giger, 2009).

While LPHN3 may induce G protein-dependent signalling cascades (see above), FLRT3 has been demonstrated to recruit fibroblast growth factor (FGF) receptor-mediated signalling (Bottcher et al., 2004) and may moderate cadherin (CDH)-mediated cell adhesion via small GTPases (Karaulanov et al., 2009). Signals conveyed by cadherin adhesion (Williams et al., 2011) as well as activation of FGF signalling pathways (Terauchi et al., 2010) were reported to moderate synapse development. In contrast to the ubiquitous presence of NRXNs and LPHN3 in the brain, FLRT3 and ODZs display a more neuron-specific expression pattern, suggesting that LPHN3 is capable of interacting with various structurally distinct postsynaptic components at different types of synapses to control network connectivity. By specifying synaptic functions, these multiple parallel trans-synaptic signalling complexes shape unique network properties (Benson et al., 2000; Bockaert et al., 2010).

The emerging relevance of LPHN3-FLRT3 interaction is further strengthened by recent genetic studies revealing frequent and rare variants associated with the ASD–ADHD spectrum. FLRT3 is a nested gene in intron 3 of a gene encoding MACROD2 and CNVs affecting *FLRT3* and/or MACROD2 were reported in five patients with ADHD and one control (Elia et al., 2010; Lionel et al., 2011; Williams et al., 2010) (Figure 2). While its function continues to remain elusive, MACROD2 is expressed in the developing and adult brain (e.g. cortex, subventricular zone of striatum, inferior colliculus of the tectum) and disruption of its transcription by deletion-induced genomic rearrangements may also impact expression of genes in close proximity including FLRT3. In support of this notion, SNPs in MACROD2 also gave GWA signals in ASD, ampetamine dependence and ADHD (Anney et al., 2010; Lesch et al., 2008; Uhl et al., 2008).

In summary, evidence is accumulating that LPHN3's cross-talk with NRXNs, ODZs and FLRT3 regulates number and function of glutamatergic (and other) synapses and detailed characterisation of these trans-synaptic signalling interfaces is likely to lead to a better understanding of the aetiopathogenesis of ADHD and related disorders. To further evaluate the relevance of LPHN3 in ADHD-associated delayed brain development and maturation, a brief appraisal of the evidence linking altered GLU system function and plasticity to ADHD will be given in the following section.

6. ADHD and the glutamate system

GLU is the major excitatory neurotransmitter in the brain and activates both ionotropic (α-amino-3-hydroxy-5-methyl-4-isoxazole propionate, AMPA; kainate; N-methyl D-aspartate, NMDA-type) and metabotropic GLU (mGLURs) receptors. mGLURs, including the subtype 5, mGLUR5 (termed GRM5 throughout the following sections) are a family of G protein-coupled receptors modulate the response to ionotropic GLU receptors, such as NMDA and AMPA receptors, and that of other neurotransmitters including DA and GABA (Figure 1). They have been divided into three groups on the basis of sequence homology, putative signal transduction mechanisms, and pharmacologic properties. GRM1 and GRM5, members of group 1, are expressed in the cortex, striatum and amygdala and activate phospholipase C. Group 2 includes GRM2 and GRM3 while group 3 comprises GRM4 and GRM6-8. Groups 2 and 3 receptors are linked to the inhibition of the cyclic AMP (cAMP) cascade but differ in their agonist selectivities.

Evidence for an involvement of GLU system in ADHD has been emerging from human genetic and animal model studies but data remain sparse and therapeutic consequences seem as yet remote. Although association studies investigating genes encoding GLU receptors and transporters have reported inconsistent results (for review: (Faraone and Mick, 2010), a GWA study examining the MPH response in children with ADHD found an association with a SNP in *GRM7* (Mick et al., 2008). The gene encoding the NMDA receptor subunit-2A (*GRIN2A*) was implicated with ADHD in a linkage study and GWA screen (Lesch et al., 2008; Turic et al., 2004), whereas both the NMDA receptor subunit-2B (*GRIN2B*) and the glial GLU transporter (*EAAT1*, *SLC1A3*) genes were found to be associated with ADHD using family-based approaches (Dorval et al., 2007; Turic et al., 2005). Finally, the gene for ionotropic GLU receptor δ2 (*GRID2*) yielded a signal in a GWA study (Stergiakouli et al., 2012).

