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REVIEW

The neuropsychopharmacology of action inhibition: cross-species translation of the stop-signal and go/no-go tasks

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Abstract
Background and rationale The term 'action inhibition' encapsulates the ability to prevent any form of planned physical response. Growing evidence suggests that different 'stages' or even subtypes of action inhibition activate subtly different neuropharmacological and neuroanatomical processes.
Objectives In this review, we present evidence from two commonly used and apparently similar behavioural tests, the stop-signal task and the go/no-go task, to determine if these have similar neuroanatomical and neurochemical modulation.
Results Whilst performance of the stop-signal and go/no-go tasks is modulated across only subtly different anatomical networks, serotonin (5-HT) is strongly implicated in inhibitory control on the go/no-go but not the stop-signal task, whereas the stop-signal reaction time appears more sensitive to the action of noradrenaline.
Conclusions There is clear neuropharmacological and neuroanatomical evidence that stop-signal and go/no-go tasks represent different forms of action inhibition. This evidence translates with remarkable consistency across species. We discuss the possible implications of this evidence with respect to the development of novel therapeutic treatments for disorders in which inhibitory deficits are prominent and debilitating.

Keywords Impulsivity · Human · Rat · Dopamine · Noradrenaline · Serotonin

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Introduction

'Action inhibition' may be defined as the inhibition of a pre-planned physical response. Without such an ability to inhibit actions, it would be impossible to perform even the simplest of everyday tasks. The more generalised term 'inhibition' has been widely used in neuroscience for over 100 years (Smith 1992 in Aron 2007), and in one sense, can be viewed as a critical executive-control mechanism, regulating a wide range of cognitive and motor processes that are required to prevent the execution of any action, for example, resisting temptation, delay of gratification, Pavlovian conditioned inhibition, motor inhibition and impulse control (Aron 2007; Harnishfeger 1995; Lister et al. 1996). Whilst recent debate has led to dispute over the precise definitions of behavioural and cognitive processes within the concept of 'inhibition', the phenomenon of 'action inhibition' is widely accepted within the psychological literature as an indisputable and plausible form of inhibition (MacLeod et al. 2003).

The unitary concept of 'action inhibition'

Action inhibition may define one specific neural process, that of simply inhibiting a pre-planned motor response or it may reflect a set of subtly different processes that are dissociable at the neural level: attending to, and interpreting, signals to inhibit; making decisions based on those signals and other internal and external cues; selecting an appropriate inhibitory action and successfully executing a motor action that counteracts the pre-planned motor response. From a clinical perspective, such a deconstruction of action inhibition into behavioural subtypes would be important if it were to reveal critical differences between

disorders showing so-called action-inhibition deficits. This might be predicted in the light of studies of impulsive behaviour, which have deconstructed a unitary concept of 'impulsivity' into several distinct behavioural subtypes, each of which can be defined pharmacologically and anatomically (Chamberlain and Sahakian 2007; Robinson et al. 2007; Winstanley et al. 2004a; Winstanley et al. 2006).

Deficient action inhibition has been characterised in a number of disorders, including attention deficit and hyperactivity disorder (ADHD), Parkinson's disease, schizophrenia, obsessive–compulsive disorder and chronic substance abuse (e.g. cocaine, amphetamine, methamphetamine), and is also seen as a useful behavioural marker of genetic risk factors (Aron 2007; Aron and Poldrack 2005; Bellgrove et al. 2006; Durston et al. 2008; Fillmore and Rush 2002; Fillmore et al. 2002, 2006; Gauggel et al. 2004; Monterosso et al. 2005; Nigg et al. 2004; Oosterlaan et al. 1998; Penades et al. 2007; Rubia et al. 1998, 2005b, 2007; Schachar et al. 2007; Schachar et al. 1995; van den Wildenberg et al. 2006). Indeed, impaired action inhibition is often considered as the core deficit in ADHD (e.g. Barkley 1997), and at the very least, one of the key executive function deficits within an integrative model of the ADHD spectrum (e.g. Castellanos et al. 2006). Test batteries that include measures of action inhibition (stop-signal and go/no-go tasks) are extensively used in ADHD research (Rubia et al. 2007). However, the majority of studies define a unitary action-inhibition deficit using a range of diagnostic tasks, such as go/no-go, stop-signal and reversal-learning tasks, that are used interchangeably, but that potentially tap into different fundamental mechanisms. Underlying pharmacological differences between action-inhibition subtypes may dictate the efficacy of a particular treatment regime and may explain why a drug that is effective at treating inhibitory deficits in some people is ineffective in others. In this review, we discuss evidence that defines separate processes within the global concept of action inhibition and show, using evidence that translates from rodent to human tasks, that these forms of inhibition are mediated via different anatomical and pharmacological substrates within the brain. This may have significant implications for the development of novel therapies for disorders such as ADHD in which action-inhibition deficits are prominent.

'Action restraint' and 'action cancellation'

Recently, Schachar et al. (2007) defined two forms of action inhibition: 'action restraint' and 'action cancellation'. With both forms of inhibition acting on pre-planned motor actions, action restraint describes the inhibition of the motor response *before* that response has been started. Action restraint is studied in tasks such as the go/no-go task and the main focus of interest is the ability or failure to withhold from responding (percentage successful inhibition, commission errors, false alarms, etc.). Action cancellation describes the inhibition of a motor response *during* its execution and is studied using the stop-signal task. The key component of the stop-signal task is the stop-signal reaction time (SSRT), which is an estimate of the time taken for a subject to attend to, process and complete an inhibitory response to the stop signal. The 'race' model (Logan 1994; Logan and Cowan 1984) provides a theoretical framework that enables the estimation of the end point of this response (the action of inhibition) for which there is no physical outcome (Appendix).

Superficially, there appears only a semantic difference between these forms of inhibition, and indeed, across the literature, particularly in studies of ADHD, go/no-go and stop-signal tasks are usually used interchangeably to describe dysfunctional action inhibition (e.g. Aron 2007; Aron et al. 2004) on the assumption that they reflect a common process and neural substrate. Indeed, the general formats of stop-signal and go/no-go tasks in behavioural research are often similar or identical with the only difference being the position of the stop signal relative to the go response (Fig. 1). Both tasks are based on repeated performance of a motor response, the 'go' response, which may be a key/lever press or touch-screen response to a visual stimulus. In a subset of trials, the subject receives a 'stop' signal (either visual or auditory) that informs the subject to inhibit the 'go' response, after which the subject must inhibit performance of the go response for a pre-defined time period. SSRT (the time required to attend to, process and complete an inhibitory response to the stop signal) is a component of both stop-signal and go/no-go tasks; however, the stop-signal task is specifically designed to evaluate the SSRT process by presenting stop signals close to the endpoint of the go response and monitoring the competition between stop and go processes in terms of which finishes first. The speed of processing of the stop signal does not affect the outcome of the go/no-go task

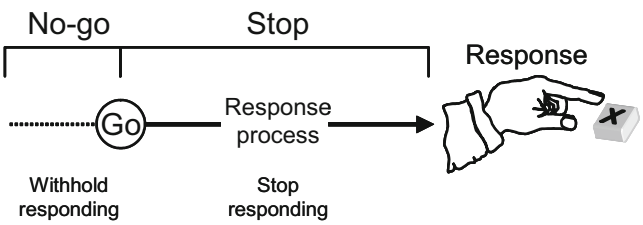

Fig. 1 Representation of the go/no-go and stop-signal tasks. In the stop-signal task, the stop signal is presented after the signal to go, so the response is in the process of completion. In the go/no-go task, the stop signal is presented before or contiguous with the go signal, so the subject must withhold a response

because the evaluation of the stop-signal occurs well in advance of the go response at a point at which the race model predicts that inhibition should be 100% accurate. Often, evaluation of the stop and go signals occurs before the subject is allowed access to the lever/button on which to make the go response. Therefore, it is not possible to estimate SSRT from the go/no-go task (see Logan 1994 for the explanation of these theoretical issues).

