Neuroscience and Biobehavioral Reviews 33 (2009) 631–646

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Insights into the neural basis of response inhibition from cognitive and clinical neuroscience

Christopher D. Chambers [a,b,*], Hugh Garavan [c], Mark A. Bellgrove [d]

[a] School of Psychology, Cardiff University, UK
[b] Institute of Cognitive Neuroscience, University College London, UK
[c] Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland
[d] School of Psychology, University of Queensland, Australia

ARTICLE INFO

Keywords:
Cognitive neuroscience
Response inhibition

ABSTRACT

Neural mechanisms of cognitive control enable us to initiate, coordinate and update behaviour. Central to successful control is the ability to suppress actions that are no longer relevant or required. In this article, we review the contribution of cognitive neuroscience, molecular genetics and clinical investigations to understanding how response inhibition is mediated in the human brain. In Section 1, we consider insights into the neural basis of inhibitory control from the effects of neural interference, neural dysfunction, and drug addiction. In Section 2, we explore the functional specificity of inhibitory mechanisms among a range of related processes, including response selection, working memory, and attention. In Section 3, we focus on the contribution of response inhibition to understanding flexible behaviour, including the effects of learning and individual differences. Finally, in Section 4, we propose a series of technical and conceptual objectives for future studies addressing the neural basis of inhibition.

Contents

* Corresponding author at: School of Psychology, Cardiff University, Park Place, CF10 3AT, United Kingdom.
E-mail address: chambersc1@cardiff.ac.uk (C.D. Chambers).

0149-7634/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neubiorev.2008.08.016

Intelligent behaviour in a rapidly changing environment requires continual monitoring and updating of our actions. A key determinant of successful cognitive and motor control is *response inhibition*: the ability to suppress behaviours that are inappropriate, unsafe, or no longer required. As reflected by this Special Issue, recent years have witnessed an unprecedented interest in understanding the neural basis of response inhibition, its underlying genetic determinants, and its significance in understanding a range of psychiatric conditions. In this review, we consider evidence from multiple sources, focusing in particular on the contribution of human cognitive and clinical neuroscience.

1. Understanding the neural architecture of response inhibition: the effects of interference and dysfunction

What can the effects of brain injury, interference, or clinical dysfunction tell us about the neural basis of response inhibition? Since early neuropsychological studies, the prefrontal cortex has been regarded as a key source of cognitive control and the ability to suppress stimulus-evoked behaviour (Holmes, 1938; Luria, 1966; Miller and Cohen, 2001). Seventy years after the seminal work of Gordon Holmes, human neuropsychology and cognitive neuroscience have uncovered a network of cortical and sub-cortical regions that is especially crucial for cancelling responses. In this section we consider the contribution of human neuropsychology and brain stimulation studies to understanding the functional neuroanatomy of response inhibition.

1.1. Behavioural measures of response inhibition in studies of neural interference

Investigations of response inhibition have employed a variety of behavioural paradigms, and it is generally assumed that each task assays a common, or at least closely related, inhibitory mechanism. Prominent among these measures are the go/no-go task (Drewe, 1975; Garavan et al., 1999; Picton et al., 2007), stop-signal task (Logan, 1994; Verbruggen and Logan, 2009), and anti-saccade task (Hallet, 1978; Butter et al., 1988; Walker et al., 1998; Anderson et al., 2008); see Fig. 1). Some investigators have also employed the Stroop task (Potenza et al., 2003), flanker task (Wylie et al., 2007), and components of neuropsychological test batteries (Konishi et al., 1999) to probe inhibitory processing. However, it remains controversial whether such tasks isolate processes of response inhibition, as opposed to related control processes such as conflict resolution, response selection, attention, and working memory (Nigg, 2000). For the purposes of the present section, therefore, we focus primarily on evidence obtained in tasks that measure the cancellation of a prepotent motor response. In Section 2, we consider response inhibition more broadly and in relation to other mechanisms of cognitive control.

1.1.1. Ventral prefrontal cortex

Converging evidence suggests that the inferior frontal gyrus (IFG) is crucial for successful response inhibition in the stop-signal task, especially in the right hemisphere (Fig. 2a; for recent reviews, see (Aron et al., 2004; Aron, 2007; Dillon and Pizzagalli, 2007; Mostofsky and Simmonds, 2008; Simmonds et al., 2008). In a pivotal study, Aron et al. (2003b) found that patients with damage to the right IFG – particularly the *pars opercularis* – exhibited significant delays in stop-signal reaction time (SSRT; Fig. 1c) relative to a healthy control group and a sample of patients with left frontal damage. Furthermore, the extent of the damaged cortex in the right IFG, but not nearby prefrontal areas, uniquely predicted the magnitude of the inhibitory impairment. Similar observations have since been reported using transcranial magnetic stimulation

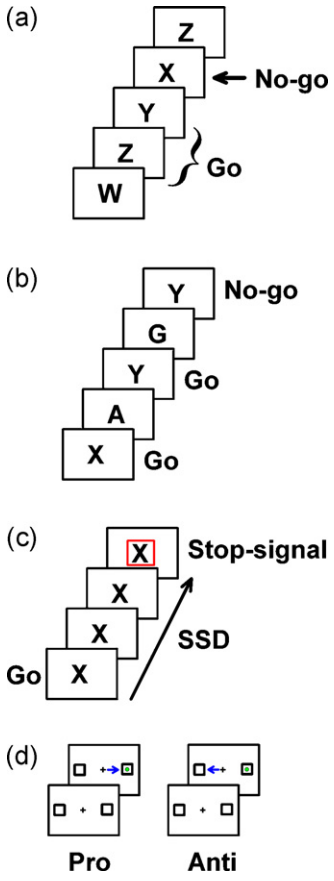

Fig. 1. Typical behavioural measures of response inhibition. (a) In a simple Go/No-go task (e.g. Menon et al., 2001; Picton et al., 2007), participants respond as quickly as possible when a target letter appears (e.g. W, Y, or Z), but must inhibit the response when an infrequent non-target occurs (X). Inhibitory performance is gauged from the percent of responses to no-go stimuli. (b) A common modification of the Go/No-go task incorporates a working memory load (e.g. Garavan et al., 1999; Hester et al., 2004b). Here participants are instructed to respond as quickly as possible to either of two targets in a stream of letters (e.g. X or Y). However, if the letter is the same as the previous target (e.g. Y followed by Y), then it becomes a non-target, as shown. (c) In the stop-signal task (Logan, 1994), participants must identify the target as rapidly as possible (e.g. X or O; here the target is an X). On a minority of trials, a stop-signal occurs, here shown as a red box (Chambers et al., 2006, 2007), but which is commonly delivered as an auditory stimulus). The stop-signal instructs participants to cancel their response. On Stop trials, the crucial manipulation is the stop-signal delay (SSD): the time (in ms) between the onset of the target and the onset of the stop signal. As the SSD increases, the likelihood of correctly inhibiting decreases. Inhibitory performance is quantified through the stop-signal reaction time (SSRT), which is determined by subtracting the SSD at which the participant inhibits correctly on 50% of Stop trials from the participant's mean reaction time on Go trials. This calculation assumes a race between Go and Stop processes, providing a latency estimate for an otherwise covert process (see Verbruggen and Logan, 2009). In healthy populations, SSRT is typically in the range of 150–200 ms. Thus, participants typically require the stop-signal to be presented 150–200 ms prior to their mean reaction time in order to cancel the response on 50% of Stop trials. (d) In an anti-saccade task, participants either execute a reflexive pro-saccade towards a peripheral target, or must suppress this initial reflexive saccade and execute an anti-saccade towards the opposite location. Whether the target requires a pro- or anti-saccade is typically blocked across trials (Hodgson et al., 2007), but can also be randomised by using an additional cue, such as the colour of the background (Chikazoe et al., 2007). In this task, the principal index of response inhibition is the relative increase in saccadic onset latency for anti- vs. pro-saccades.

(TMS) in healthy participants. Low-frequency TMS can reduce cortical excitability for several minutes following stimulation (Siebner and Rothwell, 2003), thus producing a temporary 'virtual lesion'. In two studies, repetitive stimulation of the right IFG temporarily elevated SSRT during responses with either hand (Chambers et al., 2006, 2007), whereas TMS of several other

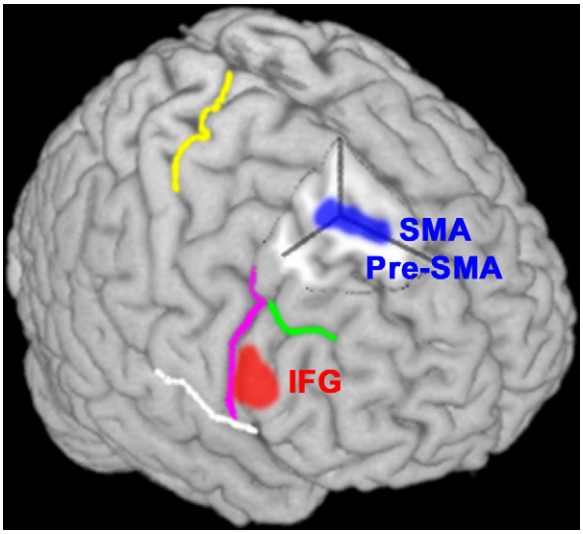

Fig. 2. Cortical substrates of response inhibition in the human brain. Converging evidence from neuroimaging, neuropsychology and TMS has established that the *pars opercularis* of the right inferior frontal gyrus (IFG) is crucial for inhibiting a prepotent motor response (red). The human IFG, as shown here, is bordered by the lateral sulcus (inferior border), precentral sulcus (posterior border) and the inferior frontal sulcus (superior order, and also anterior border with the orbitofrontal cortex). Similarly, medial prefrontal areas, including the supplementary motor area (SMA) and preSMA (blue) are implicated from neuropsychological, TMS, and fMRI studies. Recent evidence further suggests that the IFG and SMA/preSMA might coordinate inhibition through direct white-matter connections, and also via the sub-thalamic nucleus of the basal ganglia. Thus an important goal for future studies will be to establish the unique and common contributions to cognitive control in each of these cortical areas. Sulcal landmarks: yellow = central sulcus; white = lateral sulcus; magenta = precentral sulcus; green = inferior frontal sulcus.

cortical regions, including the left IFG, left or right dorsal premotor cortex, right middle frontal gyrus, and right angular gyrus, did not influence response inhibition. Considered alongside a substantial body of neuroimaging research (Kawashima et al., 1996; Garavan et al., 1999; Konishi et al., 1999; Rubia et al., 2003; Swainson et al., 2003; Aron et al., 2004, 2007a; Morita et al., 2004; Aron and Poldrack, 2006), these findings suggest that inhibitory control is mediated by a right-hemisphere network in which the IFG is a crucial node.

If the ventral prefrontal cortex is an executive controller of behavioural inhibition, then the effects of IFG interference should span multiple inhibitory tasks (e.g. stop-signal, go-no/go, anti-saccade) and multiple motor effectors (e.g. hands, eyes, speech). Recent fMRI studies have provided evidence that the right IFG may support a generalized inhibitory mechanism, which is commonly activated during suppression of speech, manual, and oculomotor responses (Leung and Cai, 2007; Xue et al., 2008). Furthermore, Hodgson et al. (2007) showed that patients with left or right IFG lesions exhibit sluggish behavioural updating in an oculomotor rule-switching paradigm, and are differentially impaired at executing antisaccades (see also Butter et al., 1988; Walker et al., 1998). In future studies, it will be important to elucidate the domain specificity of the IFG in response inhibition by correlating the effects of prefrontal interference within subjects across a range of inhibitory tasks and effectors.

1.1.2. Medial prefrontal cortex

In contrast to the evidence discussed above, several studies have revealed inhibitory deficits in patients with damage to the medial, rather than ventral, prefrontal cortex (Décary and Richer, 1995; Floden and Stuss, 2006; Picton et al., 2007); see Fig. 2b). Décary and Richer (1995), for instance, showed that excision of the dorsomedial prefrontal cortex, including the anterior cingulate and SMA, led to an increased rate of commission errors in a go/no-go task (see also Drewe, 1975; Rieger et al., 2003). More recently, Floden and Stuss (2006) demonstrated an inhibitory impairment in the stop-signal task following damage to the right SMA/preSMA. In contrast, Picton et al. (2007) found that damage to the *left*, but not right, SMA/preSMA was predictive of inhibitory impairments in a go/no-go task. In spite of such differences in cortical lateralisation, these studies consistently indicate that medial frontal regions are important for inhibitory behaviour (see also Chauvel et al., 1996; Fried, 1996). A critical role of the SMA/preSMA is consistent with an established body of evidence indicating that these regions participate in motor planning (SMA) and the updating of motor plans (preSMA; Shima et al., 1996; Ikeda et al., 1999; Mostofsky and Simmonds, 2008).

From these studies, an inhibitory function of the SMA/preSMA seems clear. But how can we reconcile evidence indicating that either IFG (Aron et al., 2003b; Chambers et al., 2006, 2007) *or* SMA/preSMA (Floden and Stuss, 2006; Picton et al., 2007) are selectively crucial for response inhibition? One possibility is that the failure to observe a critical role of IFG or SMA/preSMA reflects functional reorganization of intact areas, which then compensate for damage to centres that would be crucial in the healthy brain (Rorden and Karnath, 2004). In this regard, lesion chronicity may be an important within-subjects factor to consider in neuropsychological studies of response inhibition, in addition to fMRI experiments in brain-damaged patients to study reorganisation. Also, as noted by Floden and Stuss (2006), the inhibitory role of the preSMA may have been obscured in previous designs through 'data dilution', in which non-critical areas are included within designated regions of interest. Given the host of possibilities associated with null observations, it seems likely that the IFG and SMA/preSMA are both crucial for response inhibition (Aron et al., 2007a; Mostofsky and Simmonds, 2008; Coxon et al., in press). Indeed, recent work by Chen et al. (in press) has confirmed that event-related TMS of the preSMA temporarily elevates SSRT, consistent with the inhibitory impairments observed following IFG stimulation (Chambers et al., 2006). A key objective for ongoing studies will be to distinguish the function of the IFG and SMA/preSMA within the neural circuitry of inhibitory control. The application of TMS may be especially useful for addressing this issue by enabling reversible disruption of the cortex (Walsh and Cowey, 2000) and by interfering with neural processing at different stages in the timecourse of cognitive control (e.g. Schluter et al., 1998; Chambers et al., 2004a).

1.1.3. Basal ganglia and the neural circuitry of response inhibition

In addition to frontal substrates, converging evidence has implicated the basal ganglia (BG) in motor suppression. Circumscribed lesions of the BG impair SSRT to a comparable extent to deficits following prefrontal damage (Rieger et al., 2003). At the same time, stimulation of the sub-thalamic nucleus (STN) – an input station of the BG – facilitates stop-signal inhibition in patients with Parkinson's disease (van den Wildenberg et al., 2006). Furthermore, as outlined below in Section 1.2, inhibitory pathology in psychiatric conditions such as ADHD and OCD is associated with deficient BG function.