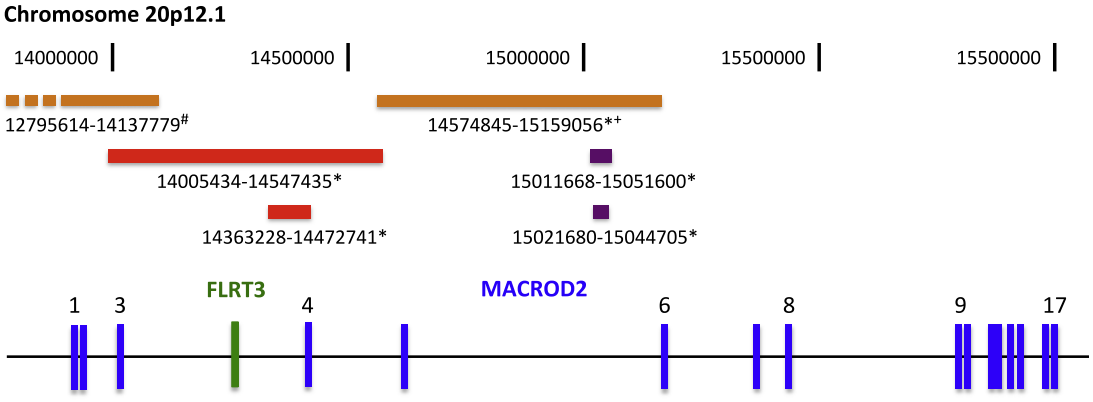

Figure 2 20p12.1 CNVs disrupting *FLRT3* and/or *MACROD2* from the Williams et al. (2010) (orange lines), Lionel et al. (2011) (red lines), Elia et al. (2010) (purple lines) in five patients with ADHD and one control. FLRT3 is a nested gene in intron 3 of *MACROD2*. The position of CNVs is according to NCBI36/hg18. *Deletion, #duplication, and +control. (For interpretation of the references to colour in this figure caption, the reader is referred to the web version of this article.)

MRS imaging showed an increased glutamatergic tone in the frontal and striatal brain of patients with ADHD that normalised with MPH and ATX (Carrey et al., 2003; MacMaster et al., 2003). Mice with a targeted inactivation of the gene encoding the DA transporter (*Dat/Slc6a3*) display locomotor hyperactivity insensitive to cocaine and MPH (Giros et al., 1996; Sora et al., 1998). Their hyperactivity is further increased by NMDA receptor inhibitors but suppressed by drugs that increase GLU signalling (Gainetdinov et al., 1999, 2001). Neonatal 6-hydroxydopamine (6-OHDA)-induced lesion studies in rats revealed time- and dose-dependent increases in *Dat/Slc6a3* and DA receptor D4 (*Drd4*) expression in the midbrain and higher expression of GLU transporter in the striatum, suggesting that decreases in DA system function alters GLU neurotransmission (Masuo et al., 2002) (also see below). Moreover, alterations in GLU-GABA system interaction were reported (Molina-Holgado et al., 1993; Podkletnova et al., 1996). Targeted inactivation of *Grin2a* in mice increased NMDA receptor sensitivity and 5-HT metabolism in the frontal cortex and striatum; increased locomotor activity is normalised by DA or 5-HT receptor antagonists in these mice (Miyamoto et al., 2001). Altered expression of glutamatergic signalling pathway genes has been observed in other ADHD-like models, such as the spontaneously hypertensive rat (SHR) (for review: (Sagvolden et al., 2009).