The go/no-go task also contains a decision-making component that is absent from the stop-signal task, as a result of the relative positioning of the stop and go signals. In the stop-signal task, each trial starts off as a go-response trial, so there is no pre-response go or no-go selection. If a further signal occurs (the stop signal), the subject must change its response, but this is always an indicator of an inhibitory response, so no decision need be made. The stop-signal task is specifically designed to eliminate decision-making from the experimental process. In the go/no-go task, the subject must select a response strategy (to go or to inhibit) before initiating the response. Indeed, many go/no-go tasks present two stimuli (for rodents) or two sets of stimuli (for humans) that are very similar in nature (e.g. lights) as their go and no-go signals, potentially increasing the difficulty of the decision-making component of this task.

Schachar et al. (2007) noted that because the critical difference between stop-signal and go/no-go tasks is often the temporal location of the inhibitory signal within the main motor task (Fig. 1), it would be possible to devise a test procedure in which both action-restraint and action-cancellation components are presented within-session. Recently, within one basic task framework, the SSRT has been measured alongside stop-trial commission errors (measured under a condition when the go and stop signals were presented together, the no-delay or zero-delay condition) (e.g. Eagle and Robbins 2003a; Eagle et al. 2007; Rubia et al. 2001; Schachar et al. 2007). Examining action restraint and action cancellation in this way eliminates potentially confounding effects of comparing between different tasks and may provide a more practical framework for further analysing these forms of inhibition. In addition, this form of task reduces the decision-making component of the no-delay (go/no-go) form of the task: as in the stop-signal task, the correct response is always to go, unless the subject detects a stop signal. Whilst this procedure helps to eliminate the potential confounds on the go/no-go task of restraint and decision making, there may be separate issues associated with presentation of the stop and go signals at the same time (such as attentional conflicts), and clearly, there is scope for further task development to clarify these issues. For the purposes of this review, action restraint encompasses all 'no-go' responding (go/no-go and no-delay stop-signal tasks), evaluated as the presence or absence of response at a position in the go trial that allows all inhibitory responses to be completed once they are initiated. Action cancellation encompasses all studies in which the stop-signal is presented after the initiation of the go response and late enough to impair inhibition because the stop process did not finish in time. We hypothesise that because action restraint effectively measures whether action inhibition can be initiated and maintained and action cancellation evaluates specifically the time required for action inhibition to be implemented (SSRT), these forms of inhibition represent fundamentally different classes of inhibitory response that are anatomically and pharmacologically separable.

Translational implications of response inhibition research

Simple tests of behavioural inhibition, such as the go/no-go and stop-signal tasks that measure action restraint and action cancellation, respectively, are excellent tools for translational research as the basic forms of these tasks are appropriate for testing human, primate and rodent subjects without significant changes in experimental design. This permits the investigation of aspects of human psychiatric dysfunction using techniques that are simply not possible to use in studies with patients, for example, during the development of novel drug therapies. For both action restraint and action cancellation, rats and humans can perform almost identical versions of these tasks. This enables simultaneous study of pre-clinical and patient populations to establish the neural basis and experimental therapeutics of particular disorders. Of course, one must exercise caution when extrapolating across species from rats to humans with respect to cortical function, as homologies between regions of the human and rat cortex are controversial (Preuss 1995). However, we will argue that it is possible to use 'functional homology' (see Robbins 1998) to make tentative comparisons between structures that appear to modulate the same behavioural functions across the different species. Within the basal ganglia, however, structure has largely been conserved in evolutionary terms, making it far more credible to make direct comparisons between these species. This is also true to a major extent for the ascending neurotransmitter systems, e.g. noradrenaline, serotonin, dopamine and acetylcholine, although there are some important species differences (Bentivoglio and Morelli 2005; Lewis 2001; Mesulam et al. 1983; Robbins et al. 2006). With respect to both action restraint and action cancellation, it is becoming clear that the cross-species comparability is very strong and this review brings together, for the first time, evidence from many directly comparable studies across species.

Neural systems underlying action restraint and action cancellation

Both action-restraint and action-cancellation impairments have been extensively documented as forms of frontostriatal dysfunction (Chamberlain and Sahakian 2007; Fuster 1988; Penades et al. 2007; Robbins 2007; Rubia et al. 2006a). Neuroanatomical studies of humans, non-human primates and rodents have pinpointed regions of the frontal cortex and basal ganglia that are critical for action inhibition, and interplay between these regions may be essential for attaining appropriate behavioural outcomes (Band and van Boxtel 1999). Early primate studies showed that lesions of the inferior convexity, a likely homologue in macaques of the right inferior frontal gyrus in humans, produced impairments in go/no-go performance (Iversen and Mishkin 1970), and in human studies, the go/no-go task has revealed action-restraint deficits following frontal cortical damage (Decary and Richer 1995; Drewe 1975; Godefroy and Rousseaux 1996). Recent studies have highlighted several cortical regions of interest with respect to both stop-signal and go/no-go tasks, in particular the inferior frontal cortex (IFC). For example, Aron et al. (2004) analysed the involvement of the dorsolateral prefrontal cortex (DLPFC), inferior frontal cortex (IFC) and dorsal anterior cingulate cortex (ACC) in behavioural inhibition tasks and concluded that the IFC and, in particular, the right IFC was critical to inhibition, whilst the other structures had more specific function in other processes within these tasks, such as maintaining the go response or generalised error monitoring.

Rubia et al. (2001) showed subtle differences between brain activation during go/no-go and stop-signal tasks in a comprehensive study using gradient-echo echoplanar MR imaging. Although selective inhibition in the stop-signal and go/no-go tasks activated a similar network of brain regions in both tasks, including IFC, ACC, pre-SMA (supplementary motor area), DLPFC and inferior parietal cortex (IPC), the pattern of activation tended to be bilateral for the go/no-go task and predominantly confined to the right hemisphere for the stop-signal task, a finding that is supported by a number of other studies (Aron et al. 2003b, 2004; Bunge et al. 2002; Garavan et al. 1999; Konishi et al. 1999; Konishi et al. 1998; Menon et al. 2001). For example, in the performance of the stop-signal task, patients with lesion damage to the frontal cortex displayed a strong correlation between lesion size within the right IFC and increased SSRT, whilst there was no such correlation between increased SSRT and lesion size to either the left hemisphere or to neighbouring regions to the right IFC within the right hemisphere (Aron et al. 2003b; Rubia et al. 2003).

In rats, the role of the prefrontal cortex in either action-restraint or action-cancellation control is far from clear. Although there are few studies in this area, the available evidence supports a role for the orbitofrontal cortex (OF) in both processes. There appears to be OF specificity for action cancellation because excitotoxic lesions of the OF, but not the anatomically adjacent infralimbic or prelimbic cortex, lengthened SSRT (Eagle et al. 2008; Eagle and Robbins 2003b). These effects were specific to SSRT as these lesions had no significant effect on the go response. Whilst direct homology between the right inferior frontal cortex in human subjects and the ventral orbitofrontal cortex in rats is unproven, these regions are currently the only cortical regions, in their respective subject species, to be specifically implicated in the control of SSRT.

There is conflicting evidence for a role for the OF in action restraint. NMDA-induced lesions of the lateral OF in rats did not impair acquisition of an odour-cued go/no-go task with subjects and control subjects able to perform no-go inhibitory responses (Schoenbaum et al. 2002). This evidence is supported by a lack of impairment following excitotoxic OF lesions in the no-delay condition in the stop-signal task (Eagle et al. 2008). Rats with OF lesions were, in fact, better at inhibiting responding in this 'no-go' condition, although they were impaired at stopping when the stop signal was presented during the go response (Eagle et al. 2008). This evidence contrasts with previous studies that found significantly impaired go/no-go performance following aspirative lesions of the OF (Eichenbaum et al. 1983; Eichenbaum et al. 1980), leading Schoenbaum et al. to conclude that OF damage was more disruptive to no-go performance if rats had pre-learned several series of discrimination tasks, but was ineffective in disrupting performance if task acquisition took place subsequent to the lesion surgery.

