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Abstract

The presence and severity of cognitive symptoms, including working memory, executive dysfunction and attentional impairment, contribute materially to functional impairment in schizophrenia. Cognitive symptoms have proven resistant to both first- and second-generation antipsychotic drugs. Efforts to develop a consensus set of cognitive domains that are both disrupted in schizophrenia and are amenable to
cross-species validation (e.g. the NIMH CNTRICS and RDoC initiatives) are an important step towards standardisation of outcome measures that can be used in preclinical testing of new drugs. While causative genetic mutations have not been identified, new technologies have identified novel genes as well as hitherto candidate genes previously implicated in the pathophysiology of schizophrenia and/or mechanisms of antipsychotic efficacy. This review comprises a selective summary of these developments, particularly phenotypic data arising from preclinical genetic models for cognitive dysfunction in schizophrenia, with the aim of indicating potential new directions for pro-cognitive therapeutics.

**Abbreviations**

AChE, acetylcholinesterase; βArr, β-arrestin; CamK, Ca2+/calmodulin-dependent protein kinase; cAMP, cyclic adenosine monophosphate; CHRNA7, α7 nicotinic acetylcholine receptor gene; CNTRICS, Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia; CNV, copy number variation; COMT, catechol-O-methyltransferase; D1R, dopamine D1 receptor; D2R, dopamine D2 receptor; DA, dopamine; DAAO, d-amino acid oxidase; DAO, diamine oxidase; DAOA, D-amino acid oxidase activator; DARPP-32, dopamine- and cAMP-regulated neuronal phosphoprotein; DISC1, disrupted in schizophrenia 1; DLPFC, dorsolateral prefrontal cortex; DNMP, delayed non-match-to-position; DNA, deoxyribonucleic acid; DTNBP1, dystrobrevin-binding protein 1 gene; EGF, epidermal growth factor; ErbB4, erb-B2 receptor tyrosine kinase 4; GlyT1, glycine transporter 1; GSK-3, glycogen synthase kinase 3; GWAS, genome-wide association studies; IGF2, insulin growth factor-2; KO, knockout; mAChR, muscarinic acetylcholine receptor; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; mGluR, metabotropic glutamate receptor; MHC, major histocompatibility complex; MMSE, mini-mental status examination; mPFC, medical prefrontal cortex; nAChR, nicotinic acetylcholine receptor; NIMH, National Institute of Mental Health; NMDAR, N-methyl-D-aspartate receptor; NRG1, neuregulin-1; PAM, positive allosteric modulator; PCP, phencyclidine; PDE, phosphodiesterase; PFC, prefrontal cortex; PI3K, phosphoinositide 3-kinase; PIP3, phosphatidyl-inositol,3,4,5 triphosphate; PRODH, proline dehydrogenase; PV, parvalbumin; RDoC, research domain criteria; SREBP, sterol regulatory element binding protein; SNP, single nucleotide polymorphism; WT, wildtype; ZDHHC8, zinc finger DHHC domain containing 8.
Introduction

Schizophrenia is a psychiatric disorder that is associated with impairment across several domains of early information processing and cognition (Waddington et al., 2012; Howes & Murray, 2014). Cognitive deficits are considered a core feature of schizophrenia; 90% of patients with schizophrenia have deficits in at least one cognitive domain, including working memory, attention, processing speed, reasoning and problem solving, social cognition, visual learning and memory, and verbal learning and memory (Carpenter, 2011). Despite considerable heterogeneity in terms of cognitive deficits in schizophrenia (Weinberg et al., 2016), these deficits often precede the emergence of psychotic symptoms and their severity at the early stage of illness represents a significant prognostic indicator of clinical course and functional outcomes (Green, 2006). The presence of cognitive deficits has also been linked reliably with poorer treatment adherence and higher rates of relapse in first-episode psychosis (Meyer et al., 2011). Conversely, improved cognitive performance has been associated with higher employment rates, more independent living and better psychosocial status (Barch & Ceaser, 2012).

Despite a relatively low prevalence (estimated by the European Burden of Disease Report to have a point prevalence of 0.25-0.56%), schizophrenia represents a significant healthcare burden across Europe (Chong et al., 2016). Current estimates of the cost of schizophrenia in high income European countries have indicated the average societal costs per individual to be between USD 63000 and USD 106000 per year (Evensen et al., 2016). Existing antipsychotic medications are only partially effective towards the clinical symptoms of the disease such as hallucinations and delusions, with approximately one third of patients experiencing little or no benefit (Stroup et al., 2016). However, current pharmacotherapeutic strategies do not effectively treat the cognitive deficits of schizophrenia (Karam et al., 2010; Pratt et al., 2012; Dunlop & Brandon, 2015), highlighting the urgent need for development of pro-cognitive therapies.

With respect to the pathogenesis of the disorder, schizophrenia remains 'the big enigma of psychiatry' (Pull et al, 1981), presenting many challenges in terms of translating etiopathological bases into strategies for improving the effectiveness of treatment.

Significant obstacles to developing effective and novel cognitive enhancing therapies have included lack of clarity regarding the neural circuitry and molecular/cellular changes underlying cognitive dysfunction.
in schizophrenia (Tandon et al., 2009; Harrison et al., 2012; Cope et al., 2015). Recent technological advances and the emergence of a “neurogenetics” approach, which seeks to investigate mechanistic links between molecular/cellular changes, alterations in brain structure and function, and expression of schizophrenia endophenotypes, is a conceptual advance in the search for new therapeutic targets for improving cognition (Bogdan et al., 2013). A further obstacle is the lack of standardised measures for cognition in schizophrenia. During the past decade, NIMH-funded initiatives such as the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and the follow-up CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) programmes have sought to provide valid, reliable, and translationally amenable measures for evaluating cognitive function in schizophrenia (Nuechterlein et al., 2004, 2008; Green et al., 2008; Kern et al., 2008; Young et al., 2009). MATRICS identified the following seven areas of impairment: attention/vigilance; working memory; reasoning and problem solving; processing speed; visual learning and memory; verbal learning and memory; social cognition. The subsequent CNTRICS program was established with a view to operationalise a small number of treatment-relevant cognitive domains that were also amenable to translational modelling using analogous cross-species paradigms (see Table 1; Carter & Barch, 2007; Cohen & Insel, 2008; Moore et al., 2013).