Finally, both pharmacological inhibition of GRM5 (Kachroo et al., 2005) and targeted inactivation of the gene encoding Grm5 result in locomotor hyperactivity and reduced habituation to novelty (Halberstadt et al., 2011). Deficits in spatial learning as well as acquisition and retrieval of stimulus-outcome memories in a fear conditioning paradigm have also been reported (Jia et al., 2001; Xu et al., 2009). Electrophysiological studies in GRM5 knockout mice revealed sensorimotor gating deficits suggesting a key role for this gene in the modulation of hippocampal NMDA receptor-dependent synaptic plasticity (Jia et al., 1998). Taken together, these findings support the notion that GRMs, specifically GRM5, are critically involved in the pathophysiology of ADHD.

7. Metabotropic glutamate receptor gene variants are linked to ADHD

Brain-expressed receptor genes affected by CNVs such as GRMs, are attractive candidates for the complex pathophysiology of neuropsychiatric syndromes such as ADHD, where the disorder is defined by a specific constellation of deficits comprising motivation, working memory and cognitive control of executive functions. While GRM5 was already implicated in several neuropsychiatric disorders including anxiety, depression, substance abuse, schizophrenia and Fragile X Syndrome (Auerbach et al., 2011; Devon et al., 2001; Schumann et al., 2008; Wang et al., 2010), a recent two-stage genome-wide CNV screen showed that the GRM gene family and genes interacting with it are enriched for CNVs in ADHD patients (Elia et al., 2012). The most frequent deletions were found in GRM5 in ten out of 3506 ADHD patients but only in one from more than 13,000 healthy individuals. Other CNV findings concerned Grm1 (duplications), GRM7 (deletions) and GRM8 (deletions). Overall the findings indicate that up to 10% of individuals with ADHD may be enriched for GRM network variants. Several of these genes play a central role in the process of neurogenesis, synaptic transmission and network connectivity that has been argued to be defective in ADHD. The observed GRM gene modules regulate mRNA generation alternative splicing and translation, processes known to influence circuitry-specific formation, activity and plasticity of synapes (Bockaert et al., 2010; Knafo and Esteban, 2012).

8. DA system-GRM5 interaction in the frontostriatal network

Given the diversity of syndromal dimensions featured by ADHD which result in behavioural deficits reflected by a wide spectrum of cognitive, emotional and psychosocial impairments, multiple brain systems and neuronal circuits are implicated in ADHD pathophysiology and treatment response. Deficits in GLU signalling influences the pathophysiology of ADHD either directly or indirectly. Since the GLU system it is tightly interconnected with other neurotransmitter systems, a conceivable mode of action in the modulation of ADHD-related core symptoms may be via an impact on DA and other monoaminergic system function. For examplar illustration, the focus in the following sections will be on DA system–GRM5 interaction.

8.1. Dopaminergic dysfunction in ADHD

Despite the still very limited insight into ADHD-related disease mechanisms, a considerable body of evidence has been accrued that points to dysfunctional DA signalling in the prefrontal cortex (PFC) and striatum as well as various connected structures, such as hippocampus and amygdala (Swanson et al., 2007). DA is released from neurons that originate from two midbrain nuclei, comprising the nigrostriatal, mesolimbic and mesocortical pathways. The DA neuron cluster in the substantia nigra pars compacta (SNc) projects to the dorsal striatum (caudate and putamen) and coordinates motor responses and participate in action initiation as well as goal-directed (action-outcome) and habitual (stimulus-response) learning (Lovinger, 2010). DA neurons in the ventral tegmental area (VTA) project to nucleus accumbens (NAc) of the ventral striatum, amygdala, hippocampus and PFC. These structures are responsible for the selection of most beneficial response, inhibiting inappropriate responses and stimuli as well as in assigning salience to cues predicting results. DA signalling is mediated by DA receptors either of the D1-like or D2-like families. Although both groups rely on regulation of cAMP as the main downstream effector, they act in opposite directions. The D1 receptor induces cAMP production and subsequently increases firing of the postsynaptic neuron. In contrast, the D2 receptor is located both pre- and post-synaptically and generally reduces synaptic signalling.

