Editorial

The behavioural pharmacology of the basal ganglia: in memory of Lex Cools

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This Special Issue of *Behavioural Pharmacology* is dedicated to the memory of Alexander (Lex) Cools, a friend, colleague and inspiration to many within the field of behavioural pharmacology, and beyond. Lex was a founder member of both the European Behavioural Pharmacology Society, serving as its second president, and of the Editorial Board of Behavioural Pharmacology. His work was characterized by leaps of imagination and ideas ahead of their time that were often met with scepticism but in general turned out to be correct. A formal obituary summarizing his achievements has been published (Ellenbroek *et al.*, 2014); this Special Issue opens with a personal memoir by Trevor Robbins that captures perfectly the way in which Lex will be remembered as a scientist and as a person.

The scientific contents of this Special Issue comprise five reviews and 17 empirical papers on aspects of the functions of the basal ganglia, which include two posthumous papers by Lex himself and several others by close colleagues. The first review paper, by van den Bos (2015), an explicit tribute to Lex Cools, considers the different roles of the dorsal and ventral striatum in social behaviour, following on from his early insight into the role of these structures in internal and external control of behaviour and in individual differences. This is followed by a fine-grained analysis by Ikeda *et al.*, again, based solidly on Cools' early work, of the relationship between neuropharmacological mechanisms with the basal ganglia and specific output pathways in the control of different orofacial movements. We then feature two papers on another of Cools' early ideas, the balance of 5-HT and dopamine systems in schizophrenia: Ellenbroek and Prinssen review the potential role of 5-HT3 receptor antagonists as adjunctive therapy for the negative and cognitive symptoms of schizophrenia that are resistant to antipsychotic medication, whereas Haleem argues for a role for 5-HT1A receptor agonists, in combination with dopamine D2 antagonists, as adjunctive treatments for schizophrenia and Parkinson's disease. In the final review paper, Moreira *et al.* summarize the role of endocannabinoids in the basal ganglia in impulsivity and anxiety, and the potential role of inhibitors of endocannabinoid metabolism in the treatment of addiction. Together, these papers illustrate the involvement of the basal ganglia in the very broad range of the functions that have intrigued behavioural pharmacologists over the 40 years since Lex Cools was among the pioneers studying them.

The first two empirical papers, on which Lex Cools features posthumously as senior author, reconnect with one of his earliest interests, noradrenaline–dopamine interactions in the basal ganglia. The first paper, by Aono *et al.*, reports the results of a pharmacological study examining the involvement of alpha-receptor subtypes in accumbal dopamine release. In the second paper, Verheij *et al.* shows that α-adrenergic receptors in the nucleus accumbens, which are known to control the release of dopamine from reserpine-sensitive storage vesicles, regulate behaviour that is mediated by dopamine release from reserpine-sensitive pools. They also demonstrate that α and β receptors have opposing effects on locomotor activity and suggest that this may help explain inconsistencies in the literature concerning the role of noradrenaline.

The next six papers describe studies in various animal models of Parkinson's disease. Aidi-Knani *et al.* demonstrate that increasing the excitability of striatal medium spiny neurons with an inhibitor of Kv4 potassium channels improves motor, cognitive and emotional symptoms in 6-OHDA-treated rats, suggesting a potential novel target for adjunctive therapies for Parkinson's disease. Huot *et al.* studied the potential of a dopamine D4 receptor antagonist to decrease the severity of the dyskinesias that limit the therapeutic use of L-DOPA in Parkinson's disease. They report that the D4 receptor agonist had very limited effects on L-DOPA-induced dyskinesias in 6-OHDA-treated rats, in contrast to an earlier report of beneficial effects in MPTP-treated monkeys. Potts *et al.* describe a novel video-based scale for assessing the severity of L-DOPA-induced dyskinesias in MPTP-treated monkeys, the Quantitative Dyskinesia Scale, which will enable more precise measurement to be made in future studies.

Two further papers report on pharmacological reversal of haloperidol-induced catalepsy, of relevance to both Parkinson's disease and the unwanted effects of neuroleptic drugs when used in the treatment of psychosis. Alatorre *et al.* studied the effects of infusing (−)−epicatechin, a flavonoid that is thought to interact with GABA-A receptors into the globus pallidus. They report that (−)−epicatechin increased the neuronal firing rate, antagonized the inhibitory effect of γ-aminobutyric acid, and reversed haloperidol-induced catalepsy. Kasture *et al.* studied the effects of two major components of tea, caffeine and epigallocatechin gallate. They report that epigallocatechin gallate potentiated the anticataleptic effect of caffeine, including

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antagonism of the sensitization of catalepsy seen with repeated haloperidol administration, and also potentiated the locomotor stimulant effects of caffeine, and suggest that drinking tea might have the potential to decrease motor side-effects of antipsychotics. In a third study relevant to the progressive augmentation of neuroleptic-induced motor impairment, Ashby *et al.* report that, unlike most antipsychotic drugs (e.g. haloperidol or, as used here, olanzapine), the effects of a novel compound, DL-govadine, remained consistent across repeated administrations in a conditioned avoidance task, suggesting that this drug may have antipsychotic potential with decreased potential for the development of motor side-effects.

