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# Assaying dissociable elements of behavioural inhibition and impulsivity: translational utility of animal models

Trevor Humby[1,3,4] and Lawrence S Wilkinson[1,2,3,4]

Inhibition is a fundamental property of behaviour required for flexible responding and humans have evolved executive brain systems that can engage inhibitory processes in order to reduce interference from irrelevant distracting stimuli, block unwanted memories and emotions and suppress inappropriate choices and actions. Without the efficient operation of these inhibitory mechanisms behaviour can become maladaptive, as seen in a large range of disorders where subjects exhibit impulsive responding, such as ADHD, mania, chronic substance abuse and schizophrenia. Animal models are making an increasing contribution to our understanding of the psychology and underlying neurobiology of behavioural inhibition and impulsivity. Here, in this short article we summarise work conducted with rat models, and also discuss recent progress in exploiting the potential of genetically engineered mice. The data so far emphasise the relatively high translational relevance of animal models in this area of behavioural neuroscience. The findings add weight to the existence of dissociable components of impulsive behaviour, they inform the human literature, and may be of significant use in the development of drug therapies to treat the many disorders where failures in behavioural inhibition are prominent.

**Addresses**
[1] Schools of Psychology, Cardiff University, Cardiff CF10 3AT, UK
[2] School of Medicine, Cardiff University, Cardiff CF10 3AT, UK
[3] MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff CF10 3AT, UK
[4] Neuroscience and Mental Health Research Institute, Cardiff University, Cardiff CF10 3AT, UK

Corresponding authors: Humby, Trevor (humbyt@cardiff.ac.uk) and Wilkinson, Lawrence S (wilkinsonL@cardiff.ac.uk)

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## Introduction

In the early 1960s Norman Rushworth and colleagues published findings on the contractions exhibited by hydra (a genus of simple predatory fresh-water animal composed of a tubular body anchored by a sticky foot and a mouth at the free end surrounded by a number of tentacles) in response to light and mechanical agitation [1]. In isolation these stimuli led to a characteristic withdrawal response involving a series of successive partial body contractions culminating in the animal forming a tight ball with contracted tentacles. However, something completely different happened in the presence of prey (Artemia salina [brine shrimp] larvae) or chemical stimuli able to evoke the feeding response. Under these conditions the light/agitation evoked withdrawal response was inhibited; complete inhibition being present initially, followed by a slow progressive recovery of the response to normal levels. Rushworth and colleagues concluded, 'such inhibition demonstrates the control of one receptor effector system by another' [1].

These simple experiments undertaken in a simple animal illustrate that inhibition is a fundamental property of behaviour. They also indicate that inhibition is an active process and that it enables flexible responding. In the case of hydra, temporary suppression of the normal response to potentially threatening stimuli, such as light and mechanical agitation, allowed feeding to occur when prey were present transiently (hydra cannot capture prey when contracted) but reinstatement of the withdrawal reflex on satiation. It may seem a long way from hydra to humans but the role of inhibitory processes in people and their involvement in the moment-to-moment refinement of behaviour to match current requirements is even more critical when considered against the complexities of the social and non-social environment faced by the average person. Think of the multiple emotional and intellectual dilemmas when meeting your new boss for the first time and noticing his rather obvious toupee had slipped a fraction, even more delicate if it was your new partner.

In the face of the challenges posed by a complex and uncertain world we have evolved executive brain systems that monitor and supervise on-going behaviour and, where appropriate, co-ordinate the engagement of inhibitory processes that enable us to reduce interference from irrelevant distracting stimuli, suppress unwanted memories, emotions, choices and actions, and avoid the concurrent activation of incompatible responses [2]. When these inhibitory mechanisms go awry the result can be maladaptive 'impulsive' behaviours. With the realisation that impulsivity (very broadly defined as action without foresight) is a key feature of numerous disorders, amongst them ADHD, schizophrenia, mania and chronic substance abuse, the study of inhibitory processes and how they go wrong is gaining increasing practical importance

[3]. In this short review we summarise, briefly, important issues and questions in the field and then move on the main focus of the article; recent progress using rodent models and the extent to which these data are translatable to human behaviour and clinical disorders.