Animal models have significantly contributed to the elucidation of dopaminergic dysfunction in ADHD and gene-targeted modification or neurotoxic lesion in rodents resulting in impaired DA reuptake or release were suggested to model distinct behavioural characteristics of ADHD. Increased locomotor activity is observed in *Dat/Slc6a3* knockout mice (Giros et al., 1996) and in a Dat/cocaine-insensitive knockin line with decreased DA reuptake efficiency (Napolitano et al., 2010), whereas the locomotor hyperactivity *Dat/Slc6a3*-deficient mice

is reversed by stimulant drugs including cocaine and MPH (Sora et al., 1998). As mentioned above, neonatally 6-OHDA lesioned rats were reported as a valid animal model of ADHD because of its hyperactivity and attention deficits that is corrected both by MPH and amphetamine (van der Kooij and Glennon, 2007). The hyperactivity is modulated by pharmacological targeting of the DA receptor D4 of the D2 family (Zhang et al., 2001, 2002). Although the findings are not always consistent, the hypothesis that monoaminergic dysfunction plays a role in ADHD is further supported by candidate gene association studies. Polymorphisms in *DRD4* and *DRD5* (for review e.g. Faraone and Mick, 2010; Franke et al., 2011) appear to be associated with ADHD, while *DAT/SLC6A3* is one of the most comprehensively assessed candidates for ADHD (Franke et al., 2010). Taken together, the DA system orchestrates functions that are defining syndromal dimensions of ADHD including attention, locomotor activity, motivation/emotion, impulsivity, and goal-directed behaviour and, as a consequence, learning and memory.

8.2. Disruption of frontostriatal connectivity in ADHD

Alterations in DA signalling in ADHD are accompanied by neuroimaging-elicited structural and functional alterations reflected for example by reduced cortical thickness, volume reduction of PFC and striatum as well as, disrupted connectivity and activity in frontostriatal and intrastriatal networks which has been described as a shift in the ventral-dorsal striatal gradient (Bush, 2011; Carmona et al., 2009; Swanson et al., 2011). Disruption of frontostriatal connections with decreased microstructural organisation is thought to represent a specifc characteristic of ADHD pathophysiology (Cubillo et al., 2012; de Zeeuw et al., 2011). Alterations are partially reversed by MPH and amphetamine treatment, underscoring involvement of DA and interconnected signalling. Positron emission tomography (PET) imaging uncovered deviations in mediators of DA signalling, including DAT, D2 receptor, DA synthesis, and release, in the reward-motivation pathway (midbrain, caudate, and ventral striatum), which were associated both with symptoms of inattention and with decreased motivation. Recently, enhanced short-range connectivity within reward-motivation networks and their decreased connectivity with structures comprising the default-mode and dorsal attention networks have been reported, indicating impaired crosstalk among control and reward pathways that may reflect attentional and motivational deficits in ADHD (Tomasi and Volkow, 2012; Volkow et al., 2012).

8.3. GRM5-mediated signal transduction in the frontostriatal network

GRM5 is abundantly expressed in NAc, dorsal striatum and PFC. In dendritic spines of these structural units GRM5 not only interacts with downstream signalling of DA receptors but also with NMDA receptors resulting in reciprocal and agonist-independent inhibition of the two receptors (Perroy et al., 2008). While GRM5 is confined to the periphery of the synapse, NMDA receptors are located vis-à-vis of the GLU release site in the postsynaptic density comprising the multiprotein HOMER-SHANK-GKAP-PSD-95) scaffolding complex physically and functionally linking the two receptors (Fagni et al., 2008) (Figure 1).