More recently, the NIMH has introduced the Research Domain Criteria (RDoC) project, which represents an attempt to move away from broad, symptom-based diagnostic categories that capture a heterogeneous range of behaviours, and to focus instead on dimensional and more standardised intermediate phenotypes, often referred to as endophenotypes. Endophenotypes are best defined as intermediate, quantifiable phenotypes which link biology to phenotype. To be considered an endophenotype, candidate traits or biological markers are required to be heritable, stable, associated with the relevant illness, and observed at a higher rate in affected and unaffected relatives compared to the general population (Gottesman & Gould 2003; Glahn et al., 2014). A typically cited example that meets each of these criteria is N100 evoked potential amplitude and gating abnormalities (Turetsky et al., 2008). However, it should be noted that the concept and supposed clinical utility of endophenotypes has recently been criticised on the basis of underestimation of the multifarious genetic architecture of candidate endophenotypes, ranging from relatively complex psychophysiological phenomena (e.g. P300 event-related potentials) to variables presumed to have a relatively straightforward and well-characterised circuitry, such as acoustic startle (Iacono et al., 2014, 2017).

The RDoC framework focuses on specific high-level functional domains (negative valence systems, positive valence systems, cognitive systems, systems for social processes, arousal/regulatory systems), which consist of various constructs and sub-constructs. These constructs can be interrogated using an array of empirical “units” of analysis (i.e. genes, molecules, circuits, behaviours, paradigms, etc.). With respect to the “cognitive systems” functional domain, the following constructs are included: attention, perception, working memory, declarative memory, language behaviour, and cognitive control. For each of these constructs, sub-constructs have also been described, e.g. working memory comprises the following four sub-constructs: active maintenance, flexible updating, limited capacity, interference control. Recent reviews have examined the heuristic value of the RDoC framework relative to traditional diagnostic
classification systems in relation to preclinical modelling of schizophrenia-related cognitive dysfunction and other psychosis-relevant features (Cuthbert & Insel, 2013; Young et al., 2016; Cope et al., 2016). The RDoc approach has been criticised as being overly reliant on psychological constructs (Lieblich et al., 2015).

Genetic Risk Factors Associated with Schizophrenia

Though no diagnostic markers are known at this time, the pathobiology of schizophrenia appears to involve variable brain structural, functional and neurochemical alterations that are thought to have their basis in genetic abnormalities and gene-environment interactions that disrupt neurodevelopmental processes (Hall et al., 2015). Only a small proportion of these DNA variants have been identified so far and it is now clear that genetic susceptibility is the result of many common variants of low penetrance and/or rare variants of moderately high penetrance (For review, see McCarroll et al., 2014). Approaches to complex disease genetics have evolved from linkage studies to candidate association studies, genome-wide association studies (GWAS) and, currently, to exome or whole-genome sequencing. A review of candidate genes identified in prior meta-analyses examining the relationship between specific genes and several major neuropsychiatric disorders, including schizophrenia, revealed that, out of 97 variants reported in schizophrenia, the strongest evidence was reported for genes involved in the modulation of dopamine (e.g., COMT, dopamine D2 receptor (D2R), glutamate (e.g., DAOA, NRG1), neuronal development and function (e.g. AHI1, MTHFR, RELN and TRKA), serotonergic function (HTR2A, SLC6A4 and TPH1) or the immune system (IL1B) (Gatt et al., 2015). The largest investigation on schizophrenia to date is a multi-stage genome-wide association study (GWAS) of up to 36989 cases and 113075 controls; this study identified 128 associations in 108 independent loci, with the strongest associated locus being an extended region of chromosome 6 containing a large number of genes that includes the MHC region (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Within the schizophrenia-associated loci were already known candidate genes such as the D2R and several genes involved in glutamatergic neurotransmission (GRM3, GRIN2A, SRR and GRIA1) reached genome-wide significance. These provide support for well-characterised gene products of therapeutic relevance to schizophrenia, and sustain leading pathophysiological hypotheses of the disorder (Morris & Pratt, 2014; Howes et al., 2017). In a recent whole-exome sequencing effort involving over 11000 cases and controls from Sweden, an excess of rare coding mutations was reported in schizophrenia, with most of these attributable to genes that are plausibly implicated in synaptic function (Genovese et al., 2016).

An issue arising from the failure of existing GWAS analyses to support previous candidate genes (e.g. NRG1, DISC1) is whether this genomic evidence is sufficiently robust to exclude such genes from further investigation, despite continually robust meta-analytic data in terms of individual genes (e.g. NRG1, Mostaid et al., 2017), or whether biological plausibility should be taken into account when evaluating the potential of a gene target to inform on the biological basis of schizophrenia and/or antipsychotic drug discovery (e.g. Porteous et al., 2014; Farrell et al, 2015; Harrison, 2015). In the context of drug discovery, important considerations include whether the gene target implicated is already associated with a known biochemical pathway implicated in schizophrenia, as well as immediate therapeutic tractability where
genes encoding receptors, ion channels, etc. are more attractive targets than non-protein encoding genes, genes of unknown function, or genes which are predominantly expressed and implicated in early brain development (Harrison, 2015).

**Translational Modelling of Cognitive Deficits of Schizophrenia**

Several reviews have focused on the utility and limitations of existing preclinical models of cognitive dysfunction in schizophrenia (e.g. Moore et al., 2013; Kaiser & Feng, 2016), and several problems in the field have been cited. Firstly, the absence of suitable rodent analogues of human cognitive measures (Young et al., 2009), although the development of the CNTRICS and, to a lesser extent, RDoC framework represent an opportunity to focus phenotypic efforts on cross-species, translationally relevant measure of cognition (Moore et al., 2013; Cope et al., 2015). Secondly, existing animal model research has been criticised due to an over-emphasis on behavioural endpoints, such that increased characterisation is required of accompanying molecular and neural circuit mechanisms (Pratt et al., 2012; Kaiser & Feng, 2016). Additionally, where modelling efforts have focused on specific cognitive endophenotypes (e.g. working memory), characterisation of additional cognitive and non-cognitive domains that might impact on such endophenotypic measures is often neglected (Cope et al., 2015). Broader characterisation of the effects of a given etiological manipulation (e.g. genetic knockout (KO) or neurodevelopmental insult) is necessary to fully validate the relationship between the experimental manipulation and the resultant cognitive phenotype.