In recent years, converging evidence from neuroimaging, neuropsychology and neurophysiology has extended the existing 'classical' model of BG function to incorporate response inhibition (Mink, 1996; Nambu et al., 2000, 2002; Kühn et al., 2004; Aron et al., 2007b; Eagle et al., 2008b; Isoda and Hikosaka, 2008; Fig. 3). According to this view, normal response execution (e.g. on a Go trial in the stop-signal task) involves three periods

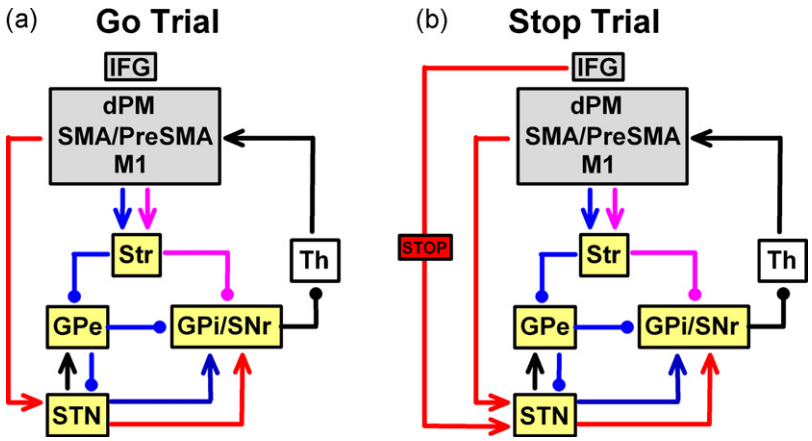

Fig. 3. A fronto-basal-ganglia model of response control. Arrows indicate excitatory (glutamatergic) connections, while circles indicate inhibitory (GABAergic) connections. Red, magenta and blue lines denote the hyperdirect, direct, and indirect pathways, respectively. (a) On a Go trial of the stop-signal task, a movement plan is initiated in cortical motor regions (including dorsal premotor cortex, dPM), which send corollary excitatory signals to the subthalamic nucleus (STN; hyperdirect pathway) and striatum (Str; direct and indirect pathways). Initial activation of the hyperdirect pathway suppresses all competing motor programmes by exciting the globus pallidus pars interna (GPi) and reticular substantia nigra (SNr). Excitation of the GPi/SNr, in turn, inhibits the thalamus and suppresses excitatory projections to cortical motor areas. Thereafter, an inhibitory input to GPi/SNr via Str (direct pathway; magenta) selectively disinhibits the selected motor programme, enabling response execution. Finally, the slower indirect pathway via the Str (blue) inhibits the global pallidus pars externa (GPe), down-regulating inhibitory connections between GPe-GPi/SNr and GPe-STN. In this way, inhibition of GPe via the indirect pathway leads to increased activity in GPi/SNr, suppressing thalamocortical projections and terminating the motor response at the appropriate time. (b) On a Stop trial, the sequence of events proceeds identically until the stop-signal is processed. Then an additional hyperdirect projection from the IFG excites the STN, activating the GPI/SNr and suppressing the thalamus. If this 'kill switch' is triggered in time, then response execution via the direct pathway can be cancelled. (Figure adapted from Nambu et al., 2002; Voytek, 2006.)

of processing in the BG network (Fig. 3a). First, corollary signals are sent from cortical motor areas via a *hyperdirect* pathway to suppress all motor programmes, including the selected one. Following this initial 'reset' signal, the selected response is released via a fronto-striatal *direct* pathway. Finally, the response is terminated via a slower fronto-striatal *indirect* pathway (Nambu et al., 2002). On a Stop trial (Fig. 3b), the hyperdirect pathway is reactivated via a connection between the IFG and sub-thalamic nucleus, providing a stimulus-driven 'kill switch' for braking an initiated response.

Two key features of the fronto-basal-ganglia model are especially noteworthy. First, competition between Go and Stop processes occurs within the major output nuclei of the BG (GPi/SNr), suggesting that disruption or stimulation of this area should produce especially strong effects on response inhibition. Second, while response execution is enabled by the direct pathway, successful stopping might be mediated by either the hyperdirect or indirect pathways, or both. Neurophysiological evidence suggests that either pathway might control response inhibition. Microstimulation of M1 in macaques leads to three distinct phases of activity in the output nuclei of the BG (GPi), including an initial excitation period (~8 ms), followed by a later phase of inhibition (~21 ms), and then a final period of excitation (~30 ms; Nambu et al., 2000). This sequence corresponds to the three input pathways proposed by the fronto-basal-ganglia model. In particular, rapid excitation of the GPi via the hyperdirect pathway inhibits the thalamus; the later phase of cortico-striatal inhibition via the direct pathway then releases the selected motor programme; and finally, the late period of excitation via the indirect pathway completes the response. If this correspondence is correct, then the difference in conduction times between the hyperdirect and indirect pathways is brief, averaging just 22 ms (Nambu et al., 2000). Therefore, when considered in relation to typical SSRT latencies (150–200 ms), either pathway could, in principle, participate in stimulus-driven suppression of motor programmes.

How might we distinguish between the contributions of the indirect and hyperdirect pathways to response inhibition? Although both systems activate the STN, only the indirect pathway enters the BG via the striatum and then proceeds via the external segment of the globus pallidus (GPe). Therefore, it will be important for future studies to establish the consequences of disruption or stimulation of the striatum or GPe on cognitive control. Converging evidence already points to a likely role of the indirect pathway in response inhibition. Using a stop-signal paradigm, Eagle and Robbins (2003) found that lesions of the rodent striatum increased SSRT by up to 60% (see also Dalley et al., 2004, for review). Furthermore, as discussed in Sections 1.2 and 1.3, inhibitory deficits in some clinical groups are associated with abnormal structure (e.g. Casey et al., 1997) and reduced functionality (Booth et al., 2005) of the caudate nucleus. At the same time, white-matter tracts between the human IFG, preSMA, and STN (and corresponding BOLD activations) indicate a probable role of the hyperdirect pathway in applying a rapid 'kill switch' for response inhibition (Aron et al., 2007a).

1.2. Clinical and genetic insights into the neural basis of inhibitory control

Inhibitory deficits are a common sequelae of both neurological and psychiatric dysfunction. As discussed above in Section 1.1, studying inhibitory deficits in patients with acquired frontal lobe damage (Aron et al., 2003b) has significantly advanced our understanding of the neural substrates of response inhibition. Equally, the examination of inhibitory pathology in psychiatric groups, such as attention deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD) have provided novel insights into the physiological, neurochemical and genetic correlates of cognitive control. In the sections that follow we review the extant literatures relating to ADHD and OCD, as exemplar disorders of inhibition. As will be reviewed, both ADHD and OCD are associated with response inhibition failures, the neural substrates of which appear to be dysfunction of key prefrontal areas including the IFG and orbitofrontal cortex. Whether inhibitory failures in both disorders may have a common genetic basis is discussed.

1.2.1. Attention deficit hyperactivity disorder (ADHD)

ADHD is a heritable disorder of childhood that is characterized by age-inappropriate levels of inattention and hyperactivity/impulsivity. Although estimates of the persistence of symptoms from childhood into adulthood vary widely (4–80%) (Polanczyk and Rohde, 2007), it is now recognised that ADHD is a lifelong problem for a significant proportion of children diagnosed. Aetiological accounts of ADHD have proposed a causal role for behavioural disinhibition in the development of the disorder (Barkley, 1997; Nigg, 2001). Not surprisingly numerous empirical studies of cognitive function in ADHD have employed versions of either the go/no-go or stop-signal paradigms to assay inhibitory function. Meta-analysis of this extant literature indicates that inhibitory deficits, as indicated by prolonged SSRT, for example, are associated with a large effect size (weighted mean effect size = 0.61 ± .09; Willcutt et al., 2005). It has been noted, however, that the case for a causal role of inhibitory failures in the development of ADHD is weakened by the observation that perhaps only 51% of children with ADHD display deficits that would be considered clinically impairing (Nigg et al., 2005). Whether the remaining cases of ADHD can be explained via dysfunction in other cognitive-neuroanatomical systems, including attention, arousal (Sergeant, 2000), delay aversion (Sonuga-Barke et al., 2003) or reward reinforcement (Sagvolden et al., 2005) remains to be determined. One possibility that is currently of considerable interest is whether such causal heterogeneity may be underpinned by genetic differences (see below).

Studies that have employed magnetic resonance imaging (MRI) have identified structural abnormalities within nodes of the response inhibition network in ADHD. Reduced volumes of the prefrontal cortex (including IFG), caudate and globus pallidus, particularly on the right, have been reliably reported (Castellanos et al., 1994, 1996; Aylward et al., 1996; Casey et al., 1997; Filipek et al., 1997; Sowell et al., 2003). Correlations between prefrontal morphology and behavioural measures of response inhibition have also been found (Casey et al., 1997). Numerous studies have employed functional brain imaging while ADHD and control subjects performed response inhibition tasks (Vaidya et al., 1998; Rubia et al., 1999, 2005b; Teicher et al., 2000; Durston et al., 2003; Schulz et al., 2004; Tamm et al., 2004; Booth et al., 2005). These studies have revealed under-activation in the caudate nucleus and globus pallidus of children with ADHD, relative to controls (Vaidya et al., 1998; Rubia et al., 1999; Durston et al., 2003; Booth et al., 2005). Under-activation within the IFG has also been reported in children (Booth et al., 2005) and adolescents with ADHD (Rubia et al., 1999). Reduced activation of medial structures including the anterior cingulate and/or pre-supplementary motor area have been reported in some studies (Tamm et al., 2004; Pliszka et al., 2006; Suskauer et al., 2008), however whether these medial activations are related to response inhibition *per se*, as opposed to post-error or other ancillary processes, remains debated. Increased frontal (middle, orbital and inferior frontal gyri) activation in ADHD has been reported in children (Vaidya et al., 1998) and adolescents (bilateral frontopolar; ventrolateral prefrontal) who were asymptomatic at the time of scanning but had a childhood-diagnosis of ADHD (Schulz et al., 2004). Using T2 relaxometry, Teicher and colleagues demonstrated higher T2 relaxation times (indicative of hypoperfusion) bilaterally in the putamen of children with ADHD (Teicher et al., 2000). In general these studies converge upon a view of response inhibition, particularly in children with ADHD, which is characterized by dysfunctional frontostriatal inhibitory networks. Structural and functional deficits within the IFG, caudate and basal ganglia are reliably observed and may form the pathophysiological substrate of response inhibition deficits in ADHD. Functional deficits within this inhibitory network may require the recruitment of additional and compensatory brain areas (Durston et al., 2003; Tamm et al., 2004).

Within psychiatry there is a large research effort aimed at determining whether cognitive markers of brain dysfunction, such as response inhibition, may have utility for indexing genetic risk to psychiatric disorder (Aron and Poldrack, 2005). Within the ADHD literature several lines of evidence support the contention that deficits in response inhibition may be a promising candidate endophenotype. First, response inhibition deficits in ADHD are likely to have a familial influence. Unaffected siblings of ADHD probands have been shown to exhibit deficits on response inhibition paradigms, relative to control children (Slaats-Willemse et al., 2003; Schachar et al., 2005). Since siblings share approximately 50% of their genes, the similar performance of the ADHD and unaffected siblings most likely arises from a common genetic influence. Further, response inhibition has been investigated in familial cases of ADHD. Crosbie and Schachar (2001) found higher prevalence rates of ADHD in the family members of children with ADHD who had impaired response inhibition performance, relative to ADHD children with intact response inhibition capacity. Thus by using family history as a proxy for genetic risk, Crosbie and Schachar identified that response inhibition deficits are associated with familial ADHD. Subsequent studies by Slaats-Willemse and colleagues (Slaats-Willemse et al., 2003) have confirmed that response inhibition deficits, as identified by a go/no-go task, are pronounced in the unaffected siblings of ADHD probands with a positive family history for ADHD. Further, evidence for familial clustering of response inhibition deficits was found by demonstrating strong correlations between performance indices in affected sibling pairs (Schachar et al., 2005; Slaats-Willemse et al., 2005). Familial influences on the neural networks for inhibitory control have also been reported. Durston et al. (2006) found decreased activation within the ventral prefrontal cortex (i.e., IFG) and inferior parietal cortex in both ADHD probands and their unaffected siblings relative to controls during successful inhibition (see also Mulder et al., 2008 for familial influences on cerebellar activity). These findings suggest that activation within inhibitory networks is sensitive to genetic risk for ADHD.

More recently a number of studies have sought to determine whether individual differences in response inhibition capacity may be explained by DNA variation within catecholamine genes. Variation at catecholamine genes may relate to response inhibition, since drugs with a dopaminergic (e.g. methylphenidate) or noradrenergic action improve response inhibition in healthy controls (Chamberlain et al., 2006) and patients with ADHD (Aron et al., 2003a; Lijffijt et al., 2005; Chamberlain et al., 2007). Congdon et al. (2008) recently demonstrated that alleles of the dopamine D4 receptor (DRD4) and dopamine transporter (DAT1) gene, which are associated with increased risk for ADHD (Cook et al., 1995; Faraone et al., 1999), account for significant variance in inhibitory performance in healthy, non-clinical subjects. A main effect of DRD4 genotype was found on SSRT ($n = 86$), with carriers of the 7-repeat allele of the DRD4 exon 3 polymorphism (variable number of tandem repeat: VNTR) having poorer response inhibition than those without this allele. An interaction between DRD4 and DAT1 genotypes was also found, with carriers of the ADHD-associated markers across both genes (DRD4: 7-repeat; DAT1: 10-repeat) exhibiting poorer response inhibition than the other genotype groups. Although the precise functionality of both DRD4 and DAT1 variants remains uncertain, a number of *in vitro* studies have indicated that the 10-repeat DAT1 allele is associated with increased expression of the dopamine transporter (Fuke et al., 2001; VanNess et al., 2005; Brookes et al., 2007). This scenario would lead to a relative down-regulation of dopamine, particularly

in areas of the brain, such as the striatum, where the transporter is heavily expressed. Evidence regarding the functionality of the DRD4 gene variants is somewhat more equivocal, with one study finding that the 7-repeat allele was associated with a blunted response to dopamine (Asghari et al., 1995) but another study failing to demonstrate a relationship between DNA variation at this polymorphism and receptor function (Jovanovic et al., 1999). It is perhaps important to note that, in this context, behavioural and brain indices of cognitive function, such as those reviewed here for response inhibition, can provide important collateral evidence regarding the functionality of a gene variant if a robust genotype–phenotype relationship can be demonstrated.