The next five papers in the Special Issue add to the extensive literature on behavioural sensitization, the gradual increase in the locomotor response to psychomotor stimulant drugs on repeated administration, which, although known to be mediated by changes in mesolimbic dopamine activity, remains uncertain as to its function and precise mechanisms. The first two papers in this series concern sensitization to the directly acting dopamine agonist apomorphine. The first, by Delius *et al.*, reports the results of a substantial programme of research on aporphine sensitization in pigeons. The authors present evidence, together with a neural model, that the effects described can be explained by a conditioning process in which an interoceptive drug state comes to act as a conditioned stimulus to enhance the effect of the exogenous unconditioned stimulus; they suggest that this model may also apply in the case of psychostimulant sensitization in rodents. In the following paper, Haleem and Farhan report that apomorphine sensitization in rats is blocked by chronic administration of the SSRI fluoxetine, and suggest that this could be a helpful treatment strategy for the psychosis and impulse control disorders that develop in patients receiving apomorphine for the treatment of Parkinson's disease. Igari *et al.* demonstrate a similar role for 5-HT systems in methamphetamine sensitization in rats, which was absent in genetically manipulated rats lacking the 5-HT transporter, but was restored by a selective 5-HT1B receptor agonist, suggesting that drugs targeting 5-HT1B receptors might have application in the treatment of methamphetamine abusers. In another paper reflecting long-standing concerns about a potential role of sensitization in drug abuse, Berquist *et al.* report that sensitization to amphetamine, in mice, was enhanced by concurrent administration of the cathinone derivative mephedrone. The last paper in this series, by Nona *et al.*, reports that a transient inactivation of the nucleus accumbens, brought about by high-frequency electrical stimulation, blocked the expression but not the development of sensitization to the locomotor stimulant effect of ethanol in mice. Together, these five papers illustrate the richness and variety of ongoing research on this classic problem.

The empirical studies so far described have all been concerned with aspects of motor behaviour, but the final four papers address cognitive functions relevant to, respectively, addiction, obsessive compulsive disorder, schizophrenia and attention deficit hyperactivity disorder (ADHD), providing a snapshot that illustrates Cools' dictum that the basal ganglia are not simply motor structures. In the first of these papers, Veeneman *et al.* present the results of an ingenious disconnection study showing that cocaine reinforcement, in the early stages of self-administration, which is usually thought to be mediated within the nucleus accumbens shell, also requires a serial connection from there to the dorsolateral striatum. In the second paper, González *et al.* studied the neural basis of quinpirole-induced compulsive checking, an animal model of obsessive compulsive disorder. They report that compulsive checking was not blocked by a lesion of the nucleus accumbens, implying that this effect of the quinpirole is mediated at dopamine D2/D3 receptors outside the accumbens. However, accumbens lesions did alter many of the characteristics of checking behaviour, leading the authors to suggest that the accumbens serves as a hub to coordinate the orderly activity of neural modules subserving different aspects of security motivation. In a third paper, Kucinski *et al.* took as their starting point the observation that schizophrenic patients frequently smoke cigarettes and that this appears to improve cognitive functioning. In their study, varenicline, a nicotine and 5-HT3 receptor agonist, normalized deficits of attentional gating in a transgenic mouse model of schizophrenia. Finally, Aarts *et al.* report a study in adults with ADHD showing that a subgroup of patients carrying the 9R allele of a genetic polymorphism of the dopamine transporter gene exhibited greatly augmented effects of reward on the striatal BOLD signal in a task-switching procedure, suggesting a role for genetic differences in striatal dopamine in the cognitive deficits that are present in adult ADHD. A pleasing feature of this paper is that the senior author is Lex Cools' daughter, who now is the third-generation Professor Cools at Radboud University, after Lex and his father before him.

The collection of papers and reviews in this special issue speaks directly to the creativity and intellectual energy that characterized Lex Cools. He always thought of himself as a holist, and tried to look at the broader picture. With this attitude he inspired his students and his colleagues alike. Their research is part of his legacy, which, as this Special Issue illustrates, continues to be an intellectually creative force within behavioural pharmacology.

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Reference

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