The basal ganglia are implicated in both action restraint and action cancellation. For example, adult patients with basal ganglia lesions have impaired action cancellation on a stop-signal task (Rieger et al. 2003) with a similar effect produced by excitotoxic lesions of the dorsomedial striatum in rats (Eagle and Robbins 2003a). In addition, SSRT deficits have been linked with abnormal subthalamic nucleus (STN) function in Parkinson's disease (Gauggel et al. 2004), and stimulation within the STN, but not surrounding structures, in these patients improved SSRT (van den Wildenberg et al. 2006). However, in the rat, lesions of the STN globally disrupted performance on the stop-signal task, both when the stop signal was delayed and when the stop signal was presented at the same time as the go signal, more strongly indicative of a generalised attentional or response selection (no-go-like) deficit following these lesions. This disruption of performance may have masked any effect of STN lesions on SSRT per se in the rat (Eagle et al. 2008). Subcortical function is often disrupted in ADHD during the processing of stop and no-go signals.

For example, subjects with ADHD exhibited less striatal activation than control subjects during a go/no-go task, whilst there was no difference in cortical activation between groups (Vaidya et al. 1998).

Recent studies have begun to link the frontal cortex and basal ganglia evidence into a functional circuitry of action inhibition, but in particular relating to action cancellation. One candidate is a circuit connecting the orbital/inferior frontal cortex with striatum/caudate putamen (Chamberlain et al. 2006a; Eagle et al. 2008; Penades et al. 2007). In rats, there is subcortical specificity that suggests the existence of such discrete corticostriatal circuitry, at least with respect to action cancellation. Stop-signal task deficits can be induced by both OF lesions and lesions of the dorsomedial striatum (DMStr) (Eagle et al. 2008; Eagle and Robbins 2003a). The ventral OF projects mainly to the DMStr, but not to the core region of the nucleus accumbens (Groenewegen et al. 2005; Hoover and Vertes 2004; Schilman et al. 2007), lesions of which had no effect on SSRT (Eagle and Robbins 2003b).

The second candidate involves a role for the STN in the mediation of SSRT through a 'hyperdirect' connection with the inferior frontal cortex. This pathway could provide the rapid information processing required for action cancellation. In human subjects, STN activation correlated with decreased SSRTs (Aron and Poldrack 2006), and STN activation on the stop-signal task also correlated with activation of the RIFC. The relative merits of these pathways are still under investigation, but the ability to translate behavioural effects between species groups can only facilitate our understanding in this area.

Role of serotonin (5-HT) in action inhibition

Central serotonin function is widely acknowledged as an important mediator of behavioural inhibition and response control, and it has been proposed that decreased 5-HT contributes to increased impulsivity (Evenden 1999; Soubrie 1986). However, growing evidence, translating across rodent, primate and human studies, suggests that serotonin may be critical for only some of these behavioural subtypes of inhibition (Clark et al. 2005; Clarke et al. 2005; Dalley et al. 2002; Harrison et al. 1997; 1999; Mobini et al. 2000; Passetti et al. 2003; Winstanley et al. 2004a, b).

It is clear from studies of other forms of inhibition, both animal and human, that there are mixed effects of serotonin manipulations. For example, in rats, 5-HT depletion increased premature responding on the five-choice, and the modified one-choice, serial reaction time tasks, increased locomotor activity conditioned to food presentation and increased speed and number of responses made during autoshaping (Harrison et al. 1997; Winstanley et al. 2004a); all of which are well-recognised measures of altered impulse control. However, the effects of 5-HT depletion on impulsive choice (i.e. delayed gratification) were less clear with some studies finding increased impulsive choice with 5-HT depletion, and others finding no effects (Mobini et al. 2000; Winstanley et al. 2004a). In normal healthy human volunteers, using acute tryptophan depletion (ATD) to reduce 5-HT function produced mixed effects on inhibitory control (Crean et al. 2002; LeMarquand et al. 1999; Murphy et al. 2002; Riedel 2004; Rubinsztein et al. 2001; Walderhaug et al. 2002). Clark et al. (2005) hypothesised that the cognitive effects of 5-HT challenge may vary as a function of individual differences in ratings of impulsivity. Evidence for the role of 5-HT in stop-signal and go/no-go tasks is summarised in Table 1 and discussed below.

Role of 5-HT in action restraint

There is clear evidence that 5-HT plays a role in the modulation of action-restraint inhibition. In rats, global 5-HT depletion following intra-cerebroventricular (i. c. v.) infusions of 5,7-DHT (5,7-dihydroxytryptamine) profoundly disrupted the acquisition of action restraint in response to a no-go signal and also impaired the ability of previously trained rats to subsequently inhibit correctly to a no-go signal (Harrison et al. 1999) with no change in other task measures. Similarly, rats administered parachloroamphetamine, to induce 5-HT depletion in the brain, showed impaired acquisition of a go/no-go task (Masaki et al. 2006).

Neuroimaging studies implicate the orbitofrontal cortex in relation to the effects of serotonin on action-restraint inhibition. For example, Rubia et al. (2005a) found that ATD decreased right orbito-inferior prefrontal activation in fMRI during the no-go condition, although there was no significant alteration in inhibitory performance on task. Citalopram enhanced the response of the lateral orbitofrontal cortex (BA47) to the no-go condition, whereas it attenuated the response to the no-go condition in the medial orbitofrontal (BA11), using fMRI (Del-Ben et al. 2005). In addition, fMRI investigation of healthy subjects' neural responses with or without the antidepressant mirtazapine, during performance of a go/no-go task, found significant activation in the right dorsolateral prefrontal cortex, right anterior cingulate, right temporal and right parietal cortex, left occipital cortex and left thalamus and bilateral middle frontal gyrus and orbitofrontal cortex, but of these, mirtazapine enhanced activation exclusively in the right lateral orbitofrontal cortex (Vollm et al. 2006). Anderson et al. (2002) showed an increased blood oxygen level-dependent (BOLD) signal in the right orbitofrontal cortex during go/no-go following treatment with a 5-HT2c agonist, *m*-chlorophenylpiperazine (*m*CPP) in healthy adults. There is also evidence for a negative correlation between commission errors and 5-HT synthesis capacity in

Table 1 Summary of the role of serotonin (5-HT), dopamine and noradrenaline in the stop-signal and go/no-go tasks showing the comparability of evidence between human and animal subjects