A key assumption of the endophenotype approach is that genetic effects will have greater penetrance for the endophenotype itself compared with the clinical phenotype. Thus, the observation that carriers of risk alleles for ADHD display response inhibition deficits even when they do not display the overt ADHD phenotype provides strong support for response inhibition as an endophenotype for ADHD. A number of other studies have also documented that allelic variation with the DRD4 and DAT1 genes associates with inhibitory performance in ADHD samples (Langley et al., 2004; Cornish et al., 2005). One paradox within this literature is the observation that ADHD probands who are carriers of the 7-repeat DRD4 allele have been shown to have enhanced cognitive performance, including inhibition, relative to probands without this allele (Swanson et al., 2000; Bellgrove et al., 2005; Johnson et al., 2008). Although this has led some to suggest that the 7-repeat allele in ADHD is associated with intact cognition but aberrant behaviour (Swanson et al., 2000), this finding runs counter to the hypothesis that the 7-repeat allele confers risk to ADHD, in part through its influence on intermediate cognitive and neural processes.

How might variation in the DRD4 or DAT1 genes influence the neural substrates of response inhibition? As reviewed above, structural and functional changes within prefrontal and subcortical areas have been implicated in the response inhibition deficits of ADHD. D4 receptors are known to be heavily expressed in prefrontal areas (Primus et al., 1997), while the dopamine transporter is heavily expressed in the striatum (Krause et al., 2003). Durston et al. (2005) made use of this regionally selective expression to examine prefrontal and striatal grey matter volumes, in relation to DRD4 and DAT1 gene variants in children with ADHD, their unaffected siblings and controls. Individual variation in brain structure is highly heritable (Winterer and Goldman, 2003; Winterer et al., 2005), suggesting that brain morphometry measures, such as grey matter volumes within selected regions, may be useful to index genetic susceptibility. A significant effect of the DAT1 VNTR genotype on caudate volume was found, with 10-repeat homozygotes having smaller volumes than those carrying the 9-repeat allele. This effect was most pronounced in children with ADHD, relative to their unaffected siblings and controls. There was no effect of DAT1 genotype on prefrontal grey matter volumes. Other studies have also reported that transporter densities are elevated in the striatum of children and adults with ADHD (Dresel et al., 2000; Krause et al., 2000; Cheon et al., 2003). Heinz et al. (2000) reported that 10-repeat homozygotes had higher striatal transporter densities, relative to 9-repeat carriers (see also Cheon et al., 2005 for studies in ADHD children), however, others have failed to replicate this result (Volkow et al., 2006). In contrast to the effects of DAT1 on caudate volumes, Durston et al. (2005) reported an effect of the DRD4 VNTR on prefrontal, but not striatal, grey matter volumes. Individuals who were homozygous for the 4-repeat allele had smaller prefrontal volumes than those carrying other alleles of the VNTR, such as the 7-repeat.

More recently, Durston et al. (2008) have examined the influence of variation in DAT1 gene on the neural substrates of response inhibition using fMRI. Twenty-nine boys including control children, ADHD probands and their unaffected siblings performed a go/no-go fMRI task, with patterns of activation analysed with respect to DAT1 genotype. Although there was no effect of DAT1 genotype on behavioural measures, there was a main effect of DAT1 genotype on brain activation across participants. Specifically, irrespective of diagnostic status, activation in the vermis of the cerebellum was greater for 10-repeat homozygotes, relative to those without this allele. Activation within the striatum varied by DAT1 genotype only for ADHD probands and their unaffected siblings but not for control children. In this case, activation was greater in the striatum for those without the 10-repeat allele.

In summary, substantial evidence suggests that deficient response inhibition may be reliably associated with ADHD and may be familial. Response inhibition deficits in children with ADHD are likely to reflect immaturity in ventral frontostriatal circuitry, including the IFG. Preliminary evidence suggests that dopaminergic gene variants, including those of DRD4 and DAT1, may be associated with response inhibition deficits in non-clinical participants and perhaps individuals with ADHD. One can therefore hypothesise that genetic variation within catecholaminergic genes (*a priori* DRD4, DAT1) may influence the development of the ventral frontostriatal circuitry subserving response inhibition; and variation within this system may, in turn, confer susceptibility to ADHD (Bellgrove et al., 2007).

1.2.2. Obsessive compulsive disorder

OCD is a disorder, typically with a childhood onset, in which sufferers are unable to inhibit intrusive and obsessive thoughts or compulsive behaviours. As with ADHD, investigators have sought to determine whether experimental probes of inhibition, such as the stop-signal task, might explain the symptoms of the disorder. Behavioural response inhibition deficits have been reported in OCD, with stop-signal reaction time being prolonged (Chamberlain et al., 2007; Menzies et al., 2007, e.g. Penades et al., 2007). Studies using event-related potentials (ERPs) and fMRI indicate that response inhibition deficits in OCD are underpinned by physiological abnormalities within fronto-striatal circuits. Herrmann et al. (2003) reported that the P300 related to the No-go condition had a more anterior scalp topography in the control participants, compared with the OCD patients. This No-go 'anteriorisation' was negatively correlated with OCD symptoms, suggesting that those patients with more aberrant No-go scalp topography (i.e. less frontally localised) had more severe symptoms. Roth et al. (2007) employed event-related fMRI and a Go/No-go task in OCD patients and controls, and found that controls activated the typical right-hemisphere network, including the IFG. In contrast, patients with OCD showed less activation than the controls in a number of right-hemisphere regions including inferior and medial frontal gyri. Symptom severity was inversely correlated with activation in the right orbitofrontal cortex, an area which is thought to be of importance in OCD, and positively related to activity in the thalamus. These data broadly suggest that inhibitory deficits in OCD are underpinned by dysfunction of frontal-striatal-thalamic circuitry. Whether the contribution of orbitofrontal cortex to response inhibition deficits is specific to OCD or is seen more generally across disorders, will be an interesting question for further investigation.

Familial influences on both behavioural measures of response inhibition (Chamberlain et al., 2007; Menzies et al., 2007) and correlated structural brain changes (Menzies et al., 2007) have also been observed in OCD. Menzies et al. compared inhibitory control

in 31 patients with OCD, 31 unaffected first-degree relatives and 31 unrelated healthy volunteers. Structural MRI was also performed to determine the familial influences upon anatomical changes that might underpin behavioural inhibition deficits. Systems of grey matter that correlated positively or negatively with SSRT were identified using multivariate statistical procedures (partial least squares). Consistent with an endophenotype hypothesis, the unaffected relatives of the OCD patients exhibited behavioural inhibitory deficits that were similar to the OCD probands but significantly worse than the healthy volunteers. Across participants, elevated SSRT was associated with increased grey matter probability in areas including the middle and posterior cingulate cortices, striatum, amygdala, parietal cortex and cerebellum. By contrast, a second system marked by negative correlations between SSRT and grey matter probability (i.e., longer SSRT associated with reduced grey matter) comprised bilateral middle and medial orbitofrontal cortex, inferior frontal gyri, superior frontal and premotor cortices, anterior cingulate cortex and bilateral temporal cortex. Within this latter system group differences were most pronounced within bilateral orbitofrontal cortex. Familial influences on grey matter density were found for both the parieto-cingulo-striatal system (positively correlated with SSRT) and the frontal system (negatively correlated with SSRT). These data provide impressive evidence that the brain systems underlying inhibitory deficits in OCD show familial influences, and support the use of morphometric measures related to inhibition as an endophenotype for OCD.

It is interesting to note that, in both ADHD and OCD, familial influences have been reported on behavioural measures of response inhibition, and on the structure and/or functional integrity of inhibitory neural networks. ADHD and OCD share a degree of comorbidity, with up to 30% of children with OCD also meeting criteria for ADHD (Geller et al., 1996; Peterson et al., 2001). Common genetic influences across ADHD, OCD and other disorders of disinhibition such as Tourette's Syndrome have been noted (Grados and Mathews, 2008). One intriguing possibility is that dysfunctional inhibitory networks may be underpinned by a common genetic susceptibility that is shared across these disorders. Of course marked differences also exist between the disorders, such as the use of catecholamine transporter inhibitors in ADHD and the use of serotonergic agents in OCD. The serotonin system has been implicated in both impulsivity and response inhibition (Rubia et al., 2005a; Lamar et al., 2007), raising the possibility that inhibitory deficits in OCD might be underpinned by serotonin dysfunction. One fruitful line of research would be to compare response inhibition in OCD and ADHD populations as a function of genetic polymorphisms of the serotonin system. Tryptophan hydroxylase (TPH) is the rate-limiting enzyme in the synthesis of serotonin from tryptophan and the TPH2 gene has been implicated in both ADHD (Sheehan et al., 2005) and OCD (Mössner et al., 2006) and separately in response inhibition (Stoltenberg et al., 2006). One possibility is that a subgroup of children with ADHD might be associated with aberrant serotonin signalling in addition to the presumed catecholamine deficiency. Regardless, the literature reviewed above suggests that variation in multiple neurotransmitter systems (dopamine, noradrenaline and serotonin) may explain individual differences in the capacity for response inhibition.

1.3. Inhibitory mechanisms revealed through the effects of drug addiction

In addition to ADHD and OCD, the neurocognitive consequences of drug addiction have provided important insights into the neural basis of response inhibition. Diminished control over drug use is a core feature of substance dependence (DSM-IV; Lyvers, 2000). The known pharmacological actions of drugs of abuse can therefore also give clues to the neuropharmacology of these control functions. For example, cocaine users show impairments in laboratory measures of several aspects of impulsivity and the effects of this drug in increasing catecholamine levels, including the mesocorticolimbic dopamine system through blockade of dopamine re-uptake, identifies the catecholamines as likely to be involved in these control functions. Cocaine users show higher delayed discounting rates (Coffey et al., 2003; Simon et al., 2007), are slower or poorer at motor inhibition (Fillmore and Rush, 2002; Hester and Garavan, 2004; Colzato et al., 2007), make riskier decisions on various gambling tasks (Bartzokis et al., 2000; Monterosso et al., 2001; Bolla et al., 2003; Fishbein et al., 2005; Verdejo-Garcia et al., 2008), and amphetamine users sample less of the available information prior to making decisions (Clark et al., 2006). This range of deficits raises theoretical concerns regarding the impulsivity construct, insofar as it remains unclear to what extent these deficits are related, share common cognitive or neurobiological mechanisms, or might coalesce to form a broad impulsive phenotype (Grant, 2004; Aron, 2007).

In keeping with the generality of the impulsivity construct, many different brain structures have been implicated in the impulsivity of addicts. For example, poor motor response inhibition in cocaine users has been associated with reduced activity in dorsolateral prefrontal cortex, insula, and the anterior cingulate, and with increased activity in the cerebellum (Kaufman et al., 2003; Hester and Garavan, 2004). Stroop task performance, which incorporates attentional demands in addition to suppression of interfering motor responses, has been associated with changes in orbitofrontal activity in cocaine users (Goldstein et al., 2001). An animal model of impulsivity, characterized as an inability to delay a reward-related response, has been linked to reduced D2 receptor levels in the ventral striatum (Dalley et al., 2007).

Despite the range of brain structures implicated in the impulsivity of drug users, some commonalities have been observed. For example, as noted, motor response inhibition has been strongly associated with the right IFG, a region observed to be hypoactive in cocaine users performing a Go/No-go task (Kaufman et al., 2003). However, this same area was also involved in suppressing attention to distracting drug-related stimuli in a selective attention task (Hester et al., under review). In this study, drug users were required to perform a short-term memory task in response to numbers presented in the centre of a screen, while ignoring irrelevant picture stimuli presented behind the numbers. The memory task required subjects to store five numbers and, on the presentation of one of those numbers, report the next number in the memorised sequence. The distracting picture stimuli contained neutral, emotionally-evocative, or drug-related contents and it was expected that these stimuli would interfere with "cold" working memory processes by engaging "hot" emotional processes (Dolcos and McCarthy, 2006). Similar to investigations showing attentional biases towards drug-related stimuli (Cox et al., 2003; Waters et al., 2003; Hester et al., 2006), drug users were slower in performing the memory task when the background stimuli were drug-related, an effect that was associated with activation in early visual centres and in the right ventral prefrontal cortex. Notably, those users who exhibited the greatest activation in right prefrontal cortex showed the smallest interference effect, suggesting that the ability to suppress the processing of the drug-related stimuli was attributable to the inhibitory functions of this brain region. One possibility that follows from these findings is that the integrity and functioning of the right ventral prefrontal cortex may underlie individual differences that are of clinical relevance, given

the importance of drug cues for eliciting drug craving and drug seeking. In passing, it should be noted that this interpretation attributes an inhibitory function to right ventral PFC that goes beyond motor inhibition. Other evidence including the set-shifting of the Wisconsin Card Sorting Task (Konishi et al., 1999), the suppression of sensory aspects of emotional memories (Depue et al., 2007; Banich et al., 2009) and the suppression of interference from task-irrelevant stimuli (de Fockert et al., 2001; Dolcos and McCarthy, 2006; Michael et al., 2006) are in keeping with a broader inhibitory profile for this region.

To gain further insights into drug-related inhibitory control deficits and, *inter alia*, the pharmacology of inhibitory control, one can assess the effects of an acute drug administration on performance and brain function. Evidence shows that the administration of cocaine to cocaine-dependent individuals alters performance on Go/No-go and stop-signal tasks, although the magnitude and direction of the effects are likely to be mediated by both the task and dosage level (Fillmore and Rush, 2002; Fillmore et al., 2005, 2006). In a study that contrasted the effects of cocaine and saline administrations on Go/No-go task performance, we observed superior inhibitory performance following cocaine, which, on no-go trials, was associated with increased activity in right IFG/insula and right middle frontal gyrus (Garavan et al., 2008). This study thus demonstrates a direct effect of cocaine on the neurobiology of inhibitory control and identifies these few cortical regions as particularly important nodes in that neurobiology. That performance *improved* following the cocaine administration, to the extent that regions previously shown to be hypoactive relative to controls were now comparable, suggests that the depressed functioning of these areas (either resulting from years of use or a pre-existing risk factor) could be normalised in this group. The pharmacological effects of cocaine (increases in synaptic levels of monoamines by blocking their re-uptake) and the similar effects of medications such as methylphenidate that can improve the impulsivity of those with ADHD, implicate dopamine as an important pharmacological substrate for inhibitory control; and this is consistent with the genetic association studies described previously.