Based on current understanding of the molecular genetics of schizophrenia, but deriving primarily from candidate gene association studies, preclinical genetic models of schizophrenia offer the possibility to increase our understanding of how primary biological deficits are translated into clinically-relevant cognitive endophenotypes. Phenotypic characterisation of such in vivo models can help to define the function of genes consistently implicated in cognitive dysfunction and/or of broader etiopathogenetic interest in a schizophrenia context, with a view to identification and development of new etiologically based treatments. The present review focuses on the expression of schizophrenia-related cognitive endophenotypes in animal models for selected genes either directly associated with increased risk for schizophrenia, or candidate genes involved in neurotransmitter signalling systems implicated in schizophrenia.

A number of limitations have been commonly cited in relation to constitutive and conditional genetic models of schizophrenia. While there is important information to be gained from investigating the effects on cognition of partial or complete loss of gene function, such models do not mimic mutation in the same genes observed in schizophrenia patients (Harrison, 2015; Moran et al., 2016). Other challenges include lack of specificity with respect to potential multiple isoforms generated from a single gene (e.g. neuregulin-1 [NRG1]) (Kleinman et al., 2011), lack of control regarding the temporal/spatial expression of the target gene when using constitutive models (Siuta et al., 2010), and the influence of genetic background as a modifier of gene-phenotype relationships (Moran et al., 2016). Additionally, for many of the models discussed, the molecular specificity of the genetic manipulation is not systematically
examined, notably whether it specifically targets the gene of interest, or also alters the function of other genes, particularly neighbouring genes.

**Glutamatergic Neurotransmission**

The glutamatergic neurotransmitter system has been widely studied in relation to schizophrenia due to its excitatory properties in network functions throughout the brain, particularly in the cortex, and its putative role in the expression of psychotic and cognitive symptoms (Egerton & Stone, 2012; Falkenberg et al., 2014). Phencyclidine (PCP), an NMDA receptor antagonist, induces schizophrenia-like cognitive dysfunction and psychoses by blocking NMDA receptor-mediated transmission, and has been frequently used to model aspects of the disease in rodents (Rafter et al., 2016; Reynolds & Neill, 2016). In particular, the well-validated subchronic PCP administration procedure has been shown to produce deficits across several CNTRICS-implicated cognitive processes (see Young et al., 2012). Additionally, cortical hypoglutamatergia has been linked mechanistically with impaired activity of parvalbumin (PV)-containing interneurons, manifesting in altered gamma oscillations in the dorsolateral prefrontal cortex (DLPFC) and the emergence of schizophrenia-like cognitive dysfunction (Gonzalez-Burgos & Lewis, 2012). Many studies have focused on testing a number of glutamate receptor-based modulators as novel drugs for schizophrenia; these agents include glycine agonists, glycine transporter 1 (GlyT1) inhibitors, and metabotropic glutamate receptor agonists. Memantine, a non-competitive NMDAR antagonist, has also recently been investigated as a potential add-on therapy for cognitive impairment in schizophrenia.

The predominant pharmacological mechanism of memantine is as a non-competitive NMDAR antagonist acting through blockade of the NMDAR channel. Memantine is classed as an ‘open channel blocker’, as it can enter the channel and block current flow only after channel opening (Johnson & Kotermanski, 2008). It binds the same site as magnesium, which is suggested to differentiate it from other channel blockers such as ketamine and phencyclidine that produce psychosis-mimicking effects. Studies investigating memantine as an add-on treatment for schizophrenia, while finding small effects on negative symptoms, showed no effect on cognition (Krivoy et al, 2008; Lee et al, 2012). However, these studies have been criticised as underpowered and using only the most rudimentary cognitive assessment measures such as the Mini-Mental State Examination. Recently, Veerman et al (2016) showed that when assessed using the more comprehensive cognitive test battery CANTAB, add-on memantine therapy improved verbal and visual memory in clozapine-refractory patients.

**Glycine**

Glycine acts a co-agonist to facilitate NMDA-mediated transmission; therefore, glycine agonists promote NMDA-mediated transmission (Nong et al., 2003). A mutant line carrying a point mutation in the NMDAR glycine binding site showed abnormalities in spatial learning and memory (Ballard et al. 2002; Labrie et al., 2008). Forebrain GlyT1 deletion has been associated with enhancement of associative learning (Yee et al., 2006), object recognition memory (Singer et al., 2007), selective attention as measured by latent inhibition (Yee et al., 2006) and reversal learning in a water maze task (Singer et al., 2009); no effect of the mutation was observed on spatial working memory (Singer et al., 2009). Sarcosine,
a GlyT1 inhibitor, and sodium benzoate, a d-amino acid oxidase (DAAO) inhibitor, can both enhance NMDA receptor-mediated neurotransmission; co-administration of both agents, but not sarcosine alone, improved the cognitive and global functioning of patients with schizophrenia, even when clinical symptoms had not improved (Lin et al., 2015). While recent clinical trials of bitopertin, a non-competitive GlyT1 inhibitor that enhances NMDA receptor function, as an adjunct to antipsychotics, failed to indicate efficacy in treating clinical symptoms, cognition was not specifically assessed (Bugarski-Kirola et al., 2016, 2017).

D-Serine is another selective endogenous activator of signalling at the NMDAR. Mutants unable to produce D-serine due to disruption of its synthetic enzyme serine racemase demonstrate spatial learning deficits (Basu et al., 2009) and disrupted episodic memory performance in an object recognition paradigm, while other aspects of task performance which measured novelty detection, recognition memory and relational memory were intact (DeVito et al., 2010); these deficits were accompanied by dendritic morphological abnormalities of pyramidal neurons in the medial prefrontal cortex (mPFC). A mouse strain lacking d-amino acid oxidase (DAO; an enzyme involved in metabolism of D-serine) demonstrated increased NMDAR transmission that was accompanied by improved spatial and non-spatial short-term memory (Pritchett et al., 2015), but no changes in spatial learning (Labrie et al., 2009) or long-term spatial memory in the Morris water maze, appetitive Y-maze task, and aversive Y-maze swim-escape task (Pritchett et al., 2016). In addition, exogenous D-serine and DAO inhibitors each improve object recognition memory performance in rodents (Bado et al., 2011; Hopkins et al., 2013). However, Weiser et al. (2012) reported low-dose D-serine as an adjunct to antipsychotics to be ineffective for negative symptoms or cognitive impairment in schizophrenia; other studies have suggested that although higher-dose D-serine may provide additional opportunities to investigate pro-cognitive effects in schizophrenia, nephrotoxicity is an issue for concern (Lin et al., 2016).

