New drug targets in psychiatry: Neurobiological considerations in the genomics era

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ABSTRACT

After a period of withdrawal, pharmaceutical companies have begun to reinvest in neuropsychiatric disorders, due to improvements in our understanding of these disorders, stimulated in part by genomic studies. However, translating this information into disease insights and ultimately into tractable therapeutic targets is a major challenge. Here we consider how different sources of information might be integrated to guide this process. We review how an understanding of neurobiology has been used to advance therapeutic candidates identified in the pre-genomic era, using catechol-O-methyltransferase (COMT) as an exemplar. We then contrast with ZNF804A, the first genome-wide significant schizophrenia gene, and draw on some of the lessons that these and other examples provide. We highlight that, at least in the short term, the translation of potential targets for which there is orthogonal neurobiological support is likely to be more straightforward and productive than that relying solely on genomic information. Although we focus here on information from genomic studies of schizophrenia, the points are broadly applicable across major psychiatric disorders and their symptoms.

There is a critical need for rationally designed treatments for psychiatric disorders, since current treatments do not work for all patients, do not treat all symptoms, and are associated with significant side effects (Millan et al., 2015). After a period of retreat from neuroscience, the pharmaceutical industry is beginning to reinvest in this area. The reasons for this re-engagement are multifaceted, but advances in our understanding of neurobiology and the genetic basis of psychiatric conditions are undoubtedly contributing factors (Millan et al., 2015). Furthermore, the field is increasingly moving to focus on specific neurobiological circuits and symptom domains rather than frank diagnostic categories (Millan et al., 2015), an approach that is consistent with evidence from both neurobiological and genomic evidence, as discussed further below. Here, we consider whether either neurobiological or genomic insights should be given primacy in the search for novel therapeutic targets (Abbott, 2008), using exemplars for these different domains.

1. Insights into schizophrenia from neurobiology and genomics

Neurobiological and genomic approaches have both contributed to our understanding of schizophrenia and its symptoms (Owen et al., 2016). Findings from molecular and neuropathological studies of post-mortem tissue (e.g. reductions in neuropil volume, synaptic markers and other changes in gene expression) contributed to the conceptualisation of schizophrenia as a neurodevelopmental disorder of the synapse (Frankle et al., 2003; Harrison and Weinberger, 2005). In turn, synaptic changes are proposed to lead to the dysfunction of cortical circuits observed in functional neuroimaging studies (Meyer-Lindenberg et al., 2001; Stephan et al., 2009) and thence the symptoms experienced by patients (Lewis, 2012).

Neurobiological studies have also provided significant insights into the neurochemical systems that are most affected in schizophrenia and how these changes relate to symptoms. Most prominently, both pharmacological and neuroimaging studies suggest that the positive symptoms of schizophrenia arise from excessive subcortical presynaptic dopamine transmission, the effects of which are reduced by antipsychotic drugs, which antagonise the dopamine D2 receptor (Howes and Kapur, 2009). This excessive subcortical dopamine drive is likely downstream of changes in cortical function, particularly reductions in cortical NMDA receptor-mediated glutamate signalling acting in concert with altered cortical dopamine and GABA function; these cortical changes are thought to underlie the cognitive impairments and negative
symptoms of schizophrenia (Kantrowitz and Javitt, 2010; Harrison and Weinberger, 2005). Taken together, findings from neurobiological studies suggest that changes in synaptic function, particularly within cortical glutamatergic neurons but likely affecting other neuronal populations too, lead to cortical microcircuit dysfunction that contributes to the cognitive and negative symptoms of schizophrenia. These cortical changes in turn may drive the excessive subcortical dopamine release that underlies the positive symptoms. However, although this schema is biologically plausible and consistent with the available evidence, hypotheses about the precise nature of synaptic dysfunction in schizophrenia, and how it relates to the symptoms observed in patients, are necessarily imprecise. Furthermore, disentangling causal factors from the effects of the disease process and/or medication, comorbidities, and other epiphenomena is extremely difficult. Against this backdrop, genomic findings are appealing since genes most likely represent causative factors and have the potential to provide a ‘hypothesis-free’ window into the biological basis of schizophrenia and its symptom domains, and thence to identification of more convincing – and less confounded - therapeutic targets than was hitherto possible.