In addition to dopamine, norepinephrine and serotonin have been implicated in different forms of inhibitory control (Rubia et al., 2005a; Lamar et al., 2007) with evidence for and against a role for serotonin in motor inhibition (Clark et al., 2005; Evers et al., 2006; Eagle et al., 2008a). Chamberlain et al. (2006), for example, have shown a double dissociation wherein blocking norepinephrine re-uptake improved motor response inhibition but not probabilistic learning, while blocking serotonergic re-uptake impaired probabilistic learning but did not affect response inhibition. Other dimensions of inhibitory control, including delayed discounting and premature responding, show improvement following administration of the same norepinephrine re-uptake inhibitor (atomoxetine) in rats (Robinson et al., 2008). Indeed, some pharmacological challenge studies in rats suggest that norepinephrine and not dopamine is the critical neurotransmitter for motor inhibition (Eagle et al., 2007). Pharmacological investigations of this kind, perhaps combined with functional imaging in humans, offer great scope for understanding the neurobiological function and dysfunction of inhibitory control, while at the same time providing an experimental means to decompose the construct along pharmacological lines.

2. Links between response inhibition and related cognitive processes

The inhibition of motor responses occurs alongside a host of related behaviours, including response selection, working memory, and attention. All of these functions include components of inhibition, and an emerging question in cognitive neuroscience concerns the functional and neuroanatomical specificity of the underlying control mechanisms (e.g. Aron, 2007; Mostofsky and Simmonds, 2008; Simmonds et al., 2008). In the following sections we review evidence concerning the intersection between response inhibition and related cognitive processes.

2.1. Response inhibition and response selection

As discussed in Section 1.1.3, the selection of one motor response from numerous alternatives requires active neural suppression of irrelevant motor programmes (Mink, 1996). To what extent are the neural processes underlying the selection and inhibition of responses functionally related? As suggested in a recent review by Mostofsky and Simmonds (2008), are response inhibition and response selection different sides of the same coin?

The idea that the inhibition and selection of responses emerge from a single neural mechanism is supported by converging evidence that the same cortical areas mediate both processes. Insights from neuroimaging, primate lesion studies, clinical work, and TMS suggest that response selection and interference control recruit a similar cross-section of areas to response inhibition, including the dorsolateral prefrontal cortex, IFG, anterior cingulate, and dorsal premotor cortex (Halsband and Passingham, 1985; Schluter et al., 1998; Praamstra et al., 1999; Hazeltine et al., 2000; Rubia et al., 2001; Bunge et al., 2002b; Rushworth et al., 2002; Hazeltine et al., 2003; Schumacher et al., 2003; Koski et al., 2005; Wager et al., 2005). Especially notable among these common regions is the preSMA, a crucial node of the response inhibition network (Floden and Stuss, 2006; Picton et al., 2007; Chen et al., in press) and an area that is similarly important for preparatory selection of action (Shima et al., 1996; Ikeda et al., 1999). In principle, the preSMA might orchestrate both the selection and inhibition of behaviour using identical looped inter-connections with the basal ganglia (Fig. 3). For instance, in the case of selecting and executing a response (Fig. 3a), the initial hyperdirect input from preSMA could suppress all movement plans, followed by release of the selected motor programme (direct pathway) and then termination of the response (indirect pathway; Nambu et al., 2002). In the case of selecting *not* to respond (Fig. 3b), a similar pattern of preSMA-striatal and preSMA-subthalamic impulses may be triggered. However, the crucial difference in this case may be a reduction of cortical outputs via the *direct* pathway, such that a motor programme is not released.

If response selection and inhibition are merely different descriptions of the same process, then neurological interventions should affect performance across a range of cognitive and behavioural measures. In a key test of this hypothesis, Scheres et al. (2003) assessed the effects of administering the dopamine transporter inhibitor, methylphenidate (MPH), in children with ADHD on a variety of tasks that measured response inhibition and response selection. Interestingly, they found that MPH improved inhibitory control in the stop-signal task, but had no effect on the resolution of response interference in the Eriksen Flanker task or Stroop task. Thus, MPH decoupled neural mechanisms of response inhibition and response selection, which should not be possible if these processes are synonymous.

More recently, corroborating evidence from TMS suggests that prepotent response inhibition may be controlled by a specialised cortical mechanism that is distinct from response selection (Chambers et al., 2007). In this study, participants undertook a combined stop-signal/flanker task, which has previously been used to demonstrate close behavioural links between outright response inhibition and the suppression of interference from competing

responses (Verbruggen et al., 2004). Here, participants identified the direction of a central arrow target, which could be flanked by distractors that triggered the same response (congruent flanker), the opposite response (incongruent flankers), or no response (neutral flankers). On a minority of trials, a stop-signal instructed participants to cancel their response to the central target. To test whether the same cortical mechanism was required for response inhibition and interference control, Chambers et al. (2007) applied repetitive TMS to cortical areas previously implicated in each task component, including – in particular – the right IFG. Two key findings of this study are notable. First, IFG stimulation impaired stop-signal inhibition, but only on *incongruent* flanker trials; hence, it is conceivable that the increased demand on response selection interacted with the inhibitory function of the IFG. Second, although IFG TMS elevated SSRT on incongruent Stop trials, it did not affect the ability to resolve interference from the competing responses triggered by the flankers (that is, response execution was intact on incongruent Go trials). Furthermore, in a previous TMS study (Chambers et al., 2006), IFG stimulation selectively impaired stop-signal inhibition but not the speed or accuracy with which participants selected their response on Go trials (see also Aron et al., 2003b). Thus, while the right IFG appears to be crucial for countermanding an initiated response, and may also be sensitive to the degree of response competition that occurs during inhibition, it may not be necessary for *resolving* response competition *per se*.

How can we reconcile evidence of overlapping cortical networks for response inhibition/selection (Rubia et al., 2001; Wager et al., 2005) with the dissociable behavioural consequences of MPH (Scheres et al., 2003) or TMS (Chambers et al., 2007)? Rather than reflecting a genuine discrepancy, this difference most likely stems from the inferences permitted by neuroimaging and neurodisruption techniques (Chambers and Mattingley, 2005). In particular, common neural activity during tasks that engage response inhibition and selection need not reflect the engagement of a common cognitive system. Instead, such co-activations may reflect the coordinated – and ecologically sensible – recruitment of distinct mechanisms, even if only one such system is necessary for performance in a specific (and necessarily artificial) behavioural context (e.g. see Chambers et al., 2004b, for evidence of such dissociations in selective attention). Since neuroimaging methods cannot distinguish critical activity from redundant activity, such common activations can be difficult to interpret. In contrast, experimental methods that manipulate, rather than measure, brain activity provide key complementary insights by isolating the role of *critical* processes. On balance, therefore, the convergent conclusion reached from neuroimaging, TMS, and pharmacological evidence is that response inhibition and response selection are controlled by neural mechanisms that are at least partially distinct. A key aim for future studies will be to establish more fully the nature of their relationship, especially as regards neuroanatomical theories of response control, such as the fronto-basal-ganglia model (Fig. 3).

2.2. Response inhibition, working memory, and attention

As with response selection, inhibitory control and working memory are closely related. Indeed, the ability to maintain items actively in working memory while resisting interference is considered to be the essential determinant of working memory capacity (Engle et al., 1999; Kane et al., 2001; Kane and Engle, 2003). In the laboratory, anti-saccade task performance declines with increasing working memory load (Roberts et al., 1994; Mitchell et al., 2002). Motor response inhibition, the primary focus of this paper, also declines with increasing working memory load (Hester and Garavan, 2005). In this investigation, participants were required to maintain one, three, or five letters in working memory and then, in a subsequent serial stream of letters, had to make a button-press response to all letters bar those in the memory set. The task necessitates the integrated functioning of inhibitory control and working memory because knowing *when* to inhibit is dictated by actively maintaining the working memory set. Crucially, inhibitory control was only influenced by working memory load for letters that were in the memory set.

The neural basis for the intersection between working memory and inhibitory control was examined with this same task during fMRI (Hester et al., 2004a). Regions common to both the maintenance of items in working memory and response inhibition included bilateral middle frontal gyrus, bilateral inferior parietal lobule, the ACC, right insula and left putamen. Of these regions, the left dorsolateral prefrontal cortex and the ACC showed inhibition-related activation increases as a function of working memory load. This result is consistent with the hypothesis that the source of the interference between these two cognitive functions is their common reliance on regions of the prefrontal cortex (Bunge et al., 2001). Of note, the brain's primary response to combating this interference was to increase activation levels in those regions unique to inhibitory control and not in the common regions. These inhibition-unique regions included the right dorsolateral prefrontal cortex and thalamus.

Activation of the right dorsolateral prefrontal cortex is commonly observed on response inhibition tasks (Garavan et al., 2006; Simmonds et al., 2008), raising questions concerning the inhibitory role of this region relative to ventral prefrontal cortex (IFG). One possibility is that the more dorsal prefrontal activations reflect associated cognitive processes that coincide with response inhibition. For example, Mostofsky and colleagues have suggested that dorsal activations reflect working memory demands (Mostofsky et al., 2003; Simmonds et al., 2008). This conclusion was based on observing inhibition-related activation limited to the preSMA for a simple Go/No-go task in which subjects responded to green stimuli and inhibited to red stimuli. With additional working memory demands (subjects inhibited to just those red stimuli preceded by an even number of green stimuli) right dorsolateral prefrontal activation was observed. Since the right dorsolateral prefrontal cortex has also been implicated in response selection (Braver et al., 2001; Rowe et al., 2002) and in the active maintenance of stimulus–response rule representations (Derrfuss et al., 2004, 2005; Brass et al., 2005), it is possible that this activation reflects a more deliberative response selection process driven, perhaps, by the rules for responding and inhibiting held in working memory.

Another possibility to consider is that recruitment of the right dorsolateral prefrontal cortex during response inhibition reflects a phasic increase in a more general attentional process. Recruitment of these areas, accompanied by right parietal activation, is frequently observed during sustained, or vigilant, attention (e.g. Fassbender et al., 2004). Furthermore, the IFG, inferior parietal lobule and temporoparietal junction have been suggested to serve as a 'circuit breaker' for triggering shifts of attention to sudden, salient events (Corbetta and Shulman, 2002). In particular, an attentional role of the IFG is consistent with evidence that this region is necessary for stimulus-evoked response inhibition (Aron et al., 2003b; Chambers et al., 2006), thus raising the question of whether the attentional 'circuit breaker' is in fact the same neural mechanism as the inhibitory 'circuit braker'.

The possibility that right frontoparietal activation may subserve a more general cognitive function was tested in a study that contrasted activity during response inhibition with activity triggered by occasional alerting cues (changes in font colour), which instructed participants to attend to the task at hand

(Fassbender et al., 2006). Here the central question was whether the two events of interest, inhibitions and cues-to-attend, would evoke similar mechanisms of top-down attentional control. A conjunction analysis revealed common activations in the right cuneus, the right dorsolateral prefrontal cortex and in the right cerebellar tonsil. These results are consistent with the dorsal prefrontal and parietal components of the inhibitory control network being associated with a more general attentional process, as might be expected given that right-hemisphere frontoparietal activation has been observed in many different tasks that engage oddball (McCarthy et al., 1997), inhibitory (Garavan et al., 1999; Bunge et al., 2001; Menon et al., 2001), and working memory processes (D'Esposito et al., 1998), and in tasks that manipulate arousal (Kinomura et al., 1996; Sturm et al., 1999; Sturm and Willmes, 2001), or require participants to shift (Corbetta and Shulman, 2002; Yantis et al., 2002), or sustain attention (Coull et al., 1996; Coull and Nobre, 1998; Manly et al., 2003).

One suggestion arising out of these findings is that the right IFG performs a specific response countermanding operation, consistent with its links to the STN (Aron et al., 2007a), while the dorsal prefrontal regions host related attentional or working memory processes, consistent with their broader functional profile and ability to adaptively encode many different rules and functions. Some evidence favouring this hypothesis comes from a Go/No-go task in which the presentation rate of the Go and No-go stimuli was varied, thereby producing relatively "slow" and "fast" response inhibitions in which the response-stimulus interval varied, leading to more or less preparation time (Kelly et al., 2004). Results revealed that with a longer interval between the previous Go response and a No-go trial, there was greater inhibition-related activation in the right superior and middle frontal gyri, while the inhibitions that followed a shorter interval produced greater activation in the right IFG, right precuneus and in the left putamen and caudate. These results demonstrate that, even within one mode of inhibitory control, the cortical and sub-cortical basis for response inhibition can change flexibly to accommodate specific task demands. Thus, while evidence does converge on a role for the right IFG in response countermanding, it is clear that other prefrontal brain structures can in many circumstances also contribute to inhibiting prepotent responses.

3. Inhibitory control, individual differences, and neural plasticity

While much research has focused on identifying the cortical basis for various cognitive processes, it must be realised that there is considerable variability both between individuals who may differ on relevant personality dimensions or abilities, and also within individuals who can show substantial functional changes arising from brief periods of practice. These changes carry significant clinical relevance because the variability between individuals in cognitive abilities such as inhibitory control may constitute risk factors for psychopathologies. For example, impulsivity is a risk factor for later problems with substance abuse (Tarter et al., 2003; Dalley et al., 2007; Verdejo-Garcia et al., 2008). As a consequence, understanding the basis of these individual differences, which can include both risk and protective factors and can encompass genetic and environmental contributions, may help in understanding the aetiology of psychological disorders. Further, understanding the scope and limiting factors in intra-individual changes in improving inhibitory control, whether through training, psychotherapeutic or pharmacological interventions, is also clearly of clinical significance for treatment or prophylaxis.

Most laboratory tests of inhibitory control that have addressed individual differences have focussed on personality, performance or demographic factors. For example, inhibition-related activity on a Go/No-go task was greater in right frontoparietal regions in those who scored lowest on a paper-and-pencil test of everyday absentmindedness (Garavan et al., 2002). Similarly, individuals who exhibit more behavioural variability in performing this task (i.e., greater variance in their Go trial response times) reveal more inhibition-related activity in bilateral fronto-parietal areas, the thalamus and in the right caudate (Bellgrove et al., 2004; Simmonds et al., 2007), while those who are faster responders on Go trials also show greater activation in the insula, frontal and temporal regions and the preSMA (Garavan et al., 2006). Overall, these results suggest that inhibition may be more "effortful," requiring greater prefrontal engagement, in those who respond faster or are inclined to pay less attention to the task at hand.

Demographic differences are also observed. Older adults (aged 73–78) show more bilateral prefrontal activation during response inhibition (Nielson et al., 2002), as has been observed in other cognitive domains (Cabeza, 2002). Even within the young adult age-range (18–46) cortical activity for inhibitions tends to increase with age (Garavan et al., 2006). In children between the ages of 8 and 12, reduced inhibition-related prefrontal activity relative to young adults has been observed (Bunge et al., 2002a; see also Rubia et al., 2000). Thus, across the full age spectrum, we see a pattern of increased cortical differentiation in the period from childhood into young adulthood in which inhibitory control becomes increasingly dependent on the right prefrontal cortex. Then, as one ages, inhibitory control would appear to become less differentiated and more reliant on bilateral prefrontal structures.