Mice heterozygous for the \textit{SP4} (a member of the SP1 family of transcription factors) gene evidence a reduction in expression of the NMDAR NR1 subunit and a pattern of selective cognitive deficits has been observed in this mutant line: specifically, they demonstrate selective spatial learning and long-term memory deficits in the Barnes maze, in the absence of any changes in short-term memory as measured in the spontaneous alternation task (Zhou et al., 2010); \textit{SP4} mutants also demonstrate impaired sustained attentional performance in the 5-choice continuous performance test that was reversed by treatment with a GlyT1 inhibitor (Young et al., 2015).

\textit{Metabotropic glutamate receptors}

Metabotropic glutamate receptor (mGluR) involvement in the pathophysiology of schizophrenia has been extensively reviewed (Krivoy et al., 2008). \textit{mGluR3} KO mice show working memory deficits (Fujioka et al., 2014), and mGluR2/3 agonists have demonstrated pro-cognitive effects in animal models of schizophrenia (Woolley et al., 2008; Schlumberger et al., 2009). While an early clinical trial of the mGluR2/3 agonist pomaglumetad methionil in schizophrenia was promising (Patil et al., 2007), subsequent studies have failed to replicate efficacy in treating the clinical symptoms of schizophrenia.
Dopaminergic Neurotransmission

The prevailing dopamine (DA) hypothesis posits that subcortical (striatal) hyperdopaminergia through D2Rs contributes to the expression of positive, psychotic symptoms, and cortical (frontal) hypodopaminergia, particularly through DA D1 receptors (D1Rs), contributes to the development of negative symptoms and cognitive deficits (Howes et al., 2017; Weinstein et al., 2017). Working memory and executive function, both known to be impaired in schizophrenia, are underpinned by D1R activation in the prefrontal cortex (PFC) (Seamans & Yang, 2004). Mice with constitutive KO of the D1R gene show deficits in spatial working memory and reversal learning (Holmes et al., 2004; El-Ghundi et al., 2007). Additionally, low dose D1R agonist treatment can enhance performance on PFC-mediated working memory, although higher doses of D1R agonists impair this function, confirming an inverted-U shaped relationship between cortical D1 activation and cognitive performance in non-human primates (Vijayraghavan et al., 2007). Studies in animals have employed a range of D1R agonists and have identified GSK-3β as an interacting protein for regulating D1R function in PFC (Wang et al., 2017). In contrast, clinical studies have been restricted to studies with dihydrexidine, an agonist that shows both limited selectivity for D1R over D2R and problematic pharmacokinetics but may improve schizophrenia-spectrum working memory deficits (Rosell et al., 2015); clinical studies with more appropriate agonists are required. Recent preclinical studies have focused on the development of D1R positive allosteric modulators (PAM) that would enhance the actions of endogenous DA at D1R; such functionally selective D1R PAMs may be an important route to more selective actions in vivo that also avoid central and peripherally-mediated adverse effects such as seizures (Lewis et al., 2015; Svensson et al., 2017).

Antipsychotic efficacy is associated with antagonism of D2Rs, which activate multiple signalling pathways via G protein-dependent and -independent mechanisms. Antipsychotics can block D2Rs and increase cAMP production by removing the tonic inhibition exerted by Gi/o proteins on adenylyl cyclase activity, thereby increasing cAMP levels, activating PKA and increasing PKA-dependent phosphorylation of DARPP-32 (dopamine- and cAMP regulated phosphoprotein of molecular weight 32000) (Beaulieu et al, 2005). G protein-independent signaling is mediated through β-arrestin (βArr), and the latter signalling complex has revealed putative novel avenues for pharmacologically targeting D2Rs for antipsychotic therapies (Urs et al., 2012, 2017). In a recent report, Urs et al. (2017) examined the ability of aripiprazole (a partial agonist at both D2R-mediated Gαi and βarr2 pathways) and partial agonists at βarr2 (UNC9975 & UNC9994) to reverse the psychomotor effects of amphetamine or PCP administration in mice with region-specific (PFC and/or striatum) genetic deletion of βarr2. In the amphetamine model, UNC9994, but not aripiprazole, lost its antipsychotic-like activity (i.e. reversal of amphetamine/PCP effects) when βarr2 was deleted in striatal D2R-expressing neurons, suggesting that striatal D2R-βarr2 antagonism is
sufficient for antipsychotic-like activity. However, UNC9994 lost its activity in the PCP model only when βarr2 was simultaneously deleted in both cortical and striatal D2R neurons, while aripiprazole remained active. This finding suggests a cortical and striatal role for βarr2 in antipsychotic-like activity. Furthermore, local PFC injection of UNC9994, but not aripiprazole, inhibited PCP-induced locomotion in a GRK2-dependent manner, suggesting that D2R-βarr2-biased partial agonism in the PFC is sufficient to reverse the behavioural effects of PCP. Importantly, in mice hypomorphic for the NR1 subunit of the NMDA receptor, Park et al. (2016) examined the effects of the two D2R βArr-biased ligands UNC9975 and UNC9994 on a variety of schizophrenia-related phenotypes, including cognitive performance. It was shown that βArr-targeted compounds ameliorated object recognition memory and sensorimotor gating deficits in the NR1 knockdown model, while eliciting a lower level of catalepsy than haloperidol. The authors suggested that the availability of functionally selective D2R ligands which might target β-arrestin-mediated signalling provides the possibility to develop drugs characterised by fewer motoric side effects and possibly improved efficacy against the cognitive symptoms of schizophrenia.

Cholinergic Neurotransmission

Central muscarinic acetylcholine receptor (mAChR) and nicotinic acetylcholine receptor (nAChR) function have been implicated in cognitive dysfunction observed in schizophrenia, and have been investigated in relation to pro-cognitive therapeutic potential (Jones et al., 2012; Dunlop & Brandon, 2015).