Task	Experimental method	Effect	Notes (type or magnitude of effect)	References
Serotonin (5-HT)				
SSRT human	Citalopram (SSRI)	−	No effect on SSRT	Chamberlain et al. 2006b
	Buspirone, partial serotonin 1A receptor agonist	−	No effect on SSRT	Chamberlain et al. 2007
	Acute tryptophan depletion (ATD)	−	No effect on SSRT	Crean et al. 2002
SSRT animal	Serotonin transporter knockout mice	−	No effect on SSRT	Hausknecht et al. 2006
	Global 5-HT depletion (5,7-dihydroxytryptamine) in rats	−	No effect on SSRT or any other stop-task measure	Eagle et al., unpublished data
Go/no-go human	Acute tryptophan depletion (ATD) fMRI	+	No effect on no-go but decreased activity in right orbito-inferior prefrontal, superior and medial temporal cortex during no-go	Rubia et al. 2005a
	Citalopram (SSRI) fMRI	+	Enhanced lateral orbitofrontal and decreased medial orbitofrontal response to no-go	Del-Ben et al. 2005
	Mirtazapine fMRI	+	Enhanced right orbitofrontal activity to no-go	Vollm et al. 2006
	m-chlorophenylpiperazine (*m*CPP) 5-HT(2c) agonist fMRI	+	Enhanced activation in right lateral orbitofrontal cortex during go/no-go	Anderson et al. 2002
	alpha-[(11)C]MTrp trapping PET in men with borderline personality disorder	+	Lower alpha-[(11)C]MTrp trapping in medial frontal gyrus, anterior cingulate gyrus, superior temporal gyrus, and striatum. Negative correlations with no-go commission errors in the medial frontal gyrus, anterior cingulate gyrus, temporal gyrus, and striatum	Leyton et al. 2001
	PET with [(18)F]altanserin to characterise 5-HT(2) receptor binding	+	A-1438A allele group made more no-go errors than those in G-1438G group	Nomura and Nomura 2006
Go/no-go animal	Global 5-HT depletion (5,7-DHT) in rats	+	Unable to withhold responding and thus correctly complete the no-go trials	Harrison et al. 1999
	Parachloroamphetamine (PCA)	+	Longer to acquire go/no-go	Masaki et al. 2006
Dopamine				
SSRT human	L-DOPA dopamine agonist	−	No effect on SSRT or any other measure	Overtoom et al. 2003
	L-DOPA dopamine agonist	−	No effect on SSRT	Clark et al., unpublished data
	Seven-repeat allele of DRD4 in children with ADHD	−	No effect on percentage of inhibitions but faster GoRT	Langley et al. 2004
SSRT Animal	*cis*-flupenthixol D1/D2 receptor antagonist	−	No effect on SSRT but slower GoRT	Eagle et al. 2007
Go/no-go human	Acute phenylalanine tyrosine depletion (APTD) +L-DOPA	−/+	In rewarded condition, APTD increased commission errors on go/no-go and L-DOPA restored baseline levels. In loss condition, APTD and L-DOPA had no significant effects	Leyton et al. 2007
	Seven-repeat allele of DRD4 in children with ADHD	−	No effect on percentage of inhibitions but faster GoRT	Langley et al. 2004
	APTD	−	No effect on no-go false alarms in either affective or non-affective go/no-go. Faster response times in both	Vrshek-Schallhorn et al. 2006
	L-DOPA fMRI	−/+	Pre-L-DOPA activity in the right parietal cortex correlated with false-alarm rate, but no significant effect of l-DOPA on overall false-alarm rate	Hershey et al. 2004

Table 1 (continued)

Task	Experimental method	Effect	Notes (type or magnitude of effect)	References
Go/no-go animal	D1 and D2 dopamine receptor agonists (SKF38393, quinpirole) and antagonists (SCH23390, sulpiride)	−	No difference in D1-and D2-drug effects on neuronal activity between go and no-go trials	Inase et al. 1997
	cis-flupenthixol D1/D2 receptor antagonist	−	No effect on no-delay percentage of inhibition (using stop-task format)	Eagle et al. 2007
Noradrenaline				
SSRT human	Atomoxetine SNRI	+	SSRT improved	Chamberlain et al. 2006b
	Desipramine	+	SSRT improved	Overtoom et al. 2003
	Guanfacine α2A receptor agonist	−	No effect	Muller et al. 2005
SSRT animal	Atomoxetine (NARI)	+	SSRT improved	Robinson et al. 2008
	Guanfacine α2A receptor agonist	−	No effect	Bari et al., unpublished findings
Go/no-go human		*		
Go/no-go animal	Clonidine (alpha-2 receptor agonist) and B-HT920 (agonist for alpha-2 and D2 receptors) examined iontophoretically on neurons in the prefrontal cortex of monkeys	+	Enhancement of neuronal activity related to both go and no-go performance. Blocked by yohimbine but not sulpiride (D2) suggesting alpha-2 receptor involvement	Li and Kubota 1998
	Yohimbine infusion into prefrontal cortex	+	No-go performance impaired selectively	Ma et al. 2003

+ indicates effect, − indicates no effect, * indicates no known studies

some cortical sites, including the medial frontal gyrus (Leyton et al. 2001).

Although this evidence pinpoints the orbitofrontal cortex as a key locus for the action of serotonin during action-restraint inhibition, the precise mechanism by which serotonin exerts its influence over performance via the orbitofrontal cortex is far from clear. Recently, it has been proposed that a polymorphism in the promoter of the 5-HT2A receptor gene may underlie some forms of behavioural inhibition, and there is evidence of a role for this receptor in action-restraint inhibition. Subjects with the A-1438A allele of the 5-HT(2A) receptor gene made more commission errors under the punishment–reward condition in a go/no-go task than those in the G-1438G group (Nomura and Nomura 2006). The role of other 5-HT receptor subtypes in action restraint is not known.

Role of 5-HT in action cancellation

In contrast to the strong evidence supporting a role for 5-HT in action restraint, there is no evidence that 5-HT plays any significant role in the modulation of action cancellation. Clark et al. (2005) found that depletion of brain serotonin had no effect on SSRT, even when subjects were stratified according to 5-HT transporter polymorphism. Neither the partial serotonin 1A receptor agonist, buspirone, nor the selective serotonin reuptake inhibitor, citalopram, had any effects on SSRT in healthy volunteers (Chamberlain et al. 2006b, 2007), and the lack of effect of citalopram on SSRT has recently been replicated in rats (Fig. 2). Furthermore, in rat studies, global (i. c. v.) 5,7-DHT lesions had no effect on SSRT or any other primary measure on the stop-signal task (Eagle et al., unpublished data), and serotonin transporter knockout mice showed no differences in any baseline measure on the stop-signal task from wild type controls (Hausknecht et al. 2006). There is also no clinical evidence to support the use of serotonin-based drugs in the treatment of the core impulsive motor symptoms of ADHD.

Indirect support for a lack of effect of serotonin in the mediation of action cancellation comes from a study by van den Bergh et al. (2006) who found no link in rats between aggression towards intruders and slowing of SSRT, although they did find a direct correlation between this form of aggression and another form of behavioural disinhibition, impulsive choice (delayed gratification). This indirectly supports the lack of effect of serotonin in the control of stopping because there are links between serotonin and some, although not all, forms of aggression. For example, serotonin depletion using ATD may increase aggression in subjective assessment and in laboratory tests such as the Point Subtraction Aggression Paradigm and Taylor Competitive Reaction Time Task (Bjork et al. 1999, 2000; Cleare and Bond 1995; Moeller et al. 1996; Pihl et al. 1995; Salomon et al. 1994).