The influence of sex differences on the neurobiology of inhibitory control is less clear. While there is evidence for greater inhibition-related activation in females (Garavan et al., 2006) there is also evidence supporting the opposite (Li et al., 2006). These inconsistencies may be driven by the time in their menstrual cycles the females were compared with males, as inhibition-related activation in females has been shown to be affected by the hormone cycle (Roberts et al., in press) and, more specifically, by estrogen levels (Protopopescu et al., 2005; Amin et al., 2006). Estrogen levels, in turn, affect neurotransmitter systems that likely play a role in inhibition (Pasqualini et al., 1995, 1996). While the effects of estrogen on dopamine synthesis (Pasqualini et al., 1995), turnover and release (Becker and Beer, 1986), and on dopamine receptor density (Hruska and Silbergeld, 1980) might be of particular relevance, which specific neurotransmitter system is affected by estrogen is unclear, as evidence shows estrogen effects on cholinergic (Gibbs et al., 1998), glutamatergic (Woolley et al., 1997), GABAergic (Murphy et al., 1998), serotonergic (Moses et al., 2000) and noradrenergic systems (Tseng et al., 1997). Sex differences in inhibitory control are of interest given the sex differences that exist in the prevalence of many impulse control disorders (Kessler et al., 2005; Neuman et al., 2005; Eme, 2007), which, one speculates, might have their basis in different evolutionary pressures on males and females to suppress sexual interests and aggression towards one's offspring (Bjorklund and Kipp, 1996).

Differences between individuals in inhibitory control are accompanied by changes within individuals. This can be most readily observed by tracking individuals as they become more skilled on a task, as even small periods of practice can produce sizeable changes in the brain areas that underlie performance. While most investigations of the brain changes accompanying task practice have focussed on visuospatial and motor skills (Kelly and Garavan, 2005), there is evidence that cognitive control functions also reveal dynamic changes in brain function. Kelly and colleagues investigated the effects of brief practice on a Go/No-go task and distinguished between item-specific effects (i.e., the ability to

inhibit responding to repeated presentations of a specific No-go stimulus) from more general inhibitory capacity (i.e., the ability to inhibit independent of any prior experience with specific stimuli; Kelly et al., 2006). Repetition of No-go stimuli led to reduced activity in the frontal cortex but increased activity in posterior regions. On the other hand, the effect of practice on the general inhibition process was associated with increased activity in bilateral dorsolateral prefrontal cortex and inferior parietal cortex. The results indicate that a cognitive control process such as motor inhibition is amenable to functional changes arising from learning and rapid plasticity. Of note, the inhibition-related regions whose activity increased with practice were the same areas that were also shown to differ between 'good' and 'poor' performers. These results might be considered quite promising from a clinical perspective, demonstrating that there is plasticity in the brain centres that underlie a clinically important inhibitory function.

4. Future directions

In this review, we have considered the contribution of lesion, TMS, fMRI, clinical, and genetic studies to understanding neural mechanisms of response inhibition. In this final section, we outline a series of conceptual and technical advances for future studies.

4.1. Neural circuitry of inhibition

As reviewed in Section 1.1, a convergence of evidence implicates the right IFG and SMA/preSMA as crucial areas for response inhibition (Aron et al., 2003b, 2007a; Chambers et al., 2006, 2007; Floden and Stuss, 2006; Picton et al., 2007; Chen et al., in press). To date, however, it is unclear whether these regions fulfil specialised inhibitory functions. Some investigators have suggested that the IFG is a key source region for implementing an active mechanism of neural inhibition, while the preSMA is necessary for resolving conflict between responses, a role akin to response selection (Aron et al., 2007a). Other researchers, however, have concluded that the SMA/preSMA is chiefly responsible for inhibitory control (Floden and Stuss, 2006) and that 'inhibition' is simply a form of response selection (Mostofsky and Simmonds, 2008). The use of single-pulse TMS may provide useful mechanistic insights into the common and/or unique roles of these cortical regions by establishing the *timecourse* of critical involvement. For instance, if the IFG provides the initial 'kill switch' for inhibiting an initiated response then the critical epoch of inhibitory processing in the IFG should precede that of preSMA. Furthermore, if the preSMA is important for resolving pre-response conflict, then repetitive TMS of this area should influence performance on tasks that provide measures of interference control, such as the flanker paradigm (Wylie et al., 2007), conditional stopping paradigm (Aron et al., 2007a), and stop-and-change paradigm (Tannock et al., 1995; Nachev et al., 2007). Given the rich connectivity of the IFG, STN and preSMA, the localisation of TMS according to white-matter tractography may be important development for such studies.

Ultimately, the combination of TMS with neuroimaging techniques may provide the clearest insights into the functional connectivity and specificity of cognitive control in the human prefrontal cortex. Using sequential TMS and fMRI, for instance, it will be important to test whether inhibitory impairments following stimulation of the right IFG and/or preSMA are accompanied by predictive changes in STN activity. Furthermore, by comparing the effects of IFG stimulation on STN and striatal responses, it may be possible to distinguish between the inhibitory role of the hyperdirect (cortex → STN) and indirect pathways (cortex → striatum; see Fig. 3).

4.2. Pharmacogenetic developments

In recent times there has been considerable interest in the field of pharmacogenetics, in which individual differences in drug response might be predicted by underlying genetics. Cognitive and neural measures that are objective, reliable and grounded in biological processes have significant advantages as measures of clinical response, relative to subjectively rated behavioural symptoms.

In the current context, there is significant evidence to suggest that behavioural and neural markers of response inhibition might have utility as surrogate endpoints for evaluating clinical response in a range of disorders, including ADHD and potentially also OCD and schizophrenia. First, the neurochemical bases of response inhibition are becoming increasingly clear, with dopamine and noradrenaline emerging as important neuromodulators (Aron et al., 2003a; Chamberlain et al., 2006). Further, as reviewed above, several studies have begun to document the association between genes of the catecholamine system and response inhibition (Congdon et al., 2008). These lines of evidence raise the possibility that psychotropic agents, such as the stimulant MPH that is used to treat ADHD, may alter response inhibition differentially as a function of underlying genotype. One example of this approach is provided by the study of Gilbert et al. (2006), in which a TMS-derived neurophysiological measure of inhibition – short intra-cortical inhibition (SICI) – was used to probe the clinical effects of methylphenidate and atomoxetine in a sample of children with ADHD. As reviewed by Stinear and colleagues (this issue), SICI is a measure of GABAergic inhibition in the primary motor cortex that has been shown to relate to cognitive measures of inhibitory control, such as Go/No-go and stop-signal performance (Coxon et al., 2006). Furthermore, children with ADHD have been shown to have reduced cortical inhibition, with this deficit negatively related to symptom severity (Gilbert et al., 2004, 2005). Gilbert et al. (2006) conducted a randomised, double-blind, single-dose, crossover study comparing the effects of a single-dose of MPH (0.5 mg/kg) to the non-stimulant, noradrenaline transporter inhibitor atomoxetine (1.0 mg/kg). The effects of these drugs were compared as a function of allelic variation in a polymorphism (10-repeat allele) of the dopamine transporter gene (DAT1). Both MPH and atomoxetine increased (i.e. tended to normalise) cortical inhibition in 10-repeat heterozygotes; however, this did not occur in 10-repeat homozygotes. Insofar as cortical inhibition may serve as a marker of clinical response, these data suggest that homozygosity for the 10-repeat is associated with a poorer clinical outcome. Although we are not aware of any studies that have attempted to use behavioural measures of response inhibition as a marker of treatment response, together or independent of genetic effects, clearly this may have promise for clinical conditions such as ADHD.

4.3. Conclusions

This review has considered the contribution of cognitive and clinical neuroscience to understanding response inhibition in the human brain. In Section 1, we summarised evidence from patient lesion studies and TMS, which has highlighted the role of a fronto-basal-ganglia network in cancelling initiated responses. Crucial sites of inhibitory control in this network appear to be the IFG and SMA/preSMA, although future research is required to elucidate the precise role of each area. In this section, we also considered clinical studies of substance dependence, ADHD and OCD, which have highlighted deficits of response inhibition linked to abnormalities in prefrontal and sub-cortical systems. In the case of ADHD and OCD, inhibitory deficits are likely to be familial and reflect

immature development of frontostriatal circuitry. Furthermore, dopaminergic gene variants, including DRD4 and DAT1 are associated with deficits of inhibitory control in ADHD. In Section 2, we examined the relationship between response inhibition and other cognitive processes, including response selection, working memory, and attention. In each case, evidence suggests that neural mechanisms of response inhibition interact closely with these related processes, while nevertheless maintaining a degree of separability. In Section 3, we reviewed the effects of individual differences and flexible cognition on response inhibition, which indicate that the neural substrates of inhibitory control are highly dependent on learning and rapid plasticity. Finally, in Section 4, we proposed a series of future advances, including the use of TMS and combined TMS-fMRI to probe the neural circuitry of inhibitory control, and the use of response inhibition and genetic precursors as a marker for treatment responses in psychiatric disorders.

Acknowledgements

Preparation of this manuscript was supported by the Australian Research Council (Discovery Grant DP0770337; MAB & CDC) and a BBSRC David Phillips Fellowship (CDC).

References

Amin, Z., Epperson, C.N., Constable, R.T., Canli, T., 2006. Effects of estrogen variation on neural correlates of emotional response inhibition. Neuroimage 32, 457–464.

Anderson, E.J., Husain, M., Sumner, P., 2008. Human intraparietal sulcus (IPS) and competition between exogenous and endogenous saccade plans. Neuroimage 40.

Aron, A.R., 2007. The neural basis of inhibition in cognitive control. The Neuroscientist 13, 1–15.

Aron, A.R., Behrens, T.E., Smith, S., Frank, M.J., Poldrack, R.A., 2007a. Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. Journal of Neuroscience 27, 3743–3752.

Aron, A.R., Dowson, J.H., Sahakian, B.J., Robbins, T.W., 2003a. Methylphenidate improves response inhibition in adults with attention-deficit/hyperactivity disorder. Biological Psychiatry 54, 1465–1468.

Aron, A.R., Durston, S., Eagle, D.M., Logan, G., Stinear, C.M., Stuphorn, V., 2007b. Converging evidence for a fronto-basal-ganglia network for inhibitory control of action and cognition. Journal of Neuroscience 27, 11860–11864.

Aron, A.R., Fletcher, P.C., Bullmore, E.T., Sahakian, B.J., Robbins, T.W., 2003b. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. Nature Neuroscience 6, 115–116.

Aron, A.R., Poldrack, R.A., 2005. The cognitive neuroscience of response inhibition: relevance for genetic research in attention-deficit/hyperactivity disorder. Biological Psychiatry 57, 1285–1292.

Aron, A.R., Poldrack, R.A., 2006. Cortical and subcortical contributions to stop signal response inhibition: role of the subthalamic nucleus. Journal of Neuroscience 26, 2424–2433.

Aron, A.R., Robbins, T.W., Poldrack, R.A., 2004. Inhibition and the right inferior frontal cortex. Trends in Cognitive Sciences 8, 170–177.

Asghari, V., Sanyal, S., Buchwaldt, S., Paterson, A., Jovanovic, V., Van Tol, H.H., 1995. Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. Journal of Neurochemistry 65, 1157–1165.

Aylward, E.H., Reiss, A.L., Reader, M.J., Singer, H.S., Brown, J.E., Denckla, M.B., 1996. Basal ganglia volumes in children with attention-deficit hyperactivity disorder. Journal of Child Neurology 11, 112–115.

Banich, M.T., Mackiecicz, K., Depue, B.E., Whitmer, A., Heller, W., 2009. Cognitive control mechanisms, emotion and memory: a neural perspective with implications for psychopathology. Neuroscience and Biobehavioral Reviews 33, 613–630.

Barkley, R.A., 1997. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychological Bulletin 121, 65–94.

Bartzokis, G., Lu, P.H., Beckson, M., Rapoport, R., Grant, S., Wiseman, E.J., London, E.D., 2000. Abstinence from cocaine reduces high-risk responses on a gambling task. Neuropsychopharmacology 22, 102–103.

Becker, J., Beer, M., 1986. The influence of estrogen on nigrostriatal dopamine activity: behavioral and neurochemical evidence for both pre- and postsynaptic components. Behavioural Brain Research 19, 27–33.

Bellgrove, M.A., Hawi, Z., Lowe, N., Kirley, A., Robertson, I.H., Gill, M., 2005. DRD4 gene variants and sustained attention in attention deficit hyperactivity disorder (ADHD): effects of associated alleles at the VNTR and −521 SNP. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 136, 81–86.

Bellgrove, M.A., Hester, R., Garavan, H., 2004. The functional neuroanatomy of response variability: evidence from a response inhibition task. Neuropsychologia 42, 1910–1916.

Bellgrove, M.A., Robertson, I.H., Gill, M., 2007. Genes, cognition and brain activity: the endophenotype approach. In: Fitzgerald, M., et al. (Eds.), Handbook of Attention Deficit Hyperactivity Disorder (ADHD). John Wiley & Sons, Chichester, pp. 237–268.

Bjorklund, D.F., Kipp, K., 1996. Parental investment theory and gender differences in the evolution of inhibition mechanisms. Psychological Bulletin 120, 163–188.

Bolla, K.I., Eldreth, D.A., London, E.D., Kiehl, K.A., Mouratidis, M., Contoreggi, C., Matochik, J.A., Kurian, V., Cadet, J.L., Kimes, A.S., Funderburk, F.R., Ernst, M., 2003. Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. Neuroimage 19, 1085–1094.

Booth, J.R., Burman, D.D., Meyer, J.R., Lei, Z., Trommer, B.L., Davenport, N.D., Li, W., Parrish, T.B., Gitelman, D.R., Mesulam, M.M., 2005. Larger deficits in brain networks for response inhibition than for visual selective attention in attention deficit hyperactivity disorder (ADHD). Journal of Child Psychology and Psychiatry 46, 94–111.

Brass, M., Derrfuss, J., Forstmann, B., von Cramon, D.Y., 2005. The role of the inferior frontal junction area in cognitive control. Trends in Cognitive Science 9, 314–316.

Braver, T.S., Barch, D.M., Gray, J.R., Molfese, D.L., Snyder, A., 2001. Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors. Cerebral Cortex 11, 825–836.

Brookes, K.J., Neale, B.M., Sugden, K., Khan, N., Asherson, P., D'Souza, U.M., 2007. Relationship between VNTR polymorphisms of the human dopamine transporter gene and expression in post-mortem midbrain tissue. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics.