Disturbance in M1 mAChR (muscarinic receptor 1) function has been associated with cognitive deficits in schizophrenia, and a reduction in M1 mAChR expression has been documented in various brain regions of patients with the disorder. Additionally, mAChR agonists improve cognitive function in healthy individuals and schizophrenia patients (Harris et al., 2004; Shekhar et al., 2008), and the M1 receptor is involved in regulation of PFC function (Anagnostaras et al., 2003; Shirey et al., 2009). Mice with KO of the M1 receptor gene have shown deficits in some nonmatching-to-sample tasks requiring hippocampal–cortical interactions (Anagnostaras et al., 2002) but not in matching-to-sample tasks purported to be (Miyakawa et al., 2001). More recently, employing a touchscreen visual pairwise discrimination task requiring top-down processing, M1 KO demonstrated deficits in discrimination learning and acquisition (Gould et al., 2015). In contrast, previous evaluation of M1 KO mice in touchscreen-based assessments of attention, learning, and behavioural flexibility, including a pairwise discrimination task, revealed no prominent deficits (Bartko et al., 2011). In patients with schizophrenia, while M1/M4 mAChR agonists have been investigated for antipsychotic efficacy as well as cognitive improvement, effects have been modest and, due to their non-selectivity, have produced adverse peripherally-mediated effects (Shekhar et al., 2008).

A number of studies have reported on the pro-cognitive therapeutic potential of selective M1 PAMs which enhance the efficacy and/or affinity of the endogenous neurotransmitter ACh at the M1 mAChR (Grannan et al., 2016). Ghoshal et al (2016) demonstrated that systemic administration of the M1 PAM VU0453595 reversed deficits in novel object recognition memory induced by chronic PCP administration, and the M1
PAM VU6004256 reversed performance deficits in novel object recognition memory and cue-mediated fear conditioning tasks in the NMDA NR1 genetic knockdown model (Grannan et al., 2016). These preclinical studies suggest that selective M1 PAMs may provide a promising avenue for reducing cognitive deficits in schizophrenia.

The chromosomal region 15q13-q14, which includes the $\alpha$7 nicotinic acetylcholine receptor gene \textit{CHRNA7}, has been associated with increased risk for schizophrenia. A reduction in \textit{CHRNA7} mRNA expression has been reported in post mortem brain tissue samples from patients with schizophrenia (Mexal et al., 2010; Kunii et al., 2015). The emergence of the $\alpha$7-nicotinic acetylcholine receptor as a possible new therapeutic target for cognitive dysfunction in schizophrenia has been recently reviewed elsewhere (Freedman, 2014). Detailed behavioural characterisation of \textit{Chrna7} knockout mice has demonstrated impairment in working memory and sustained attention (Fernandes et al., 2006; Hoyle et al., 2006; Young et al., 2007, 2011).

Clinical trials examining the pro-cognitive properties of nAChR agonists in schizophrenia, consisting primarily of pilot studies, have produced inconsistent results. A recent randomized, placebo-controlled trial in 21 patients on stable antipsychotic treatment indicated that a nAChR agonist, EVP-6124, was associated with improvement in non-verbal learning, memory and executive function (Prickaerts et al, 2012). However, other studies of $\alpha$7 nicotinic agonists failed to show any benefit on either cognitive deficits or negative symptoms (Preskorn et al., 2014; Walling et al., 2016). PAMs with selectivity for $\alpha$7 nAChRs have been proposed as an alternative therapeutic strategy to orthosteric activation of these receptors, which might avoid producing unwanted side effects (Dunlop & Brandon, 2015; Marie et al., 2016).

Acetylcholinesterase (AChE) inhibitors such as donepezil, rivastigmine and galantamine are prescribed for cognitive impairment in Alzheimer’s Disease, and have also been evaluated in schizophrenia (Singh et al., 2012). Donepezil is a long-acting and reversible AChE inhibitor. Galantamine, in addition to acting on AChE, is an allosteric modulator of the nicotinic receptor response. There is some support for improved cognition with these drugs, particularly in attention and verbal and visual memory (Ribeiz et al., 2010; Singh et al., 2012). However, this conclusion is tempered by the observation that many of these clinical trials are of short duration and with small sample sizes (Singh et al., 2012). There are additional complications due to potential interactions with high levels of smoking in schizophrenia, as well as anticholinergic effects of some antipsychotic drugs (Sarter et al., 2012). There is a need for larger-scale trials to draw strong conclusions about the efficacy of AChE inhibitors for cognitive impairment in schizophrenia.

\textbf{Mutant Models of Candidate Risk Genes for Schizophrenia}

\textit{Dysbindin-1}

Many studies have demonstrated an association between variation in the dystrobrevin-binding protein 1 gene (\textit{DTNBP1}, which encodes dysbindin-1) and neurocognitive deficits in schizophrenia and healthy
control participants (Burdick et al., 2006; Stefanis et al., 2007; Allen et al., 2008; Zai et al., 2016). Recent findings have additionally suggested that DTNBP1 may have an epistatic interaction with COMT in the functionality of PFC and PFC-dependent cognitive performance (Papaleo et al., 2014). Reduction of dysbindin-1 expression (where the three gene isoforms consist of dysbindin-1A, -1B, and -1C) has been reported in the hippocampus (Talbot et al., 2004, 2011; Weickert et al., 2008) and DLPFC (Weickert et al., 2004; Tang et al., 2009) of patients with schizophrenia. A recent analysis of DTNBP1 promoter DNA methylation using saliva and post-mortem brain samples revealed DNA hypermethylation of the DTNBP1 promoter in the saliva of patients with schizophrenia, particularly in drug-naïve patients, and a trend toward hypermethylation in their first-degree relatives versus controls (Abdolmaleky et al., 2015). Importantly, antipsychotic treatment was associated with normalisation of these epigenetic alterations.

Phenotypic studies conducted in mice mutant for dysbindin-1 have revealed cognitive deficits, particularly in the domain of working memory, relative to wildtype (WT) controls, although the expression and/or magnitude of these deficits varies depending on genetic background (Takao et al., 2008; Papaleo et al., 2010; Petit et al., 2016). In sdy mutants (containing a deletion mutation in the gene encoding dysbindin-1) on a DBA background, male homozygous mice demonstrated deficits in long-term memory (assessed in the Barnes maze), as well as spatial working memory (T-maze, forced alternation task), in the absence of any genotypic differences across non-cognitive domains. Another study using the same mutant model demonstrated a gene-dosage reduction in working memory performance, as measured by the delayed non-match-to-position measure of spatial working memory; these deficits were accompanied by a reduction in glutamatergic transmission, at least in the PFC (Jentsch et al., 2009).