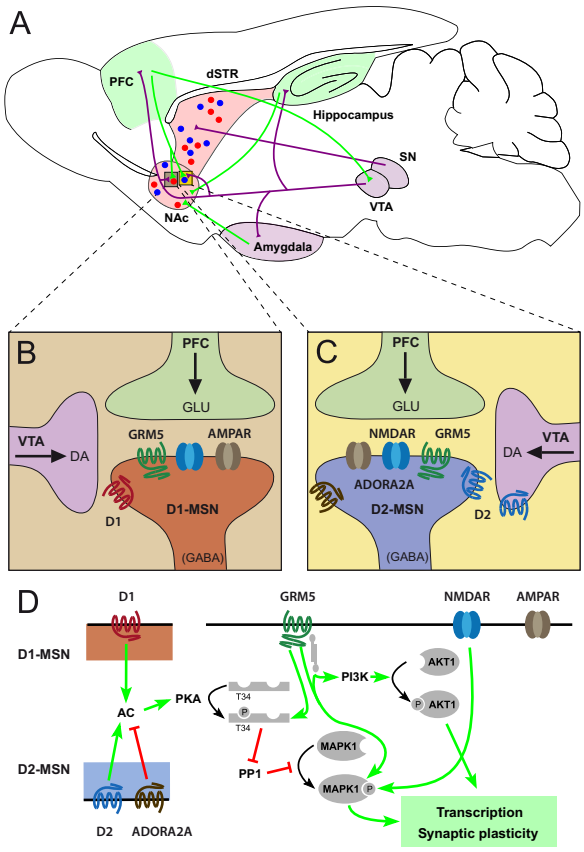

Figure 3 (A) Frontostriatal and intrastriatal dopamine (DA)-glutamate (GLU) signalling networks connecting prefrontal cortex (PFC), striatum, amygdala, hippocampus, ventral tegmental area (VTA), and substantia nigra (SN). (B and C) γ-Aminobutyric acid (GABA)ergic medium spiny neurons (MSNs) are the principal neurons both in dorsal striatum (dSTR) and the nucleus accumbens (NAc). Synapses of glutamatergic corticostriatal terminals connect to MNSs to modulate neuronal activity and DA signalling, while their activity is reciprocally regulated by DA. DA thus modulates activity in glutamatergic afferents and MNSs synapses in a bidirectional mode and the direction of DA-induced synaptic plasticity is directed by the identity of the postsynaptic MNS, that express either DA receptor D1 or D2. (D) The metabotropic GLU receptor 5 (GRM5) is expressed by both neuronal subpopulations activating distinct signalling pathways. The adenosine receptor-2A (ADORA2A) that acts in synergy with GRM5 on D2-MSN is absent from the D1-MSN population. These differences impact activity of key targets downstream of DA receptor signal transduction, such as protein phosphatase 1 regulatory subunit 1B (PPP1R1B, PP1). Phosphorylation of MAPK1 (extracellular-signal-regulated kinase 1, ERK1), the essential initial step for induction of long-term potentiation (LTP) requires that PPP1R1B is phosphorylated at Thr34. Phosphorylation of PPP1R1B is influenced by GLU transmission via multiple signalling pathways, some of which are exclusively via D2-MSN. Regardless of the signalling pathway involved, GRM5 is critically important for LTP via signalling through corticostriatal synapses on D1-MSNs. Downstream signalling involves various pathways converging on the transcriptional machinery and ultimately affect synaptic plasticity. AMPAR, AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor; NMDAR, NMDA (N-methyl-D-aspartate) receptor; AKT1, v-akt murine thymoma viral oncogene homolog 1 (protein kinase B); PI3K, phosphatidylinositol 3-kinase; PKA, protein kinase A.

GABAergic medium spiny neurons (MSNs) are the principal neurons both in dorsal striatum and NAc (Figure 3A–C). Synapses of glutamatergic corticostriatal terminals connect to MSNs to modulate neuronal activity and DA signalling (Moss and Bolam, 2008), while their activity is reciprocally regulated by DA. DA thus modulates activity in glutamatergic afferents and MSNs synapses in a bidirectional mode and the direction of DA-induced synaptic plasticity is directed by the identity of the postsynaptic MSN, that almost exclusively express either D1 or D2 receptors. Although GRM5 is expressed by both neuronal subpopulations, its impact on cellular signalling is distinct (Figure 3C). For example, the adenosine receptor-2A (ADORA2A) that acts in synergy with GRM5 on D2-MSN is absent from the D1-MSN population. These differences impact activity of key targets downstream of DA receptor signal transduction, such as protein phosphatase 1 regulatory subunit 1B (PPP1R1B), also known as DA and cAMP-regulated phosphoprotein of 32 kDa (DARPP-32). Phosphorylation of MAPK1 (extracellular-signal-regulated kinase-1, ERK1), the essential initial step for induction of long-term potentiation (LTP) requires that PPP1R1B is phosphorylated at Thr34. Moreover, phosphorylation of PPP1R1B is influenced by GLU transmission via multiple signalling pathways, some of which are exclusively via D2-MSN (Nishi et al., 2005).