Bunge, S.A., Dudukovic, N.M., Thomason, M.E., Vaidya, C.J., Gabrieli, J.D., 2002a. Immature frontal lobe contributions to cognitive control in children: evidence from fMRI. Neuron 33, 301–311.

Bunge, S.A., Hazeltine, E., Scanlon, M.D., Rosen, A.C., Gabrieli, J.D.E., 2002b. Dissociable contributions of prefrontal and parietal cortices to response selection. Neuroimage 17, 1562–1571.

Bunge, S.A., Ochsner, K.N., Desmond, J.E., Glover, G.H., Gabrieli, J.D., 2001. Prefrontal regions involved in keeping information in and out of mind. Brain 124, 2074–2086.

Butter, C.M., Rapcsak, S., Watson, R.T., Heilman, K.M., 1988. Changes in sensory inattention, directional motor neglect and "release" of the fixation reflex following a unilateral frontal lesion: a case report. Neuropsychologia 26, 533–545.

Cabeza, R., 2002. Hemispheric asymmetry reduction in older adults: the HAROLD model. Psychology and Aging 17, 85–100.

Casey, B.J., Castellanos, F.X., Giedd, J.N., Marsh, W.L., Hamburger, S.D., Schubert, A.B., Vauss, Y.C., Vaituzis, A.C., Dickstein, D.P., Sarfatti, S.E., Rapoport, J.L., 1997. Implication of right frontostriatal circuitry in response inhibition and attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry 36, 374–383.

Castellanos, F.X., Giedd, J.N., Eckburg, P., Marsh, W.L., Vaituzis, A.C., Kaysen, D., Hamburger, S.D., Rapoport, J.L., 1994. Quantitative morphology of the caudate nucleus in attention deficit hyperactivity disorder. American Journal of Psychiatry 151, 1791–1796.

Castellanos, F.X., Giedd, J.N., Marsh, W.L., Hamburger, S.D., Vaituzis, A.C., Dickstein, D.P., Sarfatti, S.E., Vauss, Y.C., Snell, J.W., Lange, N., Kaysen, D., Krain, A.L., Ritchie, G.F., Rajapakse, J.C., Rapoport, J.L., 1996. Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. Archives of General Psychiatry 53, 607–616.

Chamberlain, S.R., Fineberg, N.A., Menzies, L.A., Blackwell, A.D., Bullmore, E.T., Robbins, T.W., Sahakian, B.J., 2007. Impaired cognitive flexibility and motor inhibition in unaffected first-degree relatives of patients with obsessive-compulsive disorder. American Journal of Psychiatry 164, 335–338.

Chamberlain, S.R., Muller, U., Blackwell, A.D., Clark, L., Robbins, T.W., Sahakian, B.J., 2006. Neurochemical modulation of response inhibition and probabilistic learning in humans. Science 311, 861–863.

Chambers, C.D., Bellgrove, M.A., Gould, I.C., English, T., Garavan, H., McNaught, E.M., Kamke, M., Mattingley, J.B., 2007. Dissociable mechanisms of cognitive control in prefrontal and premotor cortex. Journal of Neurophysiology 98, 3638–3647.

Chambers, C.D., Bellgrove, M.A., Stokes, M.G., Henderson, T.R., Garavan, H., Robertson, I.H., Morris, A.P., Mattingley, J.B., 2006. Executive 'brake failure' following deactivation of human frontal lobe. Journal of Cognitive Neuroscience 18, 444–455.

Chambers, C.D., Mattingley, J.B., 2005. Neurodisruption of selective attention: insights and implications. Trends in Cognitive Sciences 9, 542–550.

Chambers, C.D., Payne, J.M., Stokes, M.G., Mattingley, J.B., 2004a. Fast and slow parietal pathways mediate spatial attention. Nature Neuroscience 7, 217–218.

Chambers, C.D., Stokes, M.G., Mattingley, J.B., 2004b. Modality-specific control of strategic spatial attention in parietal cortex. Neuron 44, 925–930.

Chauvel, P., Rey, M., Buser, P., Bancaud, J., 1996. What stimulation of the supplementary motor area in humans tells about its functional organization. Advances in Neurology 70, 199–209.

Chen, C.-Y., Muggleton, N.G., Tzeng, O.J.L., Hung, D.L., Juan, C.-H., in press. Control of prepotent responses by the superior medial frontal cortex. Neuroimage.

Cheon, K.A., Ryu, Y.H., Kim, J.W., Cho, D.Y., 2005. The homozygosity for 10-repeat allele at dopamine transporter gene and dopamine transporter density in Korean

children with attention deficit hyperactivity disorder: relating to treatment response to methylphenidate. European Neuropsychopharmacology 15, 95–101.
Cheon, K.A., Ryu, Y.H., Kim, Y.K., Namkoong, K., Kim, C.H., Lee, J.D., 2003. Dopamine transporter density in the basal ganglia assessed with [123I]IPT SPET in children with attention deficit hyperactivity disorder. European Journal of Nuclear Medicine and Molecular Imaging 30, 306–311.
Chikazoe, J., Konishi, S., Asari, T., Jimura, K., Miyashita, Y., 2007. Activation of right inferior frontal gyrus during response inhibition across response modalities. Journal of Cognitive Neuroscience 19, 69–80.
Clark, L., Robbins, T.W., Ersche, K.D., Sahakian, B.J., 2006. Reflection impulsivity in current and former substance users. Biological Psychiatry 60, 515–522.
Clark, L., Roiser, J.P., Cools, R., Rubinsztein, D.C., Sahakian, B.J., Robbins, T.W., 2005. Stop signal response inhibition is not modulated by tryptophan depletion or the serotonin transporter polymorphism in healthy volunteers: implications for the 5-HT theory of impulsivity. Psychopharmacology 182, 570–578.
Coffey, S.F., Gudleski, G.D., Saladin, M.E., Brady, K.T., 2003. Impulsivity and rapid discounting of delayed hypothetical rewards in cocaine-dependent individuals. Experimental and Clinical Psychopharmacology 11, 18–25.
Colzato, L.S., van den Wildenberg, W.P., Hommel, B., 2007. Impaired inhibitory control in recreational cocaine users. PLoS ONE 2, e1143.
Congdon, E., Lesch, K.P., Canli, T., 2008. Analysis of DRD4 and DAT polymorphisms and behavioral inhibition in healthy adults: implications for impulsivity. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 147, 27–32.
Cook, E.H., Stein, M.A., Krasowski, M.D., Cox, N.J., Olkon, D.M., Kieffer, J.E., Leventhal, B.L., 1995. Association of Attention-Deficit Disorder and the Dopamine Transporter Gene. American Journal of Human Genetics 56, 993–998.
Corbetta, M., Shulman, G., 2002. Control of goal-directed and stimulus-driven attention in the brain. Nature Reviews Neuroscience 3, 201–215.
Cornish, K.M., Manly, T., Savage, R., Swanson, J., Morisano, D., Butler, N., Grant, C., Cross, G., Bentley, L., Hollis, C.P., 2005. Association of the dopamine transporter (DAT1) 10/10-repeat genotype with ADHD symptoms and response inhibition in a general population sample. Molecular Psychiatry.
Coxon, J.P., Stinear, C.M., Byblow, W.D., in press. Stop and go: the neural basis of selective movement prevention. Journal of Cognitive Neuroscience.
Coull, J.T., Frith, C.D., Frackowiak, R.S., Grasby, P.M., 1996. A fronto-parietal network for rapid visual information processing: a PET study of sustained attention and working memory. Neuropsychologia 34, 1085–1095.
Coull, J.T., Nobre, A.C., 1998. Where and when to pay attention: The neural systems for directing attention to spatial locations and to time intervals as revealed by both PET and fMRI. Journal of Neuroscience 18, 7426–7435.
Cox, W.M., Brown, M.A., Rowlands, L.J., 2003. The effects of alcohol cue exposure on non-dependent drinkers' attentional bias for alcohol-related stimuli. Alcohol and Alcoholism 38, 45–49.
Coxon, J.P., Stinear, C.M., Byblow, W.D., 2006. Intracortical inhibition during volitional inhibition of prepared action. Journal of Neurophysiology 95, 3371–3383.
Crosbie, J., Schachar, R., 2001. Deficient inhibition as a marker for familial ADHD. American Journal of Psychiatry 158, 1884–1890.
Dalley, J.W., Cardinal, R., Robbins, T.W., 2004. Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. Neuroscience and Biobehavioural Reviews 28, 771–784.
Dalley, J.W., Fryer, T.D., Brichard, L., Robinson, E.S., Theobald, D.E., Laane, K., Pena, Y., Murphy, E.R., Shah, Y., Probst, K., Abakumova, I., Aigbirhio, F.I., Richards, H.K., Hong, Y., Baron, J.C., Everitt, B.J., Robbins, T.W., 2007. Nucleus accumbens D2/3 receptors predict trait impulsivity and cocaine reinforcement. Science 315, 1267–1270.
de Fockert, J., Rees, G., Frith, C.D., Lavie, N., 2001. The role of working memory in visual selective attention. Science 291, 1803–1806.
Décary, A., Richer, F., 1995. Response selection deficits in frontal excisions. Neuropsychologia 33.
Depue, B.E., Curran, T., Banich, M.T., 2007. Prefrontal regions orchestrate suppression of emotional memories via a two-phase process. Science 317, 215–219.
Derrfuss, J., Brass, M., Neumann, J., von Cramon, D.Y., 2005. Involvement of the inferior frontal junction in cognitive control: meta-analyses of switching and Stroop studies. Human Brain Mapping 25, 22–34.
Derrfuss, J., Brass, M., von Cramon, D.Y., 2004. Cognitive control in the posterior frontolateral cortex: evidence from common activations in task coordination, interference control, and working memory. Neuroimage 23, 604–612.
D'Esposito, M., Ballard, D., Aguirre, G.K., Zarahn, E., 1998. Human prefrontal cortex is not specific for working memory: a functional MRI study. Neuroimage 8, 274–282.
Dillon, D., Pizzagalli, D., 2007. Inhibition of action, thought, and emotion: a selective neurobiological review. Applied and Preventitive Psychology 12, 99–114.
Dolcos, F., McCarthy, G., 2006. Brain systems mediating cognitive interference by emotional distraction. Journal of Neuroscience 26, 2072–2079.
Dresel, S., Krause, J., Krause, K.H., LaFougere, C., Brinkbaumer, K., Kung, H.F., Hahn, K., Tatsch, K., 2000. Attention deficit hyperactivity disorder: binding of [99mTc]TRODAT-1 to the dopamine transporter before and after methylphenidate treatment. European Journal of Nuclear Medicine 27, 1518–1524.
Drewe, E.A., 1975. An experimental investigation of Luria's theory on the effects of frontal lobe lesions in man. Neuropsychologia 13, 421–429.
Durston, S., Fossella, J.A., Casey, B.J., Hulshoff Pol, H.E., Galvan, A., Schnack, H.G., Steenhuis, M.P., Minderaa, R.B., Buitelaar, J.K., Kahn, R.S., van Engeland, H., 2005. Differential effects of DRD4 and DAT1 genotype on fronto-striatal gray matter volumes in a sample of subjects with attention deficit hyperactivity disorder, their unaffected siblings, and controls. Molecular Psychiatry.
Durston, S., Fossella, J.A., Mulder, M.J., Casey, B.J., Ziermans, T.B., Vessaz, M.N., Van Engeland, H., 2008. Dopamine transporter genotype conveys familial risk of attention-deficit/hyperactivity disorder through striatal activation. Journal of the American Academy of Child and Adolescent Psychiatry 47, 61–67.
Durston, S., Mulder, M., Casey, B.J., Ziermans, T., van Engeland, H., 2006. Activation in Ventral Prefrontal Cortex is Sensitive to Genetic Vulnerability for Attention-Deficit Hyperactivity Disorder. Biological Psychiatry.
Durston, S., Tottenham, N.T., Thomas, K.M., Davidson, M.C., Eigsti, I.M., Yang, Y., Ulug, A.M., Casey, B.J., 2003. Differential patterns of striatal activation in young children with and without ADHD. Biological Psychiatry 53, 871–878.
Eagle, D.M., Bari, A., Robbins, T.W., 2008a. The neuropsychopharmacology of action inhibition: cross-species translation of the stop-signal and go/no-go tasks. Psychopharmacology 199, 439–456.
Eagle, D.M., Baunez, C., Hutcheson, D., Lehmann, O., Shah, A., Robbins, T.W., 2008b. Stop-signal reaction-time task performance: role of prefrontal cortex and subthalamic nucleus. Cerebral Cortex 18, 178–188.
Eagle, D.M., Robbins, T.W., 2003. Inhibitory control in rats performing a stop-signal reaction-time task: effects of lesions of the medial striatum and *d*-Amphetamine. Behavioral Neuroscience 117, 1302–1317.
Eagle, D.M., Tufft, M., Goodchild, H., Robbins, T.W., 2007. Differential effects of modafinil and methylphenidate on stop-signal reaction time task performance in the rat, and interactions with the dopamine receptor antagonist cis-flupenthixol. Psychopharmacology 192, 193–206.
Eme, R.F., 2007. Sex differences in child-onset, life-course-persistent conduct disorder. A review of biological influences. Clinical Psychology Review 27, 607–627.
Engle, R.W., Tuholski, S.W., Laughlin, J.E., Conway, A.R., 1999. Working memory, short-term memory, and general fluid intelligence: a latent-variable approach. Journal of Experimental Psychology: General 128, 309–331.
Evers, E., van der Veen, F., van Deursen, J., Schmitt, J., Deutz, N., Jolles, J., 2006. The effect of acute tryptophan depletion on the BOLD response during performance monitoring and response inhibition in healthy male volunteers. Psychopharmacology 187, 200–208.
Faraone, S.V., Biederman, J., Weiffenbach, B., Keith, T., Chu, M.P., Weaver, A., Spencer, T.J., Wilens, T.E., Frazier, J., Cleves, M., Sakai, J., 1999. Dopamine D4 gene 7-repeat allele and attention deficit hyperactivity disorder. American Journal of Psychiatry 156, 768–770.
Fassbender, C., Murphy, K., Foxe, J.J., Wylie, G.R., Javitt, D.C., Robertson, I.H., Garavan, H., 2004. A topography of executive functions and their interactions revealed by functional magnetic resonance imaging. Cognitive. Brain Research 20, 132–143.
Fassbender, C., Simoes-Franklin, C., Murphy, K., Hester, R., Meaney, J., Robertson, I.H., Garavan, H., 2006. The role of a right fronto-parietal network in cognitive control: common activations for 'cues-to-attend' and response inhibition. Journal of Psychophysiology 20, 286–296.
Filipek, P.A., Semrud-Clikeman, M., Steingard, R.J., Renshaw, P.F., Kennedy, D.N., Biederman, J., 1997. Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. Neurology 48, 589–601.
Fillmore, M.T., Rush, C.R., 2002. Impaired inhibitory control of behavior in chronic cocaine users. Drug and Alcohol Dependence 66, 265–273.
Fillmore, M.T., Rush, C.R., Hays, L., 2005. Cocaine improves inhibitory control in a human model of response conflict. Experimental and Clinical Psychopharmacology 13, 327–335.
Fillmore, M.T., Rush, C.R., Hays, L., 2006. Acute effects of oral cocaine on inhibitory control of behavior in humans. Drug and Alcohol Dependence 67, 157–167.
Fishbein, D.H., Eldreth, D.L., Hyde, C., Matochik, J.A., London, E.D., Contoreggi, C., Kurian, V., Kimes, A.S., Breeden, A., Grant, S., 2005. Risky decision making and the anterior cingulate cortex in abstinent drug abusers and nonusers. Brain Research. Cognitive Brain Research 23, 119–136.
Floden, D., Stuss, D.T., 2006. Inhibitory control is slowed in patients with right superior medial frontal damage. Journal of Cognitive Neuroscience 18, 1843–1849.
Fried, I., 1996. Electrical stimulation of the supplementary motor area. Advances in Neurology 70.
Fuke, S., Suo, S., Takahashi, N., Koike, H., Sasagawa, N., Ishiura, S., 2001. The VNTR Polymorphism of the Human Dopamine Transporter (DAT1) Gene Affects Gene Expression. The Pharmacogenomics Journal 1, 152–156.
Garavan, H., Hester, R., Murphy, K., Fassbender, C., Kelly, C., 2006. Individual differences in the functional neuroanatomy of inhibitory control. Brain Research 1105, 130–142.
Garavan, H., Kaufman, J.N., Hester, R., 2008. Acute effects of cocaine on the neurobiology of cognitive control. Philosophical Transactions of the Royal Society B 363, 3267–3276.
Garavan, H., Ross, T.J., Murphy, K., Roche, R.A., Stein, E.A., 2002. Dissociable executive functions in the dynamic control of behavior: inhibition, error detection, and correction. Neuroimage 17, 1820–1829.
Garavan, H., Ross, T.J., Stein, E.A., 1999. Right hemispheric dominance of inhibitory control: An event-related functional MRI study. Proceedings of the National Academy of Sciences of the United States of America 96, 8301–8306.
Geller, D.A., Biederman, J., Griffin, S., Jones, J., Lefkowitz, T.R., 1996. Comorbidity of juvenile obsessive-compulsive disorder with disruptive behavior disorders. Journal of the American Academy of Child and Adolescent Psychiatry 35, 1637–1646.