Other studies have examined cognitive function in sdy/DBA mice backcrossed to a C57BL/6J background. Papaleo and colleagues (2010) reported no differences in reference memory, faster acquisition of a working memory task (T-maze) but overall poorer performance on the same test under more challenging (proactive interference) or more stressful (transfer in a new cage) conditions. The same authors then evaluated D2R modulation of the dysbindin-1-working memory relationship, revealing that selected effects of DTNBP1 KO on working memory were associated with changes in cortical activity and CaMK components of the mPFC and were induced via upregulation of D2R. In a subsequent study, the same authors demonstrated that dysbindin-1 mutants exhibited impaired performance in a reward-based operant task, which they attributed to increased compulsive and impulsive behaviour (Carr et al., 2012).

Consistent with the earlier report linking cognitive deficits observed in sdy mice with cortical hypoglutamatergic function, a gene-dosage effect of DTNBP1 KO was associated with a decrease in working memory performance (delayed non-match-to-position test, DNMP) compared to controls; these deficits were correlated with degree of NR1 mRNA expression in the PFC (Karlsgodt et al., 2011). In a more recent study examining the effect of selective deletion of the dysbindin-1A subtype on schizophrenia-related measures, no genotypic differences were observed during acquisition or during...
performance in a low-interference working memory task (DNMP procedure); however, in a high-interference variant of the DNMP procedure, male homozygous mutants demonstrated impairment in sensitivity to interference (Petit et al., 2017). Taken together, these data suggest working memory deficits in dysbindin-1 mutants; such deficits appear to vary depending on behavioural parameters and involve separate or combined effects of modification of D2R and glutamatergic processes (Papaleo & Weinberger, 2011). Other studies have linked reduced dysbindin-1 expression in schizophrenia with altered regulation of sterol regulatory element binding proteins (SREBPs), a family of proteins which regulate the expression of genes involved in the biosynthesis of fatty acids, cholesterol, triglycerides and phospholipids (Chen et al., 2006).

Neuregulin-1

Neuregulin-1 (NRG1) is a growth factor that binds to the ErbB family of tyrosine kinase transmembrane receptors, and whose pleiotropic role in neurodevelopmental processes extends to cell migration, synaptic development, and neuronal plasticity (Falls, 2003; Mei & Xiong, 2008; Iwakura & Nawa, 2013). Multiple promoter usage and abundant alternative splicing has produced several distinct isoforms of the NRG1 gene, which have been classified into a minimum of seven subtypes (types I-VI; Mei & Xiong, 2008). NRG1 is a schizophrenia susceptibility gene that has been linked with the pathogenesis of schizophrenia (Gong et al., 2009; Munafo et al., 2008; Mostaid et al., 2017). Post-mortem brain and serum-based analyses from schizophrenia cases have demonstrated both increased NRG1 signalling and up-regulation of specific NRG1/ErbB4 splice variants (Hahn et al., 2006; Chong et al., 2008; Hashimoto et al., 2006; Law et al., 2006, 2007), or decreased isoform-specific expression of NRG1 transcripts (Parlapani et al., 2010). Antipsychotic administration has been linked with altered NRG1/ErbB4 expression in both brain and serum in human and preclinical studies (Wang et al., 2008; Zhang et al., 2008; Pan et al., 2011), and NRG1-ErbB4 signalling has been implicated in several neurotransmitter pathways implicated in antipsychotic activity (Neddens et al, 2011). Specifically, NRG1 has been implicated in DAergic (Abe et al., 2009), glutamatergic (Hahn et al., 2006; Li et al., 2007) and GABAergic (Neddens & Buonanno, 2010) function. Recent work has identified a novel, genetically regulated signaling pathway that links NRG1-ErbB4 and the phosphoinositide 3-kinase (PI3K) subunit p110δ with risk for schizophrenia (Law et al., 2012). In human lymphoblasts, NRG1-mediated phosphatidyl-inositol,3,4,5 triphosphate [PIP3] signaling is predicted by ErbB4 genotype and p110δ levels and is impaired in patients with schizophrenia. In human brain, the same ErbB4 genotype again predicts increased PIK3CD expression (Law et al., 2012). By identifying a hitherto uncharacterised association between NRG1 signalling and PIK3CD in schizophrenia, these analyses have revealed a novel therapeutic target which is amenable to pharmacological targeting.
Several Nrg1 transgenic mouse lines have been used to study the impact of altered NRG1-ErbB4 signalling on schizophrenia-related cognitive endophenotypes, with phenotypic differences across the lines reflecting differences in gene targeting strategy and the truncation of different domains or exon location in the Nrg1 gene (O’Tuathaigh & Waddington, 2015). A number of research groups have employed a Nrg1 hypomorphic model involving heterozygous deletion of the transmembrane domain of the gene. Studies have demonstrated selected information processing, social cognitive, and affective phenotypes relevant to schizophrenia, as well as abnormalities across neurotransmitter systems associated with schizophrenia (DAergic, GABAergic, glutamatergic) (Moran et al., 2014; O’Tuathaigh & Waddington, 2015). Better characterised as a model of imbalanced NRG1-ErbB4 signalling rather than NRG1 down-regulation (Long et al., 2015), TM-domain Nrg1 mutants demonstrate intact spatial learning and working memory (O’Tuathaigh et al., 2007, 2017) and selective deficits in contextual fear conditioning, cued aversion, novel object recognition, and the temporal aspects of episodic memory (Duffy et al., 2010; O’Tuathaigh et al., 2017). Neonatal, peripheral administration of NRG1 Type 1 protein in mice has also been shown to produce adult deficits in sensorimotor gating and learned inattention tasks, and these were reversed by antipsychotic treatment during adulthood (Kato et al., 2011). A novel line of transmembrane-domain partial Nrg1 deletion showed a sex-specific (males only) deficit in object recognition memory, as well as in both contextual and cued fear learning (Pei et al., 2014); these cognitive deficits were reversed by chronic treatment with valproate, a mood stabiliser and anticonvulsant with actions that include potentiation of GABAergic function.

In a series of recent studies, a transgenic mouse model involving brain-specific over-expression of human NRG1-IV exhibited several deficits in information processing and cognitive function, including disrupted sensorimotor gating, temporal order discrimination, and object location memory (Papaleo et al., 2016). This pattern of cognitive deficits is consistent with cognitive endophenotypes previously associated with polymorphisms in NRG1 in human clinical and non-clinical populations (Hahn et al., 2006; Hall et al., 2006; Nicodemus et al., 2006), and is suggestive of disruption of PFC–hippocampal circuitry. NRG1-IV over-expressing mice also display increased expression of the PI3K subunit p110δ, previously linked with schizophrenia (Law et al., 2012). It was demonstrated that acute treatment with the p110δ inhibitor IC87114 reversed sensorimotor gating and temporal order discrimination deficits in NRG1-IV mutants, emphasising the putative value of targeting p110δ as a novel treatment for cognitive dysfunction in schizophrenia (Papaleo et al., 2016).

Expression of neuregulin-3 (NRG3), a specific ligand for ErbB4, has been shown to be elevated in PFC of patients with schizophrenia (Kao et al., 2010) and has been independently associated with PFC activation during working memory performance in healthy subjects (Tost et al., 2014). However, neonatal overexposure to the epidermal growth factor (EGF) domain of NRG3 (NRG3-EGF) was shown not to disrupt temporal order recency discrimination memory during adulthood in mice, which is in direct contrast with the effects of neonatal exposure to NRG1-EGF (Paterson & Law, 2014).
Disrupted in Schizophrenia (DISC1)

Disrupted in Schizophrenia 1 (DISC1) gene variation has been linked with increased risk for schizophrenia and other psychiatric disorders (Chubb et al., 2008; Johnstone et al., 2011) and has been implicated in cognitive function in both healthy individuals and patients with schizophrenia (Cannon et al., 2005; Hennah et al., 2005; Nicodemus et al., 2014). DISC1 involvement in neurodevelopment and schizophrenia appears to involve interaction with several proteins, including glycogen synthase kinase 3 (GSK-3), phosphodiesterase-4A (PDE4A), phosphodiesterase-4B (PDE4B), Fez1, NDEL1 and LIS1 (Duan et al., 2007; Chubb et al., 2008; Muir et al., 2008). Several mutant mouse models of DISC1 gene function have been shown to demonstrate deficits across various measures of working, short-term and recognition memory, as well as cognitive control (Koike et al., 2006; Clapcote et al., 2007; Kvajo et al., 2008; Li et al., 2007; Pletnikov et al., 2008; Johnson et al., 2013; Cui et al., 2016). Employing DISC1 mutant models, researchers have shown that pharmacological targeting of DISC1-GSK-3-PDE4 (Lipina et al., 2013) and DISC1-D2R (Su et al., 2014) interactions can reverse DISC1-related cognitive and other behavioural deficits. PDE inhibitors are undergoing clinical evaluation as a monotherapy and as adjunctive treatment for cognitive impairment in schizophrenia (e.g. Dunlop & Brandon, 2015; Li et al., 2016). Preclinical studies have demonstrated that PDE10A inhibitors as a class can have distinct characteristics, some of which may be preferentially associated with reversal of NMDAR antagonist-induced deficits in maze-based working memory tests, sustained/selective attention and attentional set-shifting in rodents (Suzuki et al., 2015; Shiraishi et al., 2016).

Mutant Models of Copy Number Variation in Schizophrenia

Studies of genomic copy number variation (CNV) has implicated a role for rare variants in the etiopathological basis of schizophrenia (CNV and Schizophrenia Working Groups of the Psychiatric Genomics Consortium, 2017). A higher rate of de novo CNVs has been reported in patients relative to controls (Xu et al., 2008; Kirov et al, 2012), and increased presence of rare chromosomal deletions and duplications in patients with schizophrenia vs. controls has also been reported (Walsh et al., 2008; International Schizophrenia Consortium, 2008). A recent genome-wide analysis of CNVs in a cohort of 21,094 patients and 20,227 controls, revealed that global enrichment of CNV burden was observed in patients with schizophrenia, and genome-wide significance was obtained for the following eight loci: 1q21.1, 2p16.3, 3q29, 7q11.2, 15q13.3, distal 16p11.2, proximal 16p11.2, and 22q11.2 (CNV and Schizophrenia Working Groups of the Psychiatric Genomics Consortium, 2017). With respect to common biological pathways, proteins that interact with the NMDA receptor complex and activity-regulated cytoskeleton-associated protein complex have been suggested to be of potential significance (Kirov et al., 2012; Fromer et al., 2014; CNV and Schizophrenia Working Groups of the Psychiatric Genomics Consortium, 2017).

Individuals carrying deletions at 22q11.2 show a 25-fold increase in risk for psychotic disorder (Jonas et al., 2014; Schneider et al., 2014). Mutant models carrying a multigene deletion across the 22q11.2 region
demonstrate deficits in working memory and social cognition and disruption of executive function processes, alongside cortical-hippocampal asynchrony, neuronal migratory defects, and disruption of cortical neurogenesis (Meechan et al., 2007, 2015; Stark et al., 2008; Sigurdsson et al., 2010; Piskorowski et al., 2016; however, see Simon et al., 2016). Tamura et al (2016) demonstrated that treatment with a GSK-3 inhibitor, SB-216763, between postnatal days 7-28 reversed deficits in spatial working memory and hippocampal-prefrontal connectivity in a mouse model carrying the full 22q11.2 microdeletion (Df(16)A+/-). GSK3 activity is modulated by insulin and Wnt signaling and it has been shown that intra-hippocampal injection of insulin-growth factor 2 (IGF2) reversed deficits in working memory in the Y-maze spontaneous alternation task in another full 22q11.2 model (Dgcr8+/) (Ouchi et al., 2013). Treatment with the GSK-3 antagonist Tideglusib to patients with Alzheimer’s Disease has been shown to produce at best only limited improvement in cognitive function (del Ser et al., 2013). However, as others have noted, the ubiquitous nature of these GSK-3 signaling pathways increases the risk for unwanted side effects in the absence of non-selective agents. This highlights the need for a more targeted understanding of how such pathways are affected in the brains of patients with schizophrenia (Schubert et al., 2014).