Genetic factors significantly contribute to schizophrenia susceptibility: in the largest twin-based study, heritability estimates were close to 80% (Hilker et al., 2018). In the past decade hundreds of genomic loci with robust statistical associations with disease risk have been identified. The largest schizophrenia genome wide association study (GWAS) to date, involving ~67,000 cases and ~94,000 controls, identified 270 independent loci with significant disease associations (The Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2020). Although cumulatively, they have a notable impact (the odds ratios for the top vs. the bottom decile for the risk polymorphisms combined, 1.2, and most <1.1) (Ripke et al., 2014) and polygenic risk scores currently have little diagnostic or prognostic value (Landi et al., 2021). Furthermore, translating information from GWAS into biological insights is challenging, not least because it is typically unclear which gene(s) is relevant at a given locus, which is the causal variant, and what the functional effect of the variant is (Harrison, 2015). However, in silico pathway analyses of these data are consistent with the neurobiological evidence outlined above: GWAS loci are concentrated in genes expressed in specific neuronal subpopulations, and are enriched in genes involved in synaptic function, including ion channels, several glutamate receptors, and the dopamine D2 receptor gene (Hill and Bray, 2022).

While rare variants (including copy number variants [CNVs]) only modestly contribute to the overall heritability of schizophrenia, they have a relatively large effect size in the individuals in whom they occur (Singh et al., 2022). A number of specific CNVs show robust associations with schizophrenia, including a multi-gene deletion at the 22q11 locus (odds ratio ~68) and a single gene locus (NRXN1) at 2p16 loci (odds ratio ~10)(Marshall et al., 2017). Large-scale exome and genome sequencing is also beginning to identify deleterious rare coding mutations: a meta-analysis of the whole exomes of ~24 000 schizophrenia cases and ~97 000 controls identified ten genes with significant enrichment of such mutations (Singh et al., 2022). Notably, although more rare variants remain to be found, these findings show partial convergence with the GWAS data, including the enrichment for genes impacting on synaptic function, including glutamate receptors (Singh et al., 2022).

Findings from both neurobiological and genomic studies support the increasing focus on symptom domains rather than discrete diagnostic categories. Thus, there is significant overlap in GWAS-identified candidate risk genes between psychiatric illnesses, particularly between schizophrenia and bipolar disorder (Mullins et al., 2021; The Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2020). Similarly, some rare variants associated with schizophrenia are also associated with other neurodevelopmental conditions, including autism (Singh et al., 2022). These genomic commonalities are consistent with the many clinical and neurobiological features that cut across diagnostic boundaries, such as the presence of cognitive dysfunction in both schizophrenia and bipolar disorder (Harvey et al., 2010) and overlap in some (but not all) of their neuroimaging phenotypes (Birru et al., 2017).

Notably, the large sample sizes required by genomic studies means that cohorts collected for this purpose typically have minimal phenotypic information. This has precluded investigation of the genomic basis of symptom domains, since only case-control comparisons have been possible. This situation is changing with the advent of ‘big data’ approaches. For example, a number of consortia and projects are collecting detailed phenotype information (e.g. neuroimaging and cognitive measures, healthcare data), including genomic data, at scale, permitting genomic studies of non-clinical phenotypes (Miller et al., 2016; Nymberg et al., 2013; Strawbridge et al., 2018). These academic resources are complemented by data available to researchers via direct to consumer genetic testing companies, such as 23andMe (Howard et al., 2019). Nevertheless, genomic studies of non-clinical phenotypes remain in their infancy and are potentially confounded by the non-representative nature of many of the large-scale datasets available (Tutt, 2009). Of relevance here, this shows that most genomic data described here relates to the classical diagnostic categories, rather than specific symptom domains.