Gibbs, R., Burke, A., Johnson, D., 1998. Estrogen replacement attenuates effects of scopolamine and lorazepam on memory acquisition and retention. Hormones and Behavior 34, 112–125.
Gilbert, D.L., Bansal, A.S., Sethuraman, G., Sallee, F.R., Zhang, J., Lipps, T., Wassermann, E.M., 2004. Association of cortical disinhibition with tic, ADHD, and OCD severity in Tourette syndrome. Movement Disorders 19, 416–425.
Gilbert, D.L., Sallee, F.R., Zhang, J., Lipps, T.D., Wassermann, E.M., 2005. Transcranial magnetic stimulation-evoked cortical inhibition: a consistent marker of attention-deficit/hyperactivity disorder scores in tourette syndrome. Biological Psychiatry 57, 1597–1600.
Gilbert, D.L., Wang, Z., Sallee, F.R., Ridel, K.R., Merhar, S., Zhang, J., Lipps, T.D., White, C., Badreldin, N., Wassermann, E.M., 2006. Dopamine transporter genotype influences the physiological response to medication in ADHD. Brain 129, 2038–2046.
Goldstein, R.Z., Volkow, N.D., Wang, G.J., Fowler, J.S., Rajaram, S., 2001. Addiction changes orbitofrontal gyrus function: involvement in response inhibition. Neuroreport 12, 2595–2599.
Grados, M.A., Mathews, C.A., 2008. Latent Class Analysis of Gilles de la Tourette Syndrome Using Comorbidities: Clinical and Genetic Implications. Biolical Psychiatry.
Grant, S., 2004. Let' s not be impulsive: comments on Lubman et al. (2004). Addiction 99, 1504–1505 discussion 1506–1507.
Hallet, P., 1978. Primary and secondary saccades to goals defined by instructions. Vision Research 18, 1279–1296.
Halsband, U., Passingham, R.E., 1985. Premotor cortex and the conditions for movement in monkeys (Macaca fascicularis). Behavioural Brain Research 18, 269–277.
Hazeltine, E., Bunge, S.A., Scanlon, M.D., Gabrieli, J.D.E., 2003. Material-dependent and material-independent selection processes in the frontal and parietal lobes: an event-related fMRI investigation of repsonse competition. Neuropsychologia 41, 1208–1217.
Hazeltine, E., Poldrack, R.A., Gabrieli, J.D.E., 2000. Neural activation during response competition. Journal of Cognitive Neuroscience 12, 118–129.
Heinz, A., Goldman, D., Jones, D.W., Palmour, R., Hommer, D., Gorey, J.G., Lee, K.S., Linnoila, M., Weinberger, D.R., 2000. Genotype Influences In Vivo Dopamine Transporter Availability in Human Striatum. Neuropsychopharmacology 22, 133–139.
Herrmann, M.J., Jacob, C., Unterecker, S., Fallgatter, A.J., 2003. Reduced response-inhibition in obsessive-compulsive disorder measured with topographic evoked potential mapping. Psychiatry Research 120, 265–271.
Hester, R., Dixon, V., Garavan, H., 2006. A consistent attentional bias for drug-related material in active cocaine users across word and picture versions of the emotional Stroop task. Drug and Alcohol Dependence 81, 251–257.
Hester, R., Garavan, H., 2004. Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity. Journal of Neuroscience 24, 11017–11022.
Hester, R., Garavan, H., 2005. Working memory and executive function: the influence of content and load on the control of attention. Memory and Cognition 33, 221–233.
Hester, R., Murphy, K., Garavan, H., 2004a. Beyond common resources: the cortical basis for resolving task interference. NeuroImage 23, 202–212.
Hester, R.L., Murphy, K., Foxe, J.J., Foxe, D.M., Javitt, D.C., Garavan, H., 2004b. Predicting success: patterns of cortical activation and deactivation prior to response inhibition. Journal of Cognitive Neuroscience 16, 776–785.
Hodgson, T., Chamberlain, M., Parris, B., James, M., Gutowski, N., Husain, M., Kennard, C., 2007. The role of the ventrolateral frontal cortex in inhibitory oculomotor control. Brain 130, 1525–1537.
Holmes, G., 1938. The cerebral integration of the ocular movements. British Medical Journal 2, 107–112.
Hruska, R., Silbergeld, E., 1980. Increased dopamine receptor sensitivity after estrogen treatment using the rat rotation model. Science 208, 1466–1468.
Ikeda, A., Yazawa, S., Kunieda, T., Ohara, S., Terada, K., Mikuni, N., Nagamine, T., Taki, W., Kimura, J., Shibasaki, H., 1999. Cognitive motor control in human presupplementary motor area studied by subdural recording of discrimination/selection-related potentials. Brain 122, 915–931.
Isoda, M., Hikosaka, O., 2008. Role for subthalamic nucleus neurons in switching from automatic to controlled eye movement. Journal of Neuroscience 28, 7209–7218.
Johnson, K.A., Kelly, S.P., Robertson, I.H., Barry, E., Mulligan, A., Dáibhis, A., Daly, M., Watchorn, A., Keavey, M., Lambert, D., McDonnell, C., Hawi, Z., Gill, M., Bellgrove, M.A., 2008. Absence of the 7-repeat variant of the DRD4 VNTR is associated with drifting sustained attention in children with ADHD but not in controls. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 147, 927–937.
Jovanovic, V., Guan, H.C., Van Tol, H.H., 1999. Comparative pharmacological and functional analysis of the human dopamine D4.2 and D4.10 receptor variants. Pharmacogenetics 9, 561–568.
Kane, M.J., Bleckley, M.K., Conway, A.R., Engle, R.W., 2001. A controlled-attention view of working-memory capacity. Journal of Experimental Psychology: General 130, 169–183.
Kane, M.J., Engle, R.W., 2003. Working-memory capacity and the control of attention: the contributions of goal neglect, response competition, and task set to Stroop interference. Journal of Experimental Psychology: General 132, 47–70.
Kaufman, J.N., Ross, T.J., Stein, E.A., Garavan, H., 2003. Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. Journal of Neuroscience 23, 7839–7843.
Kawashima, R., Satoh, K., Itoh, H., Ono, S., Furumoto, S., Gotoh, R., Koyama, M., Yoshioka, S., Takahashi, T., Takahashi, K., Yanagisawa, T., Fukuda, H., 1996. Functional anatomy of GO/NO-GO discrimination and response selection - a PET study in man. Brain Research 728, 79–89.
Kelly, A.M., Garavan, H., 2005. Human functional neuroimaging of brain changes associated with practice. Cerebral Cortex 15, 1089–1102.
Kelly, A.M., Hester, R., Murphy, K., Javitt, D.C., Foxe, J.J., Garavan, H., 2004. Prefrontal-subcortical dissociations underlying inhibitory control revealed by event-related fMRI. European Journal of Neuroscience 19, 3105–3112.
Kelly, C., Hester, R., Foxe, J.J., Shpaner, M., Garavan, H., 2006. Flexible cognitive control: effects of individual differences and brief practice on a complex cognitive task. Neuroimage 31, 866–886.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E., 2005. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Archives of General Psychiatry 62, 593–602.
Kinomura, S., Larsson, J., Gulyas, B., Roland, P.E., 1996. Activation by attention of the human reticular formation and thalamic intralaminar nuclei. Science 271, 512–515.
Konishi, S., Nakajima, K., Uchida, I., Kikyo, H., Kameyama, M., Miyashita, Y., 1999. Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. Brain 122, 981–991.
Koski, L., Molnar-Szakacs, I., Iacoboni, M., 2005. Exploring the contributions of premotor and parietal cortex to spatial compatibility using image-guided TMS. Neuroimage 24, 296–305.
Krause, K.H., Dresel, S.H., Krause, J., Kung, H.F., Tatsch, K., 2000. Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measures by single photon emission computed tomography. Neuoscience Letters 285, 107–110.
Krause, K.-H., Dresel, S.H., Krause, J., la Fougere, C., Ackenheil, M., 2003. The dopamine transporter and neuroimaging in attention deficit hyperactivity disorder. Neuroscience & Biobehavioral Reviews 27, 605–613.
Kühn, A.A., Williams, D., Kupsch, A., Limousin, P., Hariz, M., Schneider, G.-H., Yarrow, K., Brown, P., 2004. Event-related beta desynchronization in human subthalamic nucleus correlates with motor performance. Brain 127, 735–746.
Lamar, M., Cutter, W., Rubia, K., Brammer, M., Daly, E., Craig, M., Cleare, A.J., Murphy, D., 2007. 5-HT, prefrontal function and aging: fMRI of inhibition and acute tryptophan depletion. Neurobiology of Aging.
Langley, K., Marshall, L., Van Den Bree, M., Thomas, H., Owen, M., O'Donovan, M., Thapar, A., 2004. Association of the dopamine d(4) receptor gene 7-repeat allele with neuropsychological test performance of children with ADHD. American Journal of Psychiatry 161, 133–138.
Leung, H., Cai, W., 2007. Common and differential ventrolateral prefrontal activity during inhibition of hand and eye movements. Neuroscience and Biobehavioral Reviews 27, 9893–9900.
Li, C.S., Huang, C., Constable, R.T., Sinha, R., 2006. Gender differences in the neural correlates of response inhibition during a stop signal task. Neuroimage 32, 1918–1929.
Lijffijt, M., Kenemans, J.L., Verbaten, M.N., Van Engeland, H., 2005. A meta-analytic review of stopping performance in attention-deficit/hyperactivity disorder: deficient inhibitory motor control? Journal of Abnormal Psychology 114, 216–222.
Logan, G.D., 1994. On the Ability to Inhibit Thought and Action: A User's guide to the Stop Signal Paradigm. In: Dagenbach, D., Carr, T.H. (Eds.), Inhibitory Processes in Attention, Memory, and Language. Academic Press, San Diego, pp. 189–239.
Luria, A.R., 1966. Higher Cortical Functions in Man. Tavistock, London.
Lyvers, M., 2000. Loss of control'' in alcoholism and drug addiction: a neuroscientific interpretation. Experimental and Clinical Psychopharmacology 8, 225–249.
Manly, T., Owen, A.M., McAvinue, L., Datta, A., Lewis, G.H., Scott, S.K., Rorden, C., Pickard, J., Robertson, I.H., 2003. Enhancing the sensitivity of a sustained attention task to frontal damage: convergent clinical and functional imaging evidence. Neurocase 9, 340–349.
McCarthy, G., Luby, M., Gore, J., Goldman-Rakic, P., 1997. Infrequent events transiently activate human prefrontal and parietal cortex as measured by functional MRI. Journal of Neurophysiology 77, 1630–1634.
Menon, V., Adleman, N.E., White, C.D., Glover, G.H., Reiss, A.L., 2001. Error-related brain activation during a Go/NoGo response inhibition task. Human Brain Mapping 12, 131–143.
Menzies, L., Achard, S., Chamberlain, S.R., Fineberg, N., Chen, C.H., del Campo, N., Sahakian, B.J., Robbins, T.W., Bullmore, E., 2007. Neurocognitive endophenotypes of obsessive-compulsive disorder. Brain 130, 3223–3236.
Michael, G., Garcia, S., Fernandez, D., Sellal, F., Boucart, M., 2006. The ventral premotor cortex (vPM) and resistance to interference. Behavioral Neuroscience 120, 447–462.
Miller, E.K., Cohen, J.D., 2001. An integrative theory of prefrontal cortex function. Annual Review of Neuroscience 24.
Mink, J., 1996. The basal ganglia: focused selection and inhibition of competing motor programs. Progress in Neurobiology 50, 381–425.
Mitchell, J.P., Macrae, C.N., Gilchrist, I.D., 2002. Working memory and the suppression of reflexive saccades. Journal of Cognitive Neuroscience 14, 95–103.