Analysis of mouse models for individual genes within the 22q11.2 region (i.e. catechol-O-methyltransferase [COMT], proline dehydrogenase [PRODH], zinc finger DHHC domain containing 8 [ZDHHC8]) have revealed genotype-dependent effects on cognitive performance. Mice with knockout of the COMT gene (which encodes an enzyme responsible for clearance of DA in the PFC) show sex-specific improvement in spatial working memory (Babovic et al. 2008; Papaleo et al. 2008), while mice with overexpression of a human COMT-Val polymorphism (where the Val carriers exhibit high COMT enzyme activity) exhibit deficits in attention, working memory and recognition memory (Papaleo et al., 2008). The indirect DA agonist amphetamine impaired recognition memory in controls but ameliorated recognition memory in COMT-Val transgenics, supporting the hypothesised inverted-U relationship between extent of PFC-mediated DAergic transmission and cognitive function (Papaleo et al., 2008; Tunbridge et al. 2006; Harrison, 2015). The clinical utility of existing COMT inhibitors for treating cognitive deficits of schizophrenia is restricted due to limited brain penetration and/or are characterised by acidity and polarity profiles that challenge their CNS drug development potential (Lerner et al., 2016). Partial deletion of PRODH in mice is associated with deficits in prepulse inhibition and cued / contextual learning, as well as increased sensitivity to the disruptive effects of the COMT inhibitor tolcapone on working memory in mice (Gogos et al., 1999; Paterlini et al., 2005). Mice containing KO of the ZDHHC8 gene demonstrate sensorimotor gating deficits and changes across behavioural measures related to positive symptoms, but no changes across cognitive measures (Mukai et al., 2004). A recent study demonstrated that haploinsufficiency of a 22q11.1-containing gene Mrpl40 was associated with spatial working memory deficits (as measured in the delayed non-matched-to-position task) and accompanying impairment in hippocampal synaptic plasticity (Devaraju et al., 2016).

Mice carrying a deletion of 1.2 Mb homologous to the 15q13.3 microdeletion have recently been generated, and initial phenotypic analyses suggest the presence of behavioural phenotypes which mimic features of autism spectrum disorder rather than schizophrenia, notably decreased social interactions and repetitive self-grooming behaviour (Kogan et al., 2015). They showed deficits in sensorimotor gating but
did not, however, demonstrate any working memory deficits in a Y-maze delayed spontaneous alternation task or long-term memory impairment in a contextual fear conditioning task.

An interesting recent approach investigating CNVs that shows promise for the future might be identification of commonalities between genes containing CNVs and genes involved in specific aspects of cognition. Clifton et al., (2017) investigated whether the top 5% genes expressed during specific stages of learning in animal experiments overlapped with genes containing CNVs from patients with schizophrenia vs. controls. This study showed significant overlap in genes associated specifically with the extinction portion of fear learning in a contextual conditioning task in rats. This approach if successful might improve biological and behavioural precision in the search for novel targets for cognition not only for schizophrenia but also in other disorders associated with cognitive deficits.

Discussion

It is recognised that the development of more effective drugs to address cognitive impairment and negative symptoms, which are currently refractory to existing antipsychotic therapies, must involve the development of more sophisticated and clinically meaningful animal models, as well as selection of cognitive test measures that are based on relevance and cross-species-validity rather than practical considerations such as ease of use. Considerable work has been undertaken on the selection of behavioural measures of cognitive performance with cross-species validity. Notably, the CNTRICS initiative has elaborated a number of tasks assessing cognitive domains that can be measured across species (Moore et al., 2013). These measures were selected in part on the basis of criteria associated with translational potential, including factors such as procedural parameters, reliability, and efficiency (Cope et al., 2016). However, despite efforts to devise tasks with cross-species equivalence, procedural differences arising from how animals vs. humans are tested mean that extensive validation is required prior to exploiting its heuristic potential in the context of schizophrenia research (Young & Markou, 2015). Additionally, as indicated elsewhere (O’Tuathaigh & Waddington, 2015; Cope et al., 2016), a phenotypic strategy that restricts its focus to the measure of interest (i.e. working memory, cognitive flexibility) may fail to detect the putative influence of one or more alternative domains (e.g. anxiety) which might also be impacted upon by the study manipulation. This issue emphasises the importance of implementing a phenotyping strategy which is broader in scope, allowing consideration of relative contribution of both the construct of interest and alternative domains to task performance.

To move the field forward, there is also a requirement for more detailed characterisation of animal models based on GWAS-identified targets, as well as molecules implicated in schizophrenia-associated pathophysiological mechanisms related to inflammation, oxidative stress and neuroprotection. Consistent with the RDoC emphasis on multi-tiered characterisation of higher-level behavioural domains associated with neuropsychiatric disorders, efforts to investigate the biological underpinnings associated with cognitive deficits following etiologically-relevant manipulations in animals are essential for rational development of novel antipsychotics for treating cognitive dysfunction in psychotic illness. Some of the processes considered in this review may, in time, reveal meaningful targets for such drug development.
Understanding the biological basis for the genetic association between GWAS-identified loci and schizophrenia, crucial to identifying therapeutic potential, is a challenging process due to a number of genetic considerations discussed elsewhere (e.g. Winchester et al., 2014; Harrison, 2015). GWAS analyses have strongly implicated hitherto-unknown targets including MIR137 (the gene encoding the microRNA miR-137) and the major histocompatibility complex (MHC) locus in schizophrenia (Harrison, 2015). A SNP in the MHC region, rs6904071, has been reported to be associated with delayed episodic memory in patients with schizophrenia (Walters et al., 2013). Genetic variation in MIR137 has been linked with performance in tests of working memory function in schizophrenia (Cosgrove et al., 2017). Initial characterisation of cognitive phenotypes in heterozygous Mir-137 KO mice (where the full homozygous KO is lethal) revealed no genotypic effect in a water maze-based measure of spatial memory.

A recent investigation on the overlap between GWAS-identified schizophrenia risk loci and gene targets of a set of antipsychotic medications demonstrated genetic overlap between pathogenesis of the disorder and mechanism of antipsychotic action (Ruderfer et al., 2016). Other recent analyses of GWAS data have sought to identify susceptibility genes encoding proteins that are the targets of approved drugs (Lencz & Malhotra, 2015). Such approaches to deriving more proximate clinical utility from GWAS data may help to better characterise “druggable” known pathways as well as identifying subsets of patients where their genetic information might provide guidance regarding a suitable treatment regimen.

Declaration of Competing Interests
None

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