Activation of PPP1R1B is implicated in various phenomena relevant to ADHD and substance dependence including psychostimulant-induced hyperlocomotion, drug self-administration, conditioned place preference, induction of long-term synaptic plasticity and expression of immediate early genes (Zachariou et al., 2006; Zhang et al., 2006). In the Dat knockout mouse model of ADHD, phosphorylation of PPP1R1B and ERK is paradoxically reduced upon administration of psychostimulant drugs (Beaulieu et al., 2006). PPP1R1B phosphorylation is achieved via activation of the NOS1 pathway (Nishi et al., 2005). As mentioned above, a repeat length polymorphism in the *NOS1* promoter influences impulsivity and ADHD (Reif et al., 2006, 2009, 2011). As one of the core symptoms of ADHD, impulsivity encompasses actions which are poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation and that often result in undesirable consequences (Winstanley et al., 2006). Impulsive individuals tend to prefer smaller immediate reward to larger delayed one and have difficulty to stop ongoing actions. In line with this, *NOS1* risk allele carriers show significantly different brain activation patterns in Go/NoGo- and stop-signal tasks (Kopf et al., 2011).

Moreover, phosphorylation of PPP1R1B is also modulated by GRM1-like receptor-dependent regulation of casein kinase 1 (CK1) and cyclin-dependent kinase 5 (Cdk5) (Nishi et al., 2005). Mice overexpressing CK1δ has been proposed as a model of ADHD because of hyperactivity reduced by psychostimulant administration, reduced anxiety and reduced expression of DA receptors. Similarly, a mouse line with knockout of Cdk5 activator p35 is deficient in cortical lamination (Drerup et al., 2010) and shows locomotor hyperactivity that is corrected by psychostimulants (Krapacher et al., 2010).

8.4. Motivational and emotional circuitries of learning

The fundamental characteristic of inattention observed in ADHD may arise from deficits in vigilance and/or motivation and the degree of attention critically determines performance especially in goal-directed learning (Caron and Wightman, 2009). Impaired learning performance in scholastic settings and functional abnormalities in the intrinsic microcircuitries of the basolateral (BLA) and lateral amygdala (LA), structures central to learning the emotional and motivational significance of environmental stimuli (Cardinal et al., 2002; LeDoux, 2003), have been linked to ADHD (Plessen et al., 2006) (Figure 3A). The LA merges thalamic and cortical afferents conveying sensory information on environmental cues and primary reinforcers, as well as participates in the acquisition and retrieval of stimulus-outcome memories (Doron and Ledoux, 1999; Reijmers et al., 2007). Furthermore, D1 receptor-dependent mechanisms predict thalamo-amygdalar synaptic strength and thus success of cue-reward learning, whereas memory consolidation is facilitated via the D2 receptors by acute administration of MPH in the amygdala (Tye et al., 2008, 2010). Since DA circuitry function codes for differences between expected and received reward, i.e. ''reward-prediction error'' (Montague et al., 2004), it has a crucial role in goal-directed learning. Based on the received reward the particular action is then assigned a salient value in a process called ''incentive'' learning. More salient tasks have then higher probability to be repeated in the future, i.e. they are ''reinforced''. GRM5 is involved in such incentive learning in the mouse (Novak et al., 2010).

Regardless of the signalling pathway involved, GRM5 is critically important for LTP via signalling through corticostriatal synapses on D1-MSNs (Gubellini et al., 2003; Schotanus and Chergui, 2008) and group-1 GRM-dependent long-term depression (LTD) in D2-MSN (Lüscher and Huber, 2010; Shen et al., 2008). Although the interactions in signalling downstream DA receptors are complex, many pathways converge on ERK. ERK thus couples extracellular signals with transcriptional changes and ultimately synaptic plasticity. Psychostimulants, used in treatment of ADHD, were shown to activate ERK specifically in D1-MSNs via D1, NMDA, and GRM5-dependent mechanism (Mao et al., 2005; Schotanus and Chergui, 2008; Valjent et al., 2005; Voulalas et al., 2005).

9. Role of GRM5 in goal-directed learning

Attention critically determines performance especially in goal-directed learning (Caron and Wightman, 2009). Goal-directed learning is a process of modifying behaviour in order to maximise the chance to obtain reward. Under normal circumstances a reward is coupled with the completion of pro-survival action, such as food intake. However, drugs of abuse have the potential to disrupt the system by delivering reward without accomplishment of a pro-survival task. The DA system is therefore essential for the assignment of motivational value to a goal by coding for difference between expected and received reward, i.e. ''reward-prediction error'' (Montague et al., 2004).

We have previously shown that GRM5 is involved in assignment of motivational values (Novak et al., 2010). Genetically modified mice lacking GRM5 specifically on DRD1-expressing neurons did not reinstate the drug seeking when drug-paired cues were presented. The phenotype was not caused by the inability of the drug to reinforce

consumption but by the failure to assign motivational value to a drug-paired cue. Thus, GRM5 seems to be important for shaping of attention and for successful completion of a task. Since ADHD patients have considerable difficulties in finishing tasks (one of the diagnostic criteria) GRM5 is likely to play a central role in ADHD aetiopathogenesis and may be a potential target of future treatment strategies of ADHD. Actually, evidence is accumulating that compounds modulating GRM5 have pro-cognitive effects, improve performance in various learning and memory tasks, including extinction, and reverse cognitive deficits by enhancing synaptic plasticity (Cleva and Olive, 2011; Conn et al., 2009; Olive et al., 2012).

Taken together, an increasing body of evidence suggests that GRM5 closely interacts with DA signalling and that this interaction plays a pivotal role in pathophysiology of ADHD. Despite the usefulness of the genome-wide approaches as an unbiased source of discovery, as it has been proven with the identification of deletions of *GRM5*, they are merely the first step on the way to the understanding of the aetiopathogenesis of ADHD. Further research is a desiderate to understand the behavioural, biochemical and electrophysiological consequences of the loss-of-function associated with *GRM5* deletion, to assign a precise role of GRM5 in the pathophysiological processes in ADHD, and finally attribute those processes to the behavioural impairments observed in ADHD patients. Since GRM5 is expressed in both D1- and D2-MSN and mediates the induction of some forms of synaptic plasticity in both subpopulations, it is predicted that dissection of the molecular mechanism of GRM5–DA system interaction impinging on the two GABA neuron populations will contribute to elucidation of ADHD pathophysiology.

10. Conclusion and outlook

Pertinent genome-wide analyses for ADHD risk gene revealed synaptic adhesion molecule, receptors for GLU and mediators of intracellular signalling pathways. These genes encode principal components of the molecular machinery that connects pre- and postsynaptic neurons, facilitates glutamatergic transmission, controls synaptic plasticity and empowers intersecting neural circuits to process and refine information. Regular brain function is contingent on structured patterns of connections between neurons of distinct specification. The formation of this connectivity entails the targeting of axons to dendrites of demarcated circuits, the recognition of individual target neurons, the formation of synapses on precise regions of the dendritic tree, and the differentiation of pre- and postsynaptic specialisations. The identification of genetic variation affecting a remarkable number of molecules essential for the formation, specification and function of excitatory synapses is refocussing research efforts on ADHD pathogenesis to include the long-neglected GLU system. These findings also suggest that the coordinated actions of a number of molecular signals contribute to the specification and differentiation of synaptic connections in the developing brain.

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Contributors

K.P.L., A.R. and M.N. developed the paper's concept, S.M. and M.N. performed analysis of the literature, and K.P.L., S.M., A.R. and M.N. wrote the review.

Conflict of interest

None of the authors has any potential conflict of interest or financial interests to disclosure.

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