Monterosso, J., Ehrman, R., Napier, K.L., O'Brien, C.P., Childress, A.R., 2001. Three decision-making tasks in cocaine-dependent patients: do they measure the same construct? Addiction 96, 1825–1837.
Morita, M., Nakahara, K., Hayashi, T., 2004. A rapid presentation event-related functional magnetic resonance imaging study of response inhibition in macaque monkeys. Neuroscience Letters 356, 203–206.
Moses, E., Drevets, W., Smith, G., Mathis, C., Kalro, B., Butters, M., Leondires, M., Greer, P., Lopresti, B., Loucks, T., Berga, S., 2000. Effects of estradiol and progesterone administration on human serotonin 2A receptor binding: a PET study. Biological Psychiatry 48, 854–860.
Mössner, R., Walitza, S., Geller, F., Scherag, A., Gutknecht, L., Jacob, C., Bogusch, L., Remschmidt, H., Simons, M., Herpertz-Dahlmann, B., Fleischhaker, C., Schulz, E., Warnke, A., Hinney, A., Wewetzer, C., Lesch, K.P., 2006. Transmission disequilibrium of polymorphic variants in the tryptophan hydroxylase-2 gene in children and adolescents with obsessive–compulsive disorder. International Journal of Neuropsychopharmacology 9.
Mostofsky, S.H., Schafer, J.G., Abrams, M.T., Goldberg, M.C., Flower, A.A., Boyce, A., Courtney, S.M., Calhoun, V.D., Kraut, M.A., Denckla, M.B., Pekar, J.J., 2003. fMRI evidence that the neural basis of response inhibition is task-dependent. Brain Research. Cognitive Brain Research 17, 419–430.
Mostofsky, S.H., Simmonds, D.J., 2008. Response inhibition and response selection: Two sides of the same coin. Journal of Cognitive Neuroscience 20, 1–11.
Mulder, M.J., Baeyens, D., Davidson, M.C., Casey, B.J., van den Ban, E., van Engeland, H., Durston, S., 2008. Familial vulnerability to ADHD affects activity in the cerebellum in addition to the prefrontal systems. Journal of the American Academy of Child and Adolescent Psychiatry 47, 68–75.
Murphy, D., Cole, N., Segal, M., 1998. Brain-derived neurotrophic factor mediates estradiol-induced dendritic spine formation in hippocampal neurons. Proceedings of the National Academy of Sciences of the United States of America 95, 11412–11417.
Nachev, P., Wydell, H., O'Neill, K., Husain, M., Kennard, C., 2007. The role of the pre-supplementary motor area in the control of action. NeuroImage Cortical Control of Higher Motor Cognition 36, T155–T163.
Nambu, A., Tokuno, H., Hamada, I., Kita, H., Imanishi, M., Akazawa, T., Ikeuchi, Y., Hasegawa, N., 2000. Excitatory cortical inputs to pallidal neurons via the subthalamic nucleus in the monkey. Journal of Neurophysiology 84, 289–300.
Nambu, A., Tokuno, H., Takada, M., 2002. Functional significance of the cortico-subthalamo-pallidal 'hyperdirect' pathway. Neuroscience Research 43, 111–117.
Neuman, R.J., Sitdhiraksa, N., Reich, W., Ji, T.H., Joyner, C.A., Sun, L.W., Todd, R.D., 2005. Estimation of prevalence of DSM-IV and latent class-defined ADHD subtypes in a population-based sample of child and adolescent twins. Twin Research in Human Genetics 8, 392–401.
Nielson, K.A., Langenecker, S.A., Garavan, H., 2002. Differences in the functional neuroanatomy of inhibitory control across the adult life span. Psychology and Aging 17, 56–71.
Nigg, J., 2000. On inhibition/disinhibition in developmental psychopathology: views from cognitive and personality psychology and a working inhibition taxonomy. Psychological Bulletin 126, 220–246.
Nigg, J.T., 2001. Is ADHD a Disinhibitory Disorder? Psychological Bulletin 127, 571–598.
Nigg, J.T., Willcutt, E.G., Doyle, A.E., Sonuga-Barke, E.J., 2005. Causal heterogeneity in attention-deficit/hyperactivity disorder: do we need neuropsychologically impaired subtypes? Biolical Psychiatry 57, 1224–1230.
Pasqualini, C., Olivier, V., Guibert, B., Frain, O., Leviel, V., 1995. Acute stimulatory effect of estradiol on striatal dopamine synthesis. Journal of Neurochemistry 65, 1651–1657.
Pasqualini, C., Olivier, V., Guibert, B., Frain, O., Leviel, V., 1996. Rapid stimulation of striatal dopamine synthesis by estradiol. Cellular and Molecular Neurobiology 16, 411–415.
Penades, R., Catalan, R., Rubia, K., Andres, S., Salamero, M., Gasto, C., 2007. Impaired response inhibition in obsessive compulsive disorder. European Psychiatry 22, 404–410.
Peterson, B.S., Pine, D.S., Cohen, P., Brook, J.S., 2001. Prospective, longitudinal study of tic, obsessive-compulsive, and attention-deficit/hyperactivity disorders in an epidemiological sample. Journal of the American Academy of Child and Adolescent Psychiatry 40, 685–695.
Picton, T.W., Stuss, D.T., Alexander, M.P., Shallice, T., Binns, M.A., Gillingham, S., 2007. Effects of focal frontal lesions on response inhibition. Cerebral Cortex 17, 826–838.
Pliszka, S.R., Glahn, D.C., Semrud-Clikeman, M., Franklin, C., Perez 3rd, R., Xiong, J., Liotti, M., 2006. Neuroimaging of inhibitory control areas in children with attention deficit hyperactivity disorder who were treatment naive or in long-term treatment. American Journal of Psychiatry 163, 1052–1060.
Polanczyk, G., Rohde, L.A., 2007. Epidemiology of attention-deficit/hyperactivity disorder across the lifespan. Current Opinion in Psychiatry 20, 386–392.
Potenza, M., Leung, H., Blumberg, H., Peterson, B., Fulbright, R., Lacadie, C., Skudlarski, P., Gore, J., 2003. An FMRI Stroop task study of ventromedial prefrontal cortical function in pathological gamblers. American Journal of Psychiatry 160, 1990–1994.
Praamstra, P., Kleine, B.-U., Schnitzler, A., 1999. Magnetic stimulation of the dorsal premotor cortex modulates the Simon effect. NeuroReport 10, 3671–3674.
Primus, R.J., Thurkauf, A., Xu, J., Yevich, E., McInerney, S., Shaw, K., Tallman, J.F., Gallagher, D.W., 1997. II. Localization and characterization of dopamine D4 binding sites in rat and human brain by use of the novel, D4 receptor-selective ligand [3H]NGD 94-1. Journal of Pharmacology and Experimental Therapeutics 282, 1020–1027.
Protopopescu, X., Pan, H., Altemus, M., Tuescher, O., Polanecsky, M., McEwen, B., Silbersweig, D., Stern, E., 2005. Orbitofrontal cortex activity related to emotional processing changes across the menstrual cycle. Proceedings of the National Academy of Sciences of the United States of America 102, 16060–16065.
Rieger, M., Gauggel, S., Burmeister, K., 2003. Inhibition of ongoing responses following frontal, nonfrontal and basal ganglia lesions. Neuropsychology 17, 272–282.
Roberts, R.J., Hager, L.D., Heron, C., 1994. Prefrontal cognitive processes: Working memory and inhibition in the antisaccade task. Journal of Experimental Psychology: General 123, 374–393.
Robinson, E.S., Eagle, D.M., Mar, A.C., Bari, A., Banerjee, G., Jiang, X., Dalley, J.W., Robbins, T.W., 2008. Similar effects of the selective noradrenaline reuptake inhibitor atomoxetine on three distinct forms of impulsivity in the rat. Neuropsychopharmacology 33, 1028–1037.
Rorden, C., Karnath, H.O., 2004. Using human brain lesions to infer function: a relic from a past era in the fMRI age? Nature Reviews Neuroscience 5, 813–819.
Roth, R.M., Saykin, A.J., Flashman, L.A., Pixley, H.S., West, J.D., Mamourian, A.C., 2007. Event-related functional magnetic resonance imaging of response inhibition in obsessive-compulsive disorder. Biological Psychiatry 62, 901–909.
Rowe, J., Friston, K., Frackowiak, R., Passingham, R., 2002. Attention to action: specific modulation of corticocortical interactions in humans. Neuroimage 17, 988–998.
Rubia, K., Lee, F., Cleare, A.J., Tunstall, N., Fu, C.H., Brammer, M., McGuire, P., 2005a. Tryptophan depletion reduces right inferior prefrontal activation during response inhibition in fast, event-related fMRI. Psychopharmacology 179, 791–803.
Rubia, K., Overmeyer, S., Taylor, E., Brammer, M., Williams, S.C., Simmons, A., Andrew, C., Bullmore, E.T., 2000. Functional frontalisation with age: mapping neurodevelopmental trajectories with fMRI. Neuroscience & Biobehavioral Reviews 24, 13–19.
Rubia, K., Overmeyer, S., Taylor, E., Brammer, M., Williams, S.C., Simmons, A., Bullmore, E.T., 1999. Hypofrontality in attention deficit hyperactivity disorder during higher-order motor control: a study with functional MRI. American Journal of Psychiatry 156, 891–896.
Rubia, K., Russell, T., Overmeyer, S., Brammer, M.J., Bullmore, E.T., Sharma, T., Simmons, A., Williams, S.C., Giampietro, V., Andrew, C.M., Taylor, E., 2001. Mapping motor inhibition: conjunctive brain activations across different versions of go/no-go and stop tasks. Neuroimage 13, 250–261.
Rubia, K., Smith, A.B., Brammer, M.J., Taylor, E., 2003. Right inferior prefrontal cortex mediates response inhibition while mesial prefrontal cortex is responsible for error detection. Neuroimage 20, 351–358.
Rubia, K., Smith, A.B., Brammer, M.J., Toone, B., Taylor, E., 2005b. Abnormal brain activation during inhibition and error detection in medication-naive adolescents with ADHD. American Journal of Psychiatry 162, 1067–1075.
Rushworth, M.F.S., Hadland, K.A., Paus, T., Sipila, P.K., 2002. Role of the human medial frontal cortex in task switching: a combined TMS and fMRI study. Journal of Neurophysiology 87, 2577–2592.
Sagvolden, T., Johansen, E.B., Aase, H., Russell, V.A., 2005. A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. The Behavioral and Brain Sciences 28, 397–419 discussion 419–368.
Schachar, R.J., Crosbie, J., Barr, C.L., Ornstein, T.J., Kennedy, J., Malone, M., Roberts, W., Ickowicz, A., Tannock, R., Chen, S., Pathare, T., 2005. Inhibition of Motor Responses in Siblings Concordant and Discordant for Attention Deficit Hyperactivity Disorder. American Journal of Psychiatry 162, 1076–1082.
Scheres, A., Oosterlaan, J., Swanson, J., Morein-Zamir, S., Meiran, N., Schut, H., Vlasveld, L., Sergeant, J.A., 2003. The effect of methylphenidate on three forms of response inhibition in boys with AD/HD. Journal of Abnormal Child Psychology 31, 105–120.
Schluter, N.D., Rushworth, M.F.S., Passingham, R.E., Mills, K.R., 1998. Temporary interference in human lateral premotor cortex suggests dominance for the selection of movements. Brain 121, 785–799.
Schulz, K.P., Fan, J., Tang, C.Y., Newcorn, J.H., Buchsbaum, M.S., Cheung, A.M., Halperin, J.M., 2004. Response inhibition in adolescents diagnosed with attention deficit hyperactivity disorder during childhood: an event-related FMRI study. American Journal of Psychiatry 161, 1650–1657.
Schumacher, E.H., Elston, G.N., D'Esposito, M., 2003. Neural evidence for representation-specific response selection. Journal of Cognitive Neuroscience 15, 1111–1121.
Sergeant, J., 2000. The cognitive-energetical model: An empirical approach to Attention-Deficit Hyperactivity Disorder. Neuroscience & Biobehavioral Reviews 24, 7–12.
Sheehan, K., Lowe, N., Kirley, A., Mullins, C., Fitzgerald, M., Gill, M., Hawi, Z., 2005. Tryptophan hydroxylase 2 (TPH2) gene variants associated with ADHD. Molecular Psychiatry 10, 944–949.
Shima, K., Mushiake, H., Saito, N., Tanji, J., 1996. Role for cells in the presupplementary motor area in updating motor plans. Proceedings of the National Academy of Sciences of the United States of America 93, 8694–8698.
Siebner, H.R., Rothwell, J.C., 2003. Transcranial magnetic stimulation: new insights into representational cortical plasticity. Experimental Brain Research 148, 1–16.

Simmonds, D.J., Fotedar, S.G., Suskauer, S.J., Pekar, J.J., Denckla, M.B., Mostofsky, S.H., 2007. Functional brain correlates of response time variability in children. Neuropsychologia 45, 2147–2157.
Simmonds, D.J., Pekar, J.J., Mostofsky, S.H., 2008. Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. Neuropsychologia 46, 224–232.
Simon, N.W., Mendez, I.A., Setlow, B., 2007. Cocaine exposure causes long-term increases in impulsive choice. Behavioral Neuroscience 121, 543–549.
Slaats-Willemse, D., Swaab-Barneveld, H., De Sonneville, L., Buitelaar, J., 2005. Familial clustering of executive functioning in affected sibling pair families with ADHD. Journal of the American Academy of Child and Adolescent Psychiatry 44, 385–391.
Slaats-Willemse, D., Swaab-Barneveld, H., De Sonneville, L., Van Der Meulen, E., Buitelaar, J., 2003. Deficient Response Inhibition as a Cognitive Endophenotype of ADHD. Journal of the American Academy of Child and Adolescent Psychiatry 42, 1242–1248.
Sonuga-Barke, E.J., Dalen, L., Remington, B., 2003. Do executive deficits and delay aversion make independent contributions to preschool attention-deficit/hyperactivity disorder symptoms? Journal of the American Academy of Child and Adolescent Psychiatry 42, 1335–1342.
Sowell, E.R., Thompson, P.M., Welcome, S.E., Henkenius, A.L., Toga, A.W., Peterson, B.S., 2003. Cortical abnormalities in children and adolescents with attention-deficit hyperactivity disorder. Lancet 362, 1699–1707.
Stoltenberg, S.F., Glass, J.M., Chermack, S.T., Flynn, H.A., Li, S., Weston, M.E., Burmeister, M., 2006. Possible association between response inhibition and a variant in the brain-expressed tryptophan hydroxylase-2 gene. Psychiatric Genetics 16, 35–38.
Sturm, W., de Simone, A., Krause, B.J., Specht, K., Hesselmann, V., Radermacher, I., Herzog, H., Tellmann, L., Muller-Gartner, H.W., Willmes, K., 1999. Functional anatomy of intrinsic alertness: evidence for a fronto-parietal-thalamic-brainstem network in the right hemisphere. Neuropsychologia 37, 797–805.
Sturm, W., Willmes, K., 2001. On the functional neuroanatomy of intrinsic and phasic alertness. Neuroimage 14, S76–84.
Suskauer, S.J., Simmonds, D.J., