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Title of special issue :

Schizophrenia in the 21st century: new insights and translation into improved therapies

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This special issue focuses on recent advances in understanding the causes and the pathophysiology of schizophrenia, the approaches that are being adopted to translate this knowledge into new treatments and the analyses of recent trials with novel non-dopamine based treatments.

Over 100 years have elapsed since schizophrenia was first described and over 50 years since chlorpromazine was utilised to alleviate hallucinations and delusions characteristic of the disorder. With the introduction of a swathe of antipsychotic drugs from the 1970s to date, there have been waves of optimism for improvements in the clinical efficacy of these drugs. Unfortunately these treatments have not fulfilled expectations. As with chlorpromazine, current medications provide relief for the positive symptoms through dopamine D2 receptor antagonism, but have limited impact on the negative symptoms and cognitive deficits. Moreover, potential drug-induced side effects such as motor dysfunction and weight gain are highly undesirable. Lack of understanding of the causes of schizophrenia together with the continued use of dopamine-based preclinical models in drug discovery, with read-outs of limited translational relevance, are arguably key factors in the lack of major breakthroughs for improved treatments.

The opening articles in this special issue are devoted to reviewing the current status of the causes and the neurobiological deficits in schizophrenia. Harrison emphasises that ''genes for schizophrenia' have unquestionably been found'. Highlighting results from the 2014 publication from the Schizophrenia Working Group of the Psychiatric Genomics Consortium (~37,000 cases and ~113,000 controls) it is noted that over 100 loci (implicating ~700 genes) are genome-wide significant. Yet, as Harrison points out, each of these single nucleotide polymorphisms (SNPs) has a very small effect on disease risk (Odds ratios typically <1.20) and even cumulatively can only partly explain genetic predisposition. Rare variants, gene-gene and gene-environment interactions can also help to explain the ~65-80% heritability in schizophrenia. Harrison underlines that the significant advances in the genetic understanding of schizophrenia poses many questions: what is the neurobiological role of the gene products?, how do genetic variants converge upon biochemical pathways and networks to impact on pathophysiology ? and what are the implications for drug discovery ?. It is also becoming apparent that schizophrenia belongs to a family of disorders with some interrelationships at the genetic level with bipolar disorder and autism.

Howes and colleagues provide a timely update of the dopamine and glutamate hypotheses of schizophrenia pathophysiology emphasising that there is evidence for DA presynaptic dysfunction and glutamatergic abnormalities. They also argue for an integrated model of these key neurotransmitter systems. Whilst it is currently challenging to mesh the genetic findings in schizophrenia with the dopamine hypothesis there is accumulating evidence that many of these risk genes are involved in glutamate synapse function. Hence the neurobiology of some genetic variants is at least aligning with some pre-existing neurochemical hypotheses of disease relevance.

A key aim of schizophrenia research is to define the disorder in biological terms rather than clinical presentation. The 'omics' era has led to considerable effort in developing biomarkers with the aim of providing a clear diagnosis or a response to treatment. Pickard reviews the range of approaches adopted, noting that rather than providing robust biomarkers, the studies have provided insights into pathological processes. New strategies for the extraction of biomarkers from the integration of large '-omics' data sets are proposed.

'Translational Medicine' has become the aspiration for many disciplines in the 21st century. Whilst this is bearing fruit in cancer research where stratification of patients according to genotype and treatment responsiveness is increasingly possible, mental health research remains less tractable. In this special issue 'translational' research is highlighted from a range of 'technical' perspectives and discussed in the context of drug discovery. Several articles discuss imaging and electrophysiological approaches as translational tools. Bois and colleagues review structural MRI studies in high risk patients, emphasising the utility of neuroanatomical markers for identifying individuals that transition to psychosis and thereby providing a rationale for early treatment intervention in the appropriate cohort.

Phillips and Uhlhaas discuss neural oscillations making the important point that brain rhythms are largely similar across species. Hence underlying abnormal rhythmic activity in animal models is potentially suitable to understand the mechanisms underlying alterations in neural oscillation in schizophrenia that may relate to deficits in perceptual processing, working memory and executive function. These translational electrophysiological paradigms offer good opportunities for drug discovery. Thalamocortical activity contributes to neural oscillations and in this context the GABAergic thalamic reticular nucleus (TRN) plays an important role. Evidence for the TRN being a functional hub in thalamocortical network dysfunction potentially leading to a range of schizophrenia symptoms is reviewed by Pratt and Morris. Recent analytical methods of imaging and electrophysiological data, characterised at the scale of whole brain networks (using algorithms of graph theory) or specific neural subsystem interactions, are providing greater insights into compromised functional brain connectivity in schizophrenia. Dawson and colleagues appraise this evidence and stress the translational value of using 'functional brain connectivity' phenotypes in preclinical models for drug discovery.

At the behavioural level, Foussias and colleagues discuss negative symptoms and Young and Geyer review cognitive processes. Foussias *et al* note that within the construct of negative symptoms, diminished expression and amotivation form the two key subdomains. Current evidence suggests that anhedonia may be intact in schizophrenia challenging traditional views of this being a key deficit. Instead other facets of motivation such as reward prediction and reward valuation are impaired. Of course both the negative symptoms and cognitive deficits are inadequately controlled by current antipsychotic drugs and so when it comes to drug discovery there are no positive controls. Two salient points made by Young and Geyer which are suggested to facilitate the drug discovery process for the identification of pro-cognitive agents are 1) the importance of understanding the neural systems underlying a particular cognitive construct and 2) the measurement of similar domains in animals and patients. Foussias and colleagues give similar opinions in terms of drug discovery for the negative symptoms. Given that the complement of negative symptom and cognitive deficits may vary between patients, the issue of personalised

medicines rather than a 'one-size fits all' approach will be a challenge for future treatment strategies.

At this point in time, no compound has reached the clinic which has emerged from the aforementioned 'translational approaches' for drug discovery. Nevertheless, a range of 'non-dopamine' based compounds have progressed to testing in clinical trials. Of particular interest are compounds such as the mGluR2/3 agonists and glycine transport (GlyT1) inhibitors, which have been developed as a result of the glutamate hypothesis of schizophrenia, and, nicotinic acetylcholine receptor activators. Unfortunately these have all met with limited success (reviewed by Rowe *et al* and Dunlop and Brandon). Dunlop and Brandon consider the potential reasons for the disappointing results which include 1) patient recruitment (prior drug history may have had a negative impact on responsiveness to the new drug) 2) the lack of consideration of genetic factors in patient selection

What does the future hold ? Genetic and –'Omics' research is likely to lead to the identification of pathways and networks that converge and which are potentially 'drugable'. A deeper understanding of how risk factors impact at the molecular and cellular level to cause brain circuity dysfunction resulting in aberrant brain rhythms, functional connectivity and behaviour will facilitate rational drug design. Ultimately by the next century our descriptions of mental health disorders may have been replaced with more mechanistically-based diagnoses; 'Neural circuit disorders' potentially characterised by a suite of defined 'omic' biomarkers. The development of new treatments to correct the neural circuit abnormalities will be dependent on the level of future investment by Research Councils, Charities and Industry and the synergistic relationship between them. Given that tens of millions of people worldwide suffer from schizophrenia and mental health disorders, this investment seems entirely justifiable.