Only one study (Crean et al. 2002) shows a weak link between serotonin and action cancellation. They found that although there was no statistically significant effect of dietary tryptophan depletion on action cancellation (SSRT)

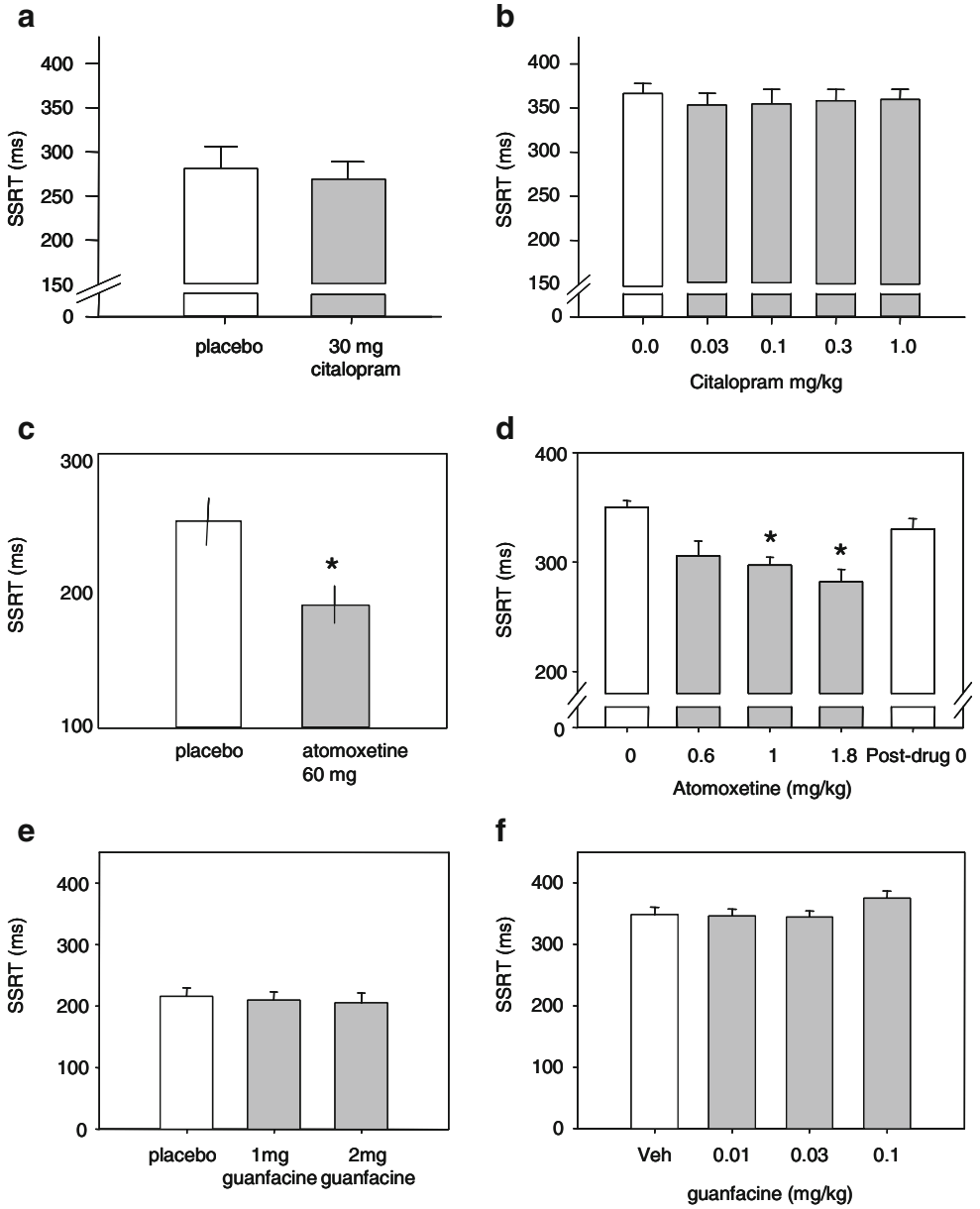

Fig. 2 **a** and **b** The lack of effect of citalopram on SSRT in **a** human and **b** rat subjects (Bari et al., unpublished findings). **a** No effect on SSRT of orally administered citalopram in a between-subjects (n=20) treatment ($p \leq 0.973$). **b** No effect on SSRT of intraperitoneally administered citalopram in a within-subjects (n=26) treatment (dose $F(4,100)=0.23$, n.s.). Methodology in **b** was identical to that described in Eagle et al. (2007) with drugs administered following a randomised Latin square design. **c** and **d** Significant effects of atomoxetine on SSRT in **c** human and **d** rat subjects. **c** Significant effect of orally administered atomoxetine in a between-subjects (n=20) treatment ($p \leq 0.014$). **d** Significant effect of intraperitoneally administered atomoxetine in a within-subjects (n=11) treatment ($p \leq 0.002$). **e** and **f** The lack of effect of guanfacine on SSRT in **e** human and **f** rat subjects (Bari et al., unpublished findings). **e** No effect on SSRT of orally administered guanfacine in a between-subjects (n=20) treatment ($F(2,55)=0.124$, n.s.). **f** No effect on SSRT of intraperitoneally administered guanfacine in a within-subjects (n=22) treatment (dose $F(3,63)=1.78$, n.s.). Methodology as for **b**. *Asterisk* indicates significant difference from vehicle. **a** with permission and adapted from Chamberlain et al. 2006a, b. **c** with permission and adapted from Chamberlain et al. 2006a, b. **d** with permission and adapted from Robinson et al. (2008). **e** with permission and adapted from Muller et al. 2005

in healthy volunteers with no family history of alcoholism following tryptophan depletion, their SSRTs were significantly faster than a group that had a family history positive for alcoholism. There may, therefore, be some effect of 5-HT depletion in populations with different baseline levels of impulsivity, and this hypothesis merits further investigation.

Clark et al. (2005) commented that the actions of 5-HT in response inhibition might be critical to stop-signal task performance only if "trial-by-trial performance was associated with motivational consequences in terms of either reinforcement or punishment" because many behaviours known to be modulated by 5-HT contain a component of

reward/punishment-related feedback. In the human stop-signal task, there is usually no formal form of reinforcement for correct trials. However, in the rat version of this task where performance was maintained using food reinforcement, there was still no effect of 5-HT depletion on performance (Eagle et al., unpublished data). Therefore, it appears that the lack of effect of 5-HT depletion in the human study may not result from the lack of reinforcement on the task. It is probable that global disruption of the 5-HT system in healthy subjects does not, in fact, influence the action-cancellation form of action inhibition.

The role of serotonin in action inhibition: a summary

Serotonin clearly influences action restraint but not action cancellation. Whilst serotonin does not influence SSRT, it may influence any one of several behavioural components in the go/no-go task, such as the discrimination of go and no-go signals, decision making, or withholding responding. Serotonin manipulations appear to be specific to the initiation or maintenance of inhibition, rather than discrimination or selection of the go and no-go signals or the processing of errors/feedback because 5-HT-depleted rats have unimpaired acquisition of conditional visual discriminations where both of the correct choices involve active responses (Graham et al. 1994; Ward et al. 1999). Harrison et al. (1999) suggested that the deficit following global 5-HT depletion in rats was the inability to withhold responding following inhibition. This is further supported by evidence that 5-HT receptor manipulations affect premature responding (decrease the ability to withhold) on the five-choice serial reaction time task (Koskinen et al. 2000; Ruotsalainen et al. 1997), whereas there is no evidence that 5-HT manipulations affect response selection or attention on that task (Harrison et al. 1997; Robbins 2002). In fact, in the no-delay version of the stop-signal task, rats with global serotonin depletion are also unable to withhold inhibition in an extended limited hold challenge (Eagle et al., unpublished data).

Psychostimulant effects on action inhibition: the role of catecholamines

Dopamine and noradrenaline are clearly implicated in processes of behavioural inhibition. (Arnsten 2006; Arnsten and Li 2005; Cardinal 2006; Cardinal et al. 2004; Chamberlain and Sahakian 2007; Dalley et al. 2004; Davids et al. 2003; Evenden and Ryan 1996; Robbins 2002; Robbins and Everitt 1987; Winstanley et al. 2006). However, to a large degree, our knowledge of catecholaminergic mediation of action inhibition has come from studying the action of psychostimulants, which act in general as indirect catecholamine agonists. By blocking DA reuptake and promoting the release of DA from axon terminals (Axelrod et al. 1970; Hendley et al. 1972; Ross 1978), the subsequent increase in DA, mainly in the striatum, may underlie the therapeutic effects of these drugs.

