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Themed Section: Pharmacology of Cognition: a Panacea for Neuropsychiatric Disease?

EDITORIAL

Pharmacology of cognition: a panacea for neuropsychiatric disease?

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This themed section of the *British Journal of Pharmacology* arose from a British Association for Psychopharmacology (BAP) sponsored symposium at the annual meeting of the British Pharmacological Society 'Pharmacology 2015': 'Targeting cognition: a panacea for neuropsychiatric disease?'. Reflecting BAP's founding principles and demography, the symposium addressed translational advances in understanding and treating cognition from both clinical and preclinical perspectives.

Cognition is an umbrella term that includes many complex processes such as attention, learning, consolidation, reconsolidation and retrieval. Each of these processes in turn is applicable to diverse kinds of information processing such as working memory for short-term information, episodic memory for events and procedural memory for skills. The neural basis of these processes can differ depending on many factors such as the emotional salience of the information or the context in which it is encoded. The idea that impaired cognition could potentially be treated pharmacologically came to prominence in the 1980s, in part stimulated by the cholinergic hypothesis of geriatric memory dysfunction (Bartus *et al.*, 1982) and the subsequent increased understanding of the role of both cholinergic and glutamatergic systems in learning and memory. The compelling idea that a disorder such as Alzheimer's disease, with such profound cognitive symptoms, could be treated pharmacologically gave rise to the development of acetylcholinesterase inhibitors, such as donepezil, and more recently glutamatergic drugs such as memantine. Despite their limitations, these drugs are still among the only first-line pharmacological treatments for Alzheimer's disease (O'Brien *et al.*, 2017). More recently, it has become apparent that cognitive deficits are seen in a much wider range of psychiatric disorders such as anxiety, schizophrenia and depression. Research into the neuronal networks and molecular mechanisms contributing to these cognitive symptoms should give rise to novel therapeutics to meet the clinical need in these disorders.

This themed section brings together significant advances in research into cognitive dysregulation in psychiatric illness. Several articles focus on advances in mechanisms underlying cognitive impairments and the neurotransmitter systems involved. Successful restoration of cognitive deficits will have a dramatic impact on patient outcomes. For example, in schizophrenia, cognitive function is typically two standard deviations below the norm; these deficits are observed prior to a first episode of psychosis, predict functional outcome and negatively impact on the quality of life for patients (Green, 1996; Keefe and Harvey, 2012). Green's work, highlighting this problem, led to the Measurement and Treatment Research to Improve Cognition in Schizophrenia initiative (Marder and Fenton, 2004) and identification of seven domains of cognition affected in the illness: attention, working memory, visual and verbal memory, reasoning and problem solving, processing speed and social cognition. A further aim was to support the development of

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pharmacological agents to treat this unmet need. However, in spite of over a decade of intensive research, to date, no drug has yet received a licence for cognitive impairment associated with schizophrenia (see Talpos, 2017, for a recent update on compounds in phase III clinical trials for this indication). A variety of recent approaches to enhance research into cognition in neuropsychiatric disorders, which will undoubtedly inform current and future drug development strategies, are outlined below.

Dauvermann *et al*. (2017) review how advances in neuroimaging and genetic research have furthered our understanding of the specific brain circuitries that underlie cognitive processes. These authors focus on the role of glutamatergic systems, and NMDA receptor hypofunction in particular, in the cognitive deficits observed in schizophrenia. Based on both human and rodent studies, the therapeutic potential of ketamine in modulating the brain network connectivity and the potential procognitive effects of NMDA receptor co-agonists, such as D-serine and D-cycloserine, are discussed. Imaging studies have also been essential in demonstrating that the cognitive benefits of physical exercise in schizophrenia are accompanied by changes in brain volume and connectivity (Firth *et al*., 2017). This study highlighted the need for reliable biomarkers to progress research into the precise nature of which physical activity regimes might be most beneficial and to establish the underlying neurobiological mechanisms. While potentially further from translation to therapy, O'Tuathaigh *et al*. (2017) review findings from mouse models of candidate risk genes for schizophrenia. These authors emphasized the need for detailed characterization of animal models based on genome-wide association studies in schizophrenia, which has provided new optimism for the identification of novel therapeutic agents.

Advances in cognitive behavioural neuroscience have informed the development of improved tests for measuring cognition and increased the complexity of cognitive behaviours that can be measured both in animal and human models. As an example of cross-species bidirectional translation, Robbins (2017) describes how the impulsivity seen in attention deficit hyperactivity disorder patients can be modelled in rodents to advance drug discovery. A further example of this bidirectional approach is presented by Stuart *et al*. (2017) who report a series of experiments to examine the predictive validity of the affective bias test in rats. Studies of depressed patients have revealed emotion-induced changes in cognitive processes including negative affective biases. Stuart *et al*. (2017) reason that the affective bias test may have greater translational validity than existing tests of depression-related behaviour and has particular importance for investigating the pharmacology of cognition.

The importance of GABA dysfunction in cortico-hippocampal circuits and how this links to cognitive impairments in schizophrenia and cognitive decline in ageing are discussed by Bast *et al*. (2017). They suggest that aberrant neural activity caused by neural disinhibition is a promising target for treatments, especially at early disease stages, and candidate drugs include second-generation antiepileptics and $mGlu_2$ receptor (mGluR2) positive allosteric modulators. Locci and Pinna (2017) highlight how $GABA_A$ receptors, and the progesterone derivative allopregnanolone, which acts at these receptors, could be both biomarkers and treatment targets in stress-induced cognitive impairment, occurring in disorders such as post-traumatic stress disorder. The inappropriate expression of conditioned responding to fear, evident in anxiety-related disorders, could also potentially be treated by cannabidiol (Lee *et al*., 2017). Understanding how cannabidiol regulates emotional memory processing is important not just for anxiety-related disorders but also for substance abuse disorders.

Apart from the therapeutic advances in treating cognitive impairments in disease, the pharmacotherapy of cognition has significant societal implications. The potential for 'smart' drug taking in healthy people to enhance cognitive performance is considered by d'Angelo *et al*. (2017). Prescription stimulants such as amphetamines, methylphenidate and modafinil have been shown to affect a variety of cognitive domains, while acetylcholinesterase inhibitors such as donepezil show little consistent effects in healthy people. Given the increasing 'non-medical' use of cognitive enhancers, d'Angelo *et al*. (2017) argue for more evidence of their long-term safety and efficacy in healthy people, which currently falls outside the scope of regulatory consideration.

Together, these articles highlight the advances in multidisciplinary cognitive neuroscience and genetics that have broadened the range of potential biological approaches for the treatment of cognitive symptoms, irrespective of their nosological origin. As to whether targeting cognition holds the key as a panacea for psychiatric disorders, the outcomes of current and future drug development programmes will ultimately test whether these approaches, combined with improved translational models, can deliver the therapies so urgently needed by patients.

Conflict of interest

The authors declare no conflicts of interest.

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