Thus, although genomic findings have emerged relatively recently, initial analyses show promising convergence with neurobiological observations. Both lines of evidence are consistent with the increasing therapeutic focus on symptom domains, rather than diagnostic criteria. As noted, genomic findings have the potential to provide an unbiased entry into the biology of psychiatric disorders. Nevertheless, it remains challenging to identify and advance specific novel putative targets amenable to manipulation in the adult brain (Mould et al., 2021). Here we consider the steps that are needed to achieve this and the information that can be gained from different sources, focusing on insights from neurobiology and genomics. We begin by providing an example of a rationally designed approach based on neurobiological understanding: the development of novel catechol-O-methyltransferase (COMT) inhibitors for cognitive dysfunction associated with psychiatric disorders.

### 2. COMT: a neurobiologically informed exemplar from the pre-genomic era

As highlighted above, in the last five years, pharmaceutical companies have begun to target specific symptom domains and their underlying circuitry. Although not currently part of the diagnostic criteria, cognitive impairments, particularly executive dysfunction, represent a major unmet clinical need in patients with schizophrenia and, albeit to a lesser extent, bipolar disorder (Burdict et al., 2011, 2014; Nuechterlein et al., 2004; Keefe, 2008). Executive function is critically dependent on dopaminergic signalling in the prefrontal cortex (PFC) (Goldman-Rakic et al., 2000). Animal studies demonstrate that task performance is impaired by either suboptimal or supraoptimal dopamine receptor stimulation, suggesting an inverted-U like relationship between PFC dopamine transmission and performance (particularly on working memory tasks)(Williams and Goldman-Rakic, 1995; Goldman-Rakic et al., 2000) (Fig. 1). Patients are thought to have insufficient dopaminergic signalling in the PFC that contributes to the cognitive impairments that they experience (Goldman-Rakic et al., 2004). This reduction in dopaminergic function in the PFC contrasts with the excessive presynaptic dopamine release in subcortical regions that may underly psychosis (Howes et al., 2012). Against this backdrop, multiple genes related to dopamine signalling were investigated for potential associations with schizophrenia and bipolar disorder, and with the cognitive and neural processes impaired in these condition (Talkowski et al., 2007), with a view to identify pathophysiological mechanisms and potential therapeutic candidates. Of these, catechol-O-methyltransferase (COMT), which encodes an enzyme that metabolises dopamine, rose
Dopamine signalling

**Fig. 1.** There is an inverted-U relationship between prefrontal dopamine signalling and cognitive performance, whereby either excessive (dark blue zone) or insufficient (light blue zone) signalling results in relatively poorer cognitive performance, compared with optimal levels (mid blue zone). The human Val- and rodent COMT isoforms are high activity enzymes (green circle, solid line), resulting in suboptimal dopamine signalling, whilst the Met-COMT, low activity isozyme results in more optimal dopamine levels at baseline (purple circle, solid line). Tocapone administration decreases COMT activity, thereby increasing frontal cortical dopamine transmission. This results in more optimal levels in rodents and Val-COMT carriers (green circle, dashed line) but may result in supraoptimal signalling in Met-COMT homozygotes (purple circle, dashed line). Note that a similar relationship is predicted from other dopamine agonists, e.g. amphetamine (Mattay et al., 2003).
pro-cognitive effects of COMT inhibition are most robust in, or may be limited to, COMT Val158 homozygotes, at least under basal conditions (Fig). Importantly from a therapeutic point of view however, the available evidence suggests that this pro-cognitive effect of COMT inhibition in sub-optimally performing individuals extends beyond the effect of the Val158Met polymorphism. Thus, tolcapone counteracts phencyclidine-induced recognition memory deficits in rats (Detrait et al., 2016) and in a study stratifying healthy individuals on the basis of baseline performance on the MATRICS Consensus Cognitive Battery, tolcapone was found to improve visual learning in low baseline performing individuals, but to impair performance in high baseline performing individuals (Bhakta et al., 2017). Notably, for verbal fluency, tolcapone improved performance in all individuals, irrespective of baseline performance (Bhakta et al., 2017), consistent with evidence that different cognitive domains have different underlying relationships to dopaminergic signalling, rather than there being a simple ‘one size fits all’ inverted-U that pertains across all domains (Floresco, 2013). Nevertheless, these data suggest that COMT inhibition has the potential to be generally beneficial for treating the impairments in executive function and working memory that are prominent in schizophrenia and bipolar disorder (Burlick et al., 2011, 2014; Nuechterlein et al., 2004; Keefe, 2008).

The data above provide an overview of the rationale underlying the current interest in the use of novel MB-COMT selective inhibitors to target cognitive dysfunction in schizophrenia and other disorders (Byers et al., 2020; Soeteber, 2021). We believe that the field’s experience with COMT highlights several considerations for those seeking to leverage findings from psychiatric genomic studies to identify novel therapeutic targets. We expand on a number of these points below. Fundamentally, COMT’s journey from candidate molecule to novel therapeutic target reveals the magnitude of this challenge: even for a relatively ‘simple’ gene with a clear mechanistic hypothesis and proven druggability: it still took 20 years and the collection of multidisciplinary data by many investigators to provide sufficient confidence in COMT’s therapeutic candidacy and to develop new chemical entities ready for human clinical trials.

3. From one extreme to the other: ZNF804A and AS3MT

As noted, COMT is the archetypal candidate gene: there is a compelling story about why it should be involved in the genetics of schizophrenia and related disorders based on its genotype-influenced roles in dopaminergic functioning. But, like almost all candidate genes, this turned out not to be the case in the context of the results of large scale GWAS. The unanswered and intriguing question is whether targeting illness associated pathophysiology but not genetic causation is a viable therapeutic investment in the current era of drug discovery. Zinc-finger protein 804 A (ZNF804A) is at the other extreme. In 2008 it had the distinction of being the first genome-wide significant locus in schizophrenia and it has remained significant in subsequent analyses (O’Donovan et al., 2008). However, it was - and still is - the antithesis of a candidate gene. As the authors of the original report stated, “…it is uncharacterised and of unknown function”. Almost nothing was known about the gene or the protein it encoded, and what was known bore little relation to hypotheses about the pathophysiology of schizophrenia; its name reflected its presumed role as a zinc finger transcription factor based upon an encoded peptide motif within the gene. It was also unclear whether ZNF804A is expressed in the brain, and no functional genetic variants were known. Nevertheless, its genomic status encouraged investigations into its biology, and some progress has been made (Chang et al., 2017; Harrison, 2017). Firstly, ZNF804’s mRNA and protein are expressed in human brain throughout life, notably in pyramidal neurons (Tao et al., 2014); furthermore, the risk allele is associated with altered expression and splicing of the gene in foetal brain tissue (Hill and Bray, 2012; Tao et al., 2014). The protein is present somatodendritically, as well as in the nucleus, and it interacts with post-synaptic signalling molecules giving it a putative role in synaptic function (Deans et al., 2017). There is also evidence that the risk variant within the gene impacts on functional connectivity in the brain (Rasetti et al., 2011; Cousijn et al., 2015; Esslinger et al., 2009). Along with other aspects of its biology (Girgenti et al., 2012; Zhou et al., 2018; Chapman et al., 2019), these features are of interest and readily interpretable in the context of models of schizophrenia invoking aberrant neurodevelopment and synaptic plasticity. However, despite over a decade of research, there remains no clear understanding of the role ZNF804A plays in the disease process nor any evidence that it is a tractable therapeutic target, and so it compares unfavourably with COMT in this regard notwithstanding its genomic credentials.

A similar story is true for arsenic 3-methyltransferase (AS3MT), which lies within the chromosome 10 schizophrenia GWAS peak (Ripke et al., 2014). Like ZNF804A, virtually nothing was known about its relationship to brain function at the time, though its name gave some clues. On the one hand, like COMT, as a methyltransferase enzyme it is a potential drug target; on the other hand, its expression in the brain was unknown, and the significance of arsenic as its substrate puzzling. Subsequent research (Li et al., 2016) showed that the genetic association is mediated by regulation of a specific AS3MT isoform and that the gene is robustly expressed in human brain, with later work showing this occurs especially in GABergic interneurons, a cell population implicated in schizophrenia (Takahashi et al., 2021). As with ZNF804A, these discoveries provided some interesting and potentially relevant neurobiological information to complement the genomics. However, identifying the physiological brain substrate(s) of AS3MT has proven elusive, and without this information, or evidence that AS3MT inhibition is feasible or valuable, it is difficult to progress its therapeutic candidacy further. This, both ZNF804A and AS3MT also serve as reality checks illustrating the challenges – and the time and the money – required to investigate a genetic locus for which there is little prior neurobiological understanding and few clues as to where to focus empirical studies.

4. Between the extremes: combining neurobiology and genomics

The juxtaposition of COMT with ZNF804A and AS3MT illustrates the extremes of the evidence spectrum within which decisions about selecting therapeutic candidates for psychiatric disorders like schizophrenia are made. One could characterise the underlying (strong) hypotheses of these extremes as being: ‘Neurobiological and pharmacological rationale is necessary (and sufficient)’ versus ‘Genomic significance is necessary (and sufficient)’. We suggest both lines of evidence have their place, but that the sweet spot is targets which tick both boxes. That is, where there is genome-wide significant support as well as strong neurobiological justification. This criterion places glutamatergic synaptic targets centre stage, since glutamatergic and synaptic plasticity genes are prominent in the genomic evidence hierarchy (Bray and Hall, 2022), as well as being key players in the leading ‘pre-genomic’ theories about the pathophysiology of schizophrenia (Harrison and Weinberger, 2005; Javitt and Zukin, 1991; Coyle et al., 2020).

In particular, there is diverse evidence for NMDA receptor hypofunction in schizophrenia and consequent efforts to normalise NMDA receptor signalling via various pharmacological strategies. The molecular targets for this approach include some which are genome wide significant hits such as GRIN2A (encoding a subunit of the NMDA receptor), GRIA3 (encoding a subunit of the AMPA receptor) and GRM3 (encoding metabotropic glutamate receptor 3), but others which are not, such as D-amino-acid oxidase (DAO) or the glycine transporter GlyT1. Targets in the latter category have their candidacy enhanced by the genomic evidence that glutamate receptor signalling is a clear part of the aetiology, even if the individual target is not. That is, the genomic data serve to highlight potential therapeutic pathways – indeed, this is arguably more important than the evidence for any single target, given the very small odds ratios for all common variants and thence the very
limited therapeutic traction which is likely to occur even after effective target engagement. In this regard, a priority becomes the detailed delineation of the genetically-influenced pathways themselves and, crucially, the net effect of the genetic variants on pathway function and hence the desired direction of any therapeutic intervention (simplistically, whether to antagonize, agonize, or stabilise). Having addressed those issues, the question as to which is the best specific molecular target within a pathway to achieve these goals will be influenced primarily by its druggability and other pharmaceutical considerations.

Voltage-gated calcium channels (VGCCs) illustrate another way in which genomic information can interact with prior knowledge to enhance the attractiveness of a drug target: in this instance, via repurposing (Harrison et al., 2020). VGCCs are unequivocally druggable: they are the target of calcium channel blockers, used widely to treat hypertension, and of the gabapentinoids, used to treat pain, seizures and insomnia. GWAS and rare variant evidence now shows that many VGCC subunits are trans-diagnostic psychiatric risk genes, including for bipolar disorder and schizophrenia (Mullins et al., 2021; Ripke et al., 2014; Singh et al., 2022). The genomic findings bring into renewed focus prior evidence that calcium signalling is altered in these disorders (Harrison et al., 2021), complemented by clinical trial and epidemiological data suggesting that the calcium channel blockers may have some beneficial psychotropic effects (Cipriani et al., 2016; Hayes et al., 2019; Colbourne et al., 2021), especially those that are brain-penetrant (Colbourne and Harrison, 2022). The existing calcium channel blockers are not suitable for psychiatric repurposing (due to their cardiovascular effects and likely sub-optimal occupancy of brain VGCCs), but the genomic evidence in tandem with these other considerations does suggest that more selective and brain-penetrant calcium channel blockers – or other channel modulators – could be of value. In this regard, we have identified novel human brain-enriched VGCC isoforms which provide a potential target for modified drugs of this kind (Clark et al., 2020). Information of this type can be used to generate more specific research models to understand how the key isoforms affect neural circuit function and behaviour, in order to better define the neurobiological mechanisms underlying the observed genomic associations, as well as providing more specific targets for compound screening. As an aside, it was the convergence of the genomic data and the prior knowledge of the functional properties and druggability of VGCCs that provided the motivation for (and fundability of) this work. As such, VGCCs provide arguably the best current example of how genomics and neurobiology can combine to prioritise candidate psychiatric drug targets for detailed investigation.

As illustrated by the VGCC example, a theme that cuts across both neurobiological and genomic studies is the importance of understanding the complement of isoforms produced from a target gene of interest in order to identify the most appropriate and selective therapeutic target - as well as to help identify molecular mechanisms of genetic association (Zhang et al., 2022). Thus, given its particular importance for metabolising dopamine, MB-COMT proved a more selective therapeutic for cognitive dysfunction that the more ubiquitous S-COMT isoform, whilst in the case of ZNF804A and ASSMT, specific splice isoforms appear to mediate genomic risk and so are presumably the most significant in terms of pathophysiology. Notably, our understanding of the complement of isoforms produced in human tissues remains rudimentary, as illustrated by the CACNA1C VGCC gene (Clark et al., 2020). The advent of large-scale long-read sequencing approaches should help to address the sequencing gap, although ensuring that this information feeds into functional studies remains a challenge (Hall et al., 2021). Understanding isoform diversity is of relevance not only for identifying the optimal specific target is but also for guiding decisions about the most relevant model systems. In the case of COMT, the MB-COMT and S-COMT isoforms are well conserved across species (Chen et al., 2004), meaning that standard rodent models are suitable for assessing the circuit and behavioural effects of MB-COMT specific inhibitors. However, isoforms are not always well-conserved (Nurtidinov et al., 2003) and so it may be necessary to consider alternative species, humanised rodent models, and/or the use of models derived from human cells to investigate pathophysiological mechanisms and screen compounds (De Los Angeles et al., 2021; Peltz, 2013).

5. Conclusions

Schizophrenia has never been short of speculative hypotheses as to its nature and potential treatments, but data have been lacking to support or refute them. The emergence of genomics and the resulting identification of genes and pathways robustly associated with the disorder provides invaluable evidence to constrain and refine hypotheses. Certainly, genomic data are transforming the interest in, and the approaches to, identifying and validating new therapeutic targets, and mean that the field is in a much healthier state than a decade or so ago. However, it is important not to reify genomic information and neglect other considerations, not least since the number of genetic loci and implicated genes already far exceeds our capacity to investigate them, and this gap can only increase. We need a rational way to prioritise and select the relatively small proportion of potential targets or pathways that can undergo the requisite depth of empirical studies. Here we have highlighted how one key element in this decision making concerns the extent of prior information about their neurobiology and pharmacology, and how well this fits with current pathophysiological understanding of the disorder. While we still need to be sanguine about the latter, it is through consideration of all the available evidence that the most judicious decisions can be made, thereby maximising the chances of successful identification and validation of novel therapeutic targets. Genomic data are poised to provide critical insights into disease biology, but do not have an exclusive nor necessarily predominant role in this process. This applies not only to schizophrenia but to other psychiatric disorders and cross-disorder phenotypes.

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