Psychostimulants such as methylphenidate (Ritalin™), the most commonly prescribed drug in the treatment of ADHD, and D-amphetamine have proven modulatory effects on both action restraint and action cancellation (Aron et al. 2003a; Bedard et al. 2003; Paule et al. 2000; Solanto 1986, 1998; Spencer et al. 2001; Tannock et al. 1989; Vaidya et al. 2005). For example, methylphenidate (MPH) decreases SSRT in both adult and childhood ADHD (Aron et al. 2003a; Bedard et al. 2003; Tannock et al. 1989) and reduces commission errors in both ADHD and control subjects on go/no-go (Vaidya et al. 1998). This fMRI study by Vaidya et al. 1998 clearly shows the subcortical effects of MPH that could mediate its action-inhibition effects: control-group children had high caudate and putamen activity that was significantly reduced by MPH (Vaidya et al. 1998), whereas children with ADHD had lower baseline caudate and putamen activity that significantly increased following treatment with MPH. This may reflect differences in baseline dopamine activity, as PET imaging of MPH effects in healthy adults showed that changes in brain metabolism varied as a function of dopamine receptor availability (Volkow et al. 1997), and fits with findings that methylphenidate increases extracellular striatal DA (Volkow et al. 2001). However, behaviourally, methylphenidate had similar effects in both the control and ADHD groups, reducing commission errors during no-go trials in both groups (Vaidya et al. 1998). MPH-related striatal activation has been reported in ADHD subjects in several other studies (Lou et al. 1989; Rosa-Neto et al. 2005).

Recently, an atypical stimulant, modafinil (diphenyl-methyl-sulphinyl-2-acetamide), has gained significant interest as a potential treatment of ADHD. Modafinil improved symptoms in both childhood ADHD (Rugino and Copley 2001; Rugino and Samsock 2003) and adult ADHD (Taylor and Russo 2000; Turner et al. 2004) and decreased SSRT in healthy adults (Turner et al. 2003). Modafinil is of particular interest to this review as its effects appear to be highly specific to action cancellation. Modafinil has no effects on either the go process (GoRT) or the no-delay, action-restraint component of the stop-signal task (Eagle et al. 2007; Turner et al. 2004), unlike conventional psychostimulants which often speed GoRT and SSRT (Bedard et al. 2003; Lijffijt et al. 2006; Tannock et al. 1989). From a translational perspective, modafinil similarly improves SSRT in rats and humans (Eagle et al. 2007; Turner 2006; Turner et al. 2003, 2004), effects that are directly comparable with the effects of conventional psychostimulants.

Modafinil is conventionally used to treat narcolepsy and idiopathic hypersomnia by stimulating wakefulness and vigilance (Bastuji and Jouvet 1988; Billiard et al. 1994), leading to suggestions that the therapeutic benefits conferred to ADHD sufferers resulted from generally improved vigilance and attention. This has yet to be supported by controlled studies in experimental animals; for example, Waters et al. (2005) found no improvement in rat performance with modafinil on the five-choice serial reaction time test, a well-documented test of attentional control (Robbins 2002). However, the evidence for a specific SSRT-improving role for modafinil suggests that it may also confer non-attentional benefits because the stop-signal task measures a process with relatively low attentional demands, given the salience of the stop signal.

Evidence for baseline dependence of psychostimulant action

The apparently paradoxical efficacy of stimulant drugs to ameliorate the hyperactive or impulsive symptoms of ADHD may result from baseline dependence of some of the drugs' effects on action inhibition. This hypothesis is supported by studies of both action restraint and action cancellation. For example, D-amphetamine decreased 'false alarms' in go/no-go performance in humans (de Wit et al. 2002) with a greater improvement (reduction) in false-alarm rate for subjects with the worst initial performance. These were also the subjects who reported experiencing the lowest levels of amphetamine-induced euphoria, supporting the hypothesis that this drug acts differently upon sub-groups of a normal population. Such baseline-dependent effects of drugs are also found for action cancellation and translate well between rat and human studies (Fig. 3). In both humans and rodents, D-amphetamine decreased SSRT only when subjects had relatively slow baseline SSRT (de Wit et al. 2000; Feola et al. 2000). Similar effects can be seen for methylphenidate (Boonstra et al. 2005; Eagle et al. 2007), and modafinil in both human and rat (Eagle et al. 2007; Turner personal communication). Baseline-dependent psychostimulant action was also found in a rodent study within which the SSRT was artificially manipulated (rather than the natural within-population variability considered above). Rats with dorsomedial striatal lesions with impaired SSRTs compared with control subjects had significantly improved SSRTs following D-amphetamine treatment, whereas control subjects showed little response to the drug (Eagle and Robbins 2003a). Indeed, studies that have found little effect of stimulant drugs on SSRT have usually only considered the population as a whole (Fillmore et al. 2005). The clear benefit of using normal variation within a population to investigate disorders such as ADHD is that symptoms of these disorders can be modelled whilst making no assumptions about their underlying pathology, unlike other potential 'models' of ADHD.

Such baseline dependence may in part explain the relatively high frequency of ADHD subjects that are unresponsive to either methylphenidate or D-amphetamine. In up to 30% of ADHD cases, methylphenidate fails to improve or even worsens symptoms such as deficient action inhibition (Cantwell 1996; Krause et al. 2005), perhaps because MPH only improves deficient action inhibition in the cases that have the most pronounced action-inhibition deficits. One hypothesis is that the effectiveness of methylphenidate treatment of ADHD symptoms is correlated with DAT availability in the striatum (Krause et al. 2005), although the direct relationship between DAT availability and either action-restraint or action-cancellation forms of inhibition is unclear. It would be interesting to investigate this hypothesis further.

In summary, whilst the study of psychostimulants has improved our understanding of the pharmacological basis of both action restraint and action cancellation, the relative contributions of dopamine and noradrenaline to these processes are still far from clear. The following sections review the current evidence for specific catecholaminergic modulation of action inhibition (summary in Table 1), which is of increasing relevance as interest turns towards treating conditions such as ADHD with non-stimulant, receptor-specific drugs.

Candidate transmitter systems for psychostimulant action

As well as a clear role for dopamine, psychostimulants may also interact with noradrenaline (NA) (Kuczenski and Segal 1997), which has also been implicated in the modulation of prefrontal cortical function (e.g. Arnsten and Dudley 2005) and 5-HT (Gainetdinov et al. 1999). Thus, the effects of psychostimulants on action restraint and action cancellation may be mediated by DA, NA, 5-HT or any combination, and it is unclear exactly how psychostimulants affect catecholaminergic mechanisms to modulate either RIFG or striatal action during action inhibition. de Wit et al. 2002 presciently stated that "the abuse potential of D-amphetamine is probably related primarily to its effects at the dopamine receptor (e.g. Wise and Bozarth 1987), *but it is less clear if the effects of this drug on impulsive behaviour are mediated by DA as well*".

Action cancellation

Serotonergic mediation of psychostimulant action may be critical to some forms of inhibitory deficit, for example, serotonin-increasing agents exert the same paradoxical

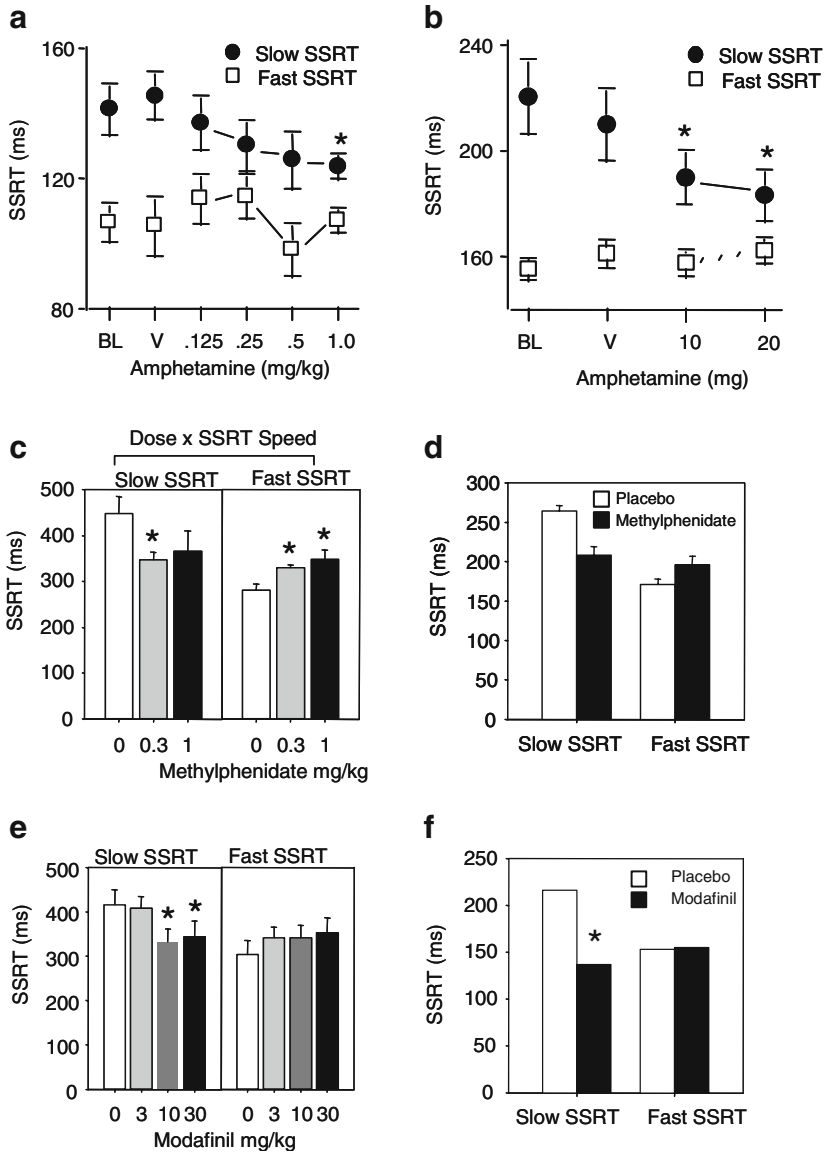

Fig. 3 Baseline-dependent effects of psychostimulants on SSRT translate between human and rat subjects. Effects of D-amphetamine on SSRT in **a** rat and **b** healthy human subjects. Effects of methylphenidate on SSRT in **c** rats and **d** human adults with ADHD. Effects of modafinil on SSRT in **e** rats and **f** human adults with ADHD. *Asterisk* represents significant difference from vehicle or placebo. **a** with permission and adapted from deWit et al. 2000. **b** with permission and adapted from Feola et al. 2000. **c** with permission and adapted from Eagle et al. 2007. **d** Data within Boonstra et al. 2005. **e** with permission and adapted from Eagle et al. 2007. **f** Data within Turner et al. 2004

calming effects as psychostimulants in DAT-KO mice (Gainetdinov et al. 1999). However, given the lack of effect of 5-HT on SSRT, it is unlikely that the SSRT-improving effects of psychostimulants are via 5-HT receptors.

Similarly, although dopaminergic drugs can clearly increase impulsive behaviour on other tasks, e.g. delayed reward (Wade et al. 2000), such drugs have little effect on action cancellation or SSRT. Overtoom et al. (2003) found no effect of L-DOPA on SSRT (findings that have been repeated by Clark et al., unpublished data). Although Fillmore and colleagues reported that cocaine users had impaired SSRTs compared with non-cocaine-using control subjects, suggesting possible dopaminergic involvement in action cancellation, it was not possible to determine whether these differences already existed or resulted from the cocaine use (Fillmore and Rush 2002; Fillmore et al. 2002).

The mixed D1/D2 receptor antagonist, *cis*-flupenthixol, had no effect on action cancellation, but perhaps more critically, it did not influence the SSRT-decreasing effects of methylphenidate and modafinil at doses that significantly increased the GoRT (Eagle et al. 2007). This is perhaps the most convincing evidence to date that D1 and D2 receptors play little role in the mediation of SSRT. Whilst it is possible that methylphenidate or D-amphetamine might act via other DA receptors, there is no clear evidence to support a dopaminergic mechanism of action cancellation with respect to SSRT. Although polymorphisms in the DA receptor D4 (DRD4) gene in ADHD are thought to be critical for cognitive function in some respects, a comparison of ADHD children with or without at least one DRD4 seven-repeat allele found no difference in action cancellation, although there was a difference in GoRTs (Langley et

al. 2004), a finding reinforced by a study by Rubia et al. (2006b) showing that the presence of the DRD4 repeat allele was related to poor inhibitory capacity in the go/no-go but not the stop-signal task. Altogether, the evidence, at present, is against a direct role for DA in action cancellation.

There is growing evidence in support of noradrenergic control of action cancellation. The selective noradrenaline reuptake inhibitor atomoxetine decreased SSRT in healthy adults (Fig. 2) with no effect on GoRT (Chamberlain et al. 2006b). This effect has recently been repeated with rats with SSRT-specific improvements following treatment with atomoxetine, but no significant change in GoRT (Robinson et al. 2008). Overtoom et al. (2003) found that desipramine also improved SSRT without affecting GoRT. Clearly, these studies provide the best evidence to date that a specific neurotransmitter, noradrenaline, is important for action cancellation, and the clear translational effect of atomoxetine on SSRT can be compared directly with the clear translational lack of effect of citalopram on the same measure (Fig. 2). In addition, the SSRT-improving specificity of noradrenergic manipulations is so similar to the pattern of effects of modafinil on this task that it would not be unreasonable to suggest that modafinil also improves SSRT via noradrenaline action. Whilst modafinil exhibits effects on catecholamines, serotonin, glutamate, gamma amino-butyric acid, orexin and histamine systems in the brain (Minzenberg and Carter 2008), the evidence reviewed in this paper suggests that it exerts its action over SSRT via noradrenaline. However, the effects of noradrenaline and, thus, the possible effects of modafinil on action cancellation may not be modulated via the α2a-adrenergic receptor specifically because guanfacine had no effect on SSRT in healthy adults (Muller et al. 2005) or in rats (Bari et al., unpublished findings; Fig. 2). It should, however, be noted that atomoxetine does influence DA release in the rat prefrontal cortex (Bymaster et al. 2002), pinpointing the need for further studies in this area.

Action restraint

Frank and colleagues suggest that dopamine dynamically modulates the balance of go and no-go basal ganglia pathways during cognitive learning and performance (Frank and O'Reilly 2006; Frank et al. 2006). However, the effects they define as increased inhibition may be construed as a negative modulation of the go pathway rather than positive modulation of the no-go pathway, and there is little evidence to support a role for either D1 or D2 receptors in no-go inhibition. Inase et al. (1997) investigated the effect of D1 and D2 receptor agonists SKF38393 and quinpirole and antagonists SCH23390 and sulpiride on single-unit activity in the putamen of monkeys performing a go/no-go task. They showed that both D1 and D2 receptor agents could modulate the activity of neurons in both go and no-go trials but found no selective difference between go and no-go trials in the effectiveness of D1 or D2 manipulations. In rats, the mixed D1/D2 antagonist, *cis*-flupenthixol, had no significant effect on no-delay (no-go) stop-trial accuracy (unpublished data from Eagle et al. 2007: comparison of no-delay stop-trial accuracy for vehicle, 0. 01 and 0. 04 mg/kg *cis*-flupenthixol; $F(2,36)$= 2. 38, n.s.), which again fails to support a role for D1 and D2 receptors in no-go inhibition. However, the highest of these doses of *cis*-flupenthixol clearly slowed the go response, suggesting that D1/D2 receptors are more strongly implicated in the regulation of the go response than in any aspect of action inhibition. One possible candidate in the control of action restraint is the D4 receptor because the presence of the DRD4 repeat allele was related to poor inhibitory capacity in the go/no-go task (Rubia et al. 2006b).