## Non-unitary nature of behavioural inhibition and impulsivity

A complete account and understanding of the psychology and underlying neurobiology of behavioural inhibition has yet to be gained. However, it is clear at least that it is probably wrong to consider inhibition as a monolithic construct. A full consideration of the complex taxonomy of inhibitory processes is beyond the scope of this review but evidence is accumulating for the existence of multiple, distinct types of inhibitory process manifest in different situations. Contrast, for example, the inhibition to countermand a well rehearsed correct motor response in order to execute another that had been previously incorrect ('reversal learning'), with that required to choose a larger reward in the future rather than a smaller one immediately ('delayed gratification'), to that needed to cease a motor response already in motion ('stopping'). These are not just academic distinctions in semantics. The notion of their being dissociable elements of inhibitory behaviour becomes of practical importance with the realisation that they appear to be mediated by subtly different processes in terms of brain circuitries and neurochemistry, and that different disorders can present with different patterns of inhibitory deficits, that is, forms of impulsivity [3]. This means that different disorders may, to an extent at least, have a particular pathogenic route to impulsivity.

As a result, some commentators suggest that efforts to develop therapies to treat maladaptive impulsive behaviour should take the probability of there being distinct 'impulsivity subtypes' into account, insofar as it predicts that it will be unlikely that a one-size-fits-all approach will be optimal across disorders [4,5]. Clinically, underlying pharmacological differences between impulsivity subtypes may dictate the efficacy of a particular treatment regime and explain why a drug that is effective at treating inhibitory deficits in some individuals is ineffective in others. Conducting research that recognises the non-unitary nature of impulsive responding is clearly of major importance for disorders such as ADHD, where failures of behavioural inhibition are overt, but this approach is also of relevance to other disorders, such as schizophrenia, where inhibitory deficits are also present, if less prominent, and co-morbid with a complex mix of other symptoms [6,7].

## Assaying impulsive behaviours in rats

Work in humans has allowed some progress to be made on the functional neuroanatomy and psychopharmacology of inhibition deficits, where there has been a particular emphasis on ADHD. These studies have highlighted dysfunction within subterritories of the prefrontal cortex and associated cortico-striatal loops in generating impulsive behaviours [5]. Other work has implicated the right inferior frontal gyrus as an important locus for response inhibition with converging evidence from brain damaged patients [8], temporary disruption using transcranial magnetic stimulation [9] and pharmacological fMRI studies investigating the effects of atomoxetine administration on inhibitory control [10•]. Another main focus has been on the diffuse ascending monoamine systems, with dopamine and especially noradrenergic transmission suggested to be of key relevance to the therapeutic effects of the main drugs used currently in the treatment of ADHD symptoms; methylphenidate, dextroamphetamine and atomoxetine [11]. Modafinil the awake-promoting drug which has therapeutic potential for ADHD [12] (though not currently approved by the Food and Drug Administration for ADHD) may also act via noradrenergic mechanisms [13]. However, human studies can be constrained by several factors (e.g. access to relevant subject groups, a relative lack of experimental control) and it is a significant bonus when able to exploit, in parallel, meaningful animal models of human function and disorders.

Behavioural inhibition and impulsivity can be assayed effectively in rat models and a variety of behavioural tasks, the majority taking advantage of the enhanced stimulus-control of operant methods but also some maze-based approaches, have been deployed successfully to examine dissociable aspects of behaviour. These include, go/no-go, delayed reinforcement, 5-choice serial reaction time and stop-signal reaction time tasks. The experimental tractability of animal models has allowed a partial, semi-systematic analysis of the effects of specific brain lesions and drug challenges across tasks measuring different aspects of behavioural inhibition; for example action restraint (go/no-go), action cancellation or stopping (stop-signal reaction time task) and delayed gratification (delayed reinforcement), as summarised in Tables 1 and 2. In general the data from rat studies have pointed towards similar fronto-striatal circuitries and transmitter systems to those thought to be important in mediating inhibitory functions in humans. Furthermore, the data add some weight to the existence of distinct components of behavioural inhibition and impulsivity, in that the effects of lesion and drug manipulations are not always the same across different tasks, with the caveat that not all comparisons have been made.

Assays of behavioural inhibition in rats show a high degree of translational relevance, an issue of major importance to their potential practical usefulness. This is particularly marked in a recent elegant work, pioneered by Robbins, Eagle and colleagues, developing a rat version of the stop-signal reaction time task (SSRTT, [23••]). The SSRTT measures the ability to stop a motor action once started and is used routinely in the clinic where it reliably detects

**Table 1**

**Effects of brain lesions on dissociable aspects of behavioural inhibition in rats**

| Brain lesion | Delayed reinforcement | Stop signal reaction time task | Go/no-go |
|---|---|---|---|
| Medial PFC, [14,15] | | No difference | ↓ |
| Orbitofrontal cortex — whole, [16–19] | ↓/No difference[a] | ↓ | |
| Orbitofrontal cortex — medial [17] | ↑ | | |
| Orbitofrontal cortex — lateral [17] | ↓ | | |
| Infralimbic cortex [16,20,21] | | No difference | ↓[a] |
| Anterior cingulate [22,20] | | | No difference[a] |
| Medial Striatum [23••] | | ↑ | |
| NAC core, [22,24,14] | ↑ | No difference | |
| Subthalamic nucleus (STN), [16,25] | ↓ | ↓ | |
| Basolateral amygdala, [19] | ↑ | | |
| Hippocampus, [26,18,27] | ↑[a] | | ↓[a] |
| Global 5-HT depletion, [28–30,19] | No difference/↓[a] | No difference | ↓ |

Arrows denote increases or decreases in inhibitory control (relative to sham lesion).
[a] Maze-based tasks, all others are operant methods.

**Table 2**

**Effects of commonly used therapeutic drugs on dissociable aspects of behavioural inhibition in rats**

| Drug manipulation (systemic administration) | Delayed reinforcement | Stop signal reaction time task | Go/no-go |
|---|---|---|---|
| Methylphenidate [31,32] | ↓ | ↓ | |
| Atomoxetine [31,33] | ↓[a] | ↓ | |
| Modafinil [32] | | ↓ | |
| SSRI [34,35,36•] | ↓[a]/no difference | No difference | |
| Benzodiazepines [37,38] | ↑ | | ↑ |

Arrows denote increases or decreases in inhibitory control (relative to vehicle treatment).
[a] Maze-based tasks, all others are operant methods.

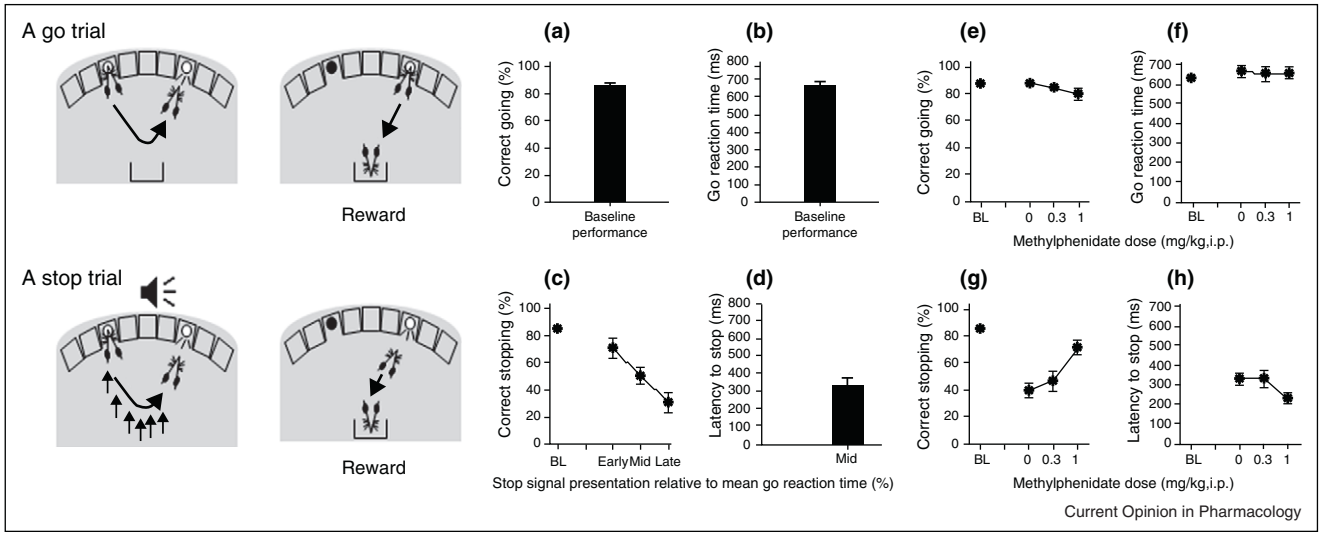
inhibitory deficits in pathological conditions such as ADHD. Rats can learn this task and show similar speeds of reaction and sensitivity to task manipulations as people do, they also show a similar pattern of effects to drug challenges, most notably recapitulating the inhibition-enhancing properties of methylphenidate, atomoxetine and modafinil [31–33]. Although rat models for impulsive responding are, arguably, already valid pre-clinical entry points for drug development they need to be further exploited. This is especially true in terms of further lesion work that maps on to relevant homologous regions of human brain, for example, inferior frontal gyrus. Also, given the emerging importance of brain noradrenaline in influencing inhibition more studies focusing on this system, and precisely what psychological function(s) mediate its actions, are warranted. Another ambitious, but exciting, development that should be encouraged is the integration of behavioural methods with electrophysiological approaches in order to gain a real-time appreciation of the dynamic communication between key brain structures involved in behavioural inhibition and the way lesions and drugs (impulsivity-inducing and impulsivity-reducing) can change this communication [39].

## Development and exploitation of mouse models

Genetics can influence impulsive responding, both in terms of monogenic, fully penetrant conditions, such as the familial tauopathy FTDP-17 (Frontotemporal dementia and parkinsonism linked to chromosome 17) and also with respect to contributing to overall risk in more complex disorders such as ADHD. This has motivated the development of mouse tasks in order to model genetic effects on aspects of behavioural inhibition, taking advantage of the superior genetic tractability of this species. Again, this has proved successful and murine versions of a range of behavioural tasks, including go/no-go, delayed reinforcement, 5-choice serial reaction time task and reversal learning are used routinely [40–43]. It is important to emphasise that, in this context mice are not ersatz versions of rat models, rather mice are adept at learning these tasks, show a high degree of cross-species validity and are making an increasingly important and distinct contribution to the field. For example, in so called phenotype-led studies (going from behaviour to gene) the highly polymorphic nature of the mouse genome across strains can be exploited to identify genetic influences, tease them apart from environmental effects and then begin to search for the specific gene variants impacting on impulsive behaviours [44,45].

Phenotype-led approaches can be augmented by a wide range of genotype-led (going from gene to behaviour) approaches using mice with known spontaneous or engineered mutations. Often the main rationale here has been to gain more information on the neurobiological

**Figure 1**




Stop signal reaction time task for mice. In a 'go' trial mice make two nose-poke responses in order to receive a reward. Go-trials make up 80% of the trials in the session, the other 20% are 'stop' trials where subjects must stop their second response on hearing a stop signal. If they do this successfully they receive a reward. The task varies the degree of difficulty in stopping by playing the stop signal at different places within the go reaction time (goRT, the time taken to make a go response) as illustrated by the arrows. Stopping is relatively easy when the stop signal is at the beginning of the goRT and progressively more difficult later in the goRT as it gets closer to the execution of the response. **(a–d)** show that C57Bl/6 mice carry out the go-response efficiently (a) and rapidly (b) that stopping becomes more difficult the later the stop signal is played (c) and that it is possible to calculate a 'latency to stop' (c. 300 ms) very similar to those seen in humans (d). Systemic dosing with methylphenidate, a drug used clinically to treat ADHD, has no effects on go-trials **(e,f)** but dose-dependently enhances the ability to stop, an effect manifest both in the % of successful stop-trials **(g)** and a reduction in the latency to stop **(h)**. A similar pattern of effects is seen with another clinically relevant drug atomoxetine (unpublished data).

mechanisms by which well established risk genes for impulsive behaviour act [42]. However, perhaps the most useful and interesting use of genetic mouse models is where new, unanticipated effects on behaviour have been observed; leading, potentially, to novel insights flowing from mouse to man. Examples reflecting this particular strength of mouse models are recent findings implicating the genes *Steroid sulfatase*, *Xlr3b* and *Snord115* (the latter via effects on post-transcriptional modifications of the 5HT2C receptor) in different aspects of behavioural inhibition [46,47••,48]. *Xlr3b* and *Snord115* are imprinted alleles and connect the exciting, emerging field of behavioural epigenetics to the molecular neurobiology of response control. Our own laboratory has been active in the development and exploitation of mouse models and recently we have established, for the first time to our knowledge, a mouse version of the stop-signal reaction time task [49•]. As illustrated in Figure 1, mice show patterns of behaviour similar to those seen in people and are sensitive in the same way to the therapeutic drugs methylphenidate and atomoxetine, enhancing the ability to stop. We anticipate that such new developments in operant task design, including recent innovations in the use of rodent touch-screen technology [50•], will be of significant use in generating viable translational models, and new therapeutic targets, for disorders where failures of behavioural inhibition are prominent.

## Summary

Efforts to understand the brain mechanisms mediating behavioural inhibition and the nature of inhibitory deficits observed in several psychological disorders constitute an important area of basic and clinical neurobiology. Studies in people are beginning to give us some idea of key brain circuitries involved in inhibition, how these circuitries may operate abnormally and neurochemical systems that might be targeted by drug therapies aiming to normalise impulsive behaviours. Animal models are making an increasingly significant contribution in this area, taking advantage of the well known enhanced experimental control allowed by animal models and also specific advances in the technologies available to assay dissociable aspects of inhibitory function. These new behavioural technologies, applied in both rat and mouse models, are allowing a detailed analysis of the biological substrates of behavioural inhibition and impulsivity at multiple levels; psychological, neuroanatomical and molecular. Animal models offer a notably high degree of translational relevance and are generating new insights that inform the work in humans, refine our understanding of drugs already in use in the clinic and are beginning to

suggest novel mechanisms by which maladaptive, impulsive behaviours can occur and potentially be treated.

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