Any studies that find effects of non-stimulant dopamine manipulations on action restraint appear to be highly dependent on the reinforcement outcome of no-go trials. For example, acute phenylalanine/tyrosine depletion (APTD) increased commission errors on a go/no-go task (Leyton et al. 2007), a deficit that was reversed by treatment with L-DOPA. However, this was only the case for trials in which a correct no-go response was rewarded: neither APTD nor l-DOPA affected no-go trials during which a correct inhibition instead prevented punishment. Other studies, which gave no trial-by-trial reinforcement, failed to find either an effect of APTD (Vrshek-Schallhorn et al. 2006) or L-DOPA (Hershey et al. 2004) on no-go errors.

There are few studies that directly address the role of noradrenaline in action restraint, but those that do implicate alpha-2 adrenoceptors. Neurons that responded specifically to the no-go signal, but not the go or waiting signals, displayed increased activity in response to a mixed alpha-2/D2 agonist, B-HT920, and this increase in activity was blocked by the alpha-2 antagonist yohimbine, but not the D2 antagonist sulpiride (Li and Kubota 1998). Further work showed that infusion of yohimbine directly into the prefrontal cortex of macaques selectively impaired inhibition following a no-go signal (Ma et al. 2003).

Summary

This review has assessed the anatomical and pharmacological evidence relating to the modulation of two apparently similar forms of inhibition, action restraint, as measured in go/no-go tasks, and action cancellation, as measured in stop-signal tasks. Whilst there is a degree of overlap in the neural circuitry involved in controlling both types of inhibition, there are clear

and critical neuropharmacological differences between action restraint and action cancellation. This is particularly the case with respect to the involvement of 5-HT, which is implicated in action restraint but not significantly in action cancellation. Perhaps most surprisingly, there is no clear evidence to support a role for dopamine in action cancellation with even the role of dopamine in action restraint being very unclear, although it does have very strong associations with the go response. Instead, growing evidence supports noradrenaline as a candidate neurotransmitter in the mediation of the action-cancellation form of inhibition.

Of particular interest, though, is the excellent translation of effects between species, in terms of basic behavioural findings, neuroanatomical substrates and response to drug/neurochemical manipulations of the dopaminergic, noradrenergic or serotonergic systems. Especially striking are the effects of psychomotor-stimulant drugs such as methylphenidate or modafinil which appear to have broadly similar qualitative effects in humans and experimental animals. The demonstration of baseline-dependent effects in both species for psychostimulant-induced improvements in SSRT is of evident translational relevance for the treatment of such neuropsychiatric disorders as ADHD, the inhibitory deficits of which are commonly assessed using go/no-go or stop-signal tasks such as those reviewed in this paper.

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Appendix

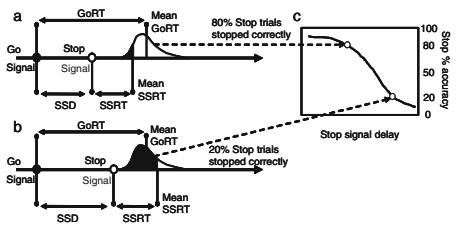
The stop-signal reaction time task (adapted from Logan 1994 and Eagle and Robbins 2003a).

The stop-signal reaction time task (SSRT) task assesses the time required to stop a response that is already in the process of being executed. The key measure on this task, SSRT (the time taken, after a stop signal is presented, for inhibition to be completed) cannot be measured directly as there is no observable endpoint to the response inhibition. Logan and Cowan (1984) presented a method of estimating the finishing point of the stop process, which proposes that the 'stop' and 'go' processes are independent of one another, that a 'race' occurs between the two processes for completion, and that whichever process finishes first wins the race. If the go process wins, a response occurs, and if the stop process wins, a response is inhibited. The finishing times of these processes are assumed to vary randomly, so the outcome of the race is a matter of probability. The race model assumes the stop process to be faster than the go process, and the placement of the stop signal during the go process biases the race in favour of one process or the other. For example, if the stop signal occurs early in the trial, the response will usually be inhibited (Fig. a). Conversely, if the stop signal occurs late enough, the response will rarely be inhibited (Fig. b). An inhibition function can be generated between these two extremes by plotting the probability of inhibition against stop-signal delay (SSD; Fig. c). An estimate of SSRT is calculated from the inhibition function and distribution of go-trial reaction times (GoRT). In general, lower, flatter inhibition functions indicate deficits in inhibitory control.

In order for the race model to be applicable, subjects must attempt to perform go trials as quickly as possible, while attempting to stop on all trials in which they detect a stop signal. The 'race' model fails if subjects slow their response on go trials to anticipate presentation of the stop signal. In the rat task, response speed on go trials is encouraged by restricting the trial length (limited hold; LH), resulting in an incorrect response if subjects are too slow. In the human task, subjects receive verbal instructions about maintaining response speed, but some tasks also include a LH to prevent response slowing.

Subjects must also attempt to stop on all stop trials. Failure to trigger the inhibition process on a constant proportion of trials, regardless of the position of the stop signal produces lower inhibition functions that may result in inflated estimates of SSRT.

This task provides an estimate of the time taken to stop a response (SSRT) from measurable task parameters, the go-trial reaction time distribution, and the accuracy of stopping on stop trials (Figs. a–c). The GoRT provides a measure of the speed of the go process.

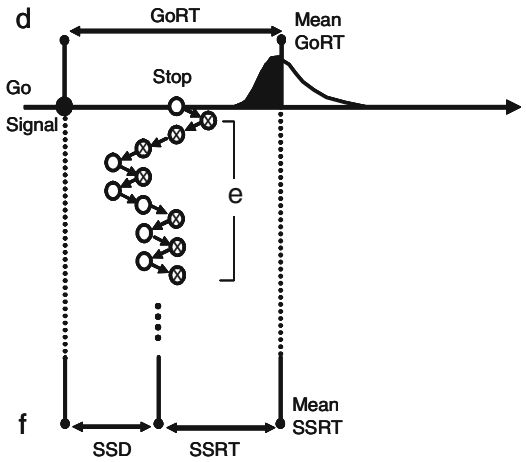


Estimation of stop-signal reaction time.

SSRT can be estimated using the protocol described in Logan (1994). Reaction times on go trials (on which no stop signal occurred) are rank ordered. The *n*th RT is selected from the ranked list of GoRTs for a particular delay session, where *n* is obtained by multiplying the number of RTs in the distribution by the probability of responding on

stop trials in the same session. This is an estimate of the time at which the stopping process finished, relative to the onset of the go signal. To estimate stop signal reaction time (the time at which stopping finished relative to the stop signal), stop-signal delay is subtracted from this value. This is done for each subject for each delay, and the resulting mean taken for lesion and sham groups.

SSRT can also be estimated using a staircase tracking procedure (e.g., Aron et al. 2003a), in which the initial position of the stop signal (Fig. d) is adjusted to be closer to the mean GoRT following a correct stop trial, but adjusted to be further away from the mean GoRT following an incorrect stop trial (Fig. e), resulting, over the course of many trials, in the stop signal position settling at a point at which 50% of stop trials are performed correctly (Fig. f). At this point, subtraction of the SSD from the median GoRT gives an estimate of the SSRT.



Control for differences in baseline performance.

In the stop-signal task, errors on stop trials may occasionally occur as a result of failed attentional or response selection processes that are unrelated to the speed of the stop process. These errors can be detected on no-delay (no-go) trials as changes in performance accuracy. Inhibition function data can be corrected for baseline differences in performance using the procedure presented in the SSRT task for rats, summarised in Eagle and Robbins 2003a, or using alternative procedures presented in Tannock et al. (1989) and Solanto et al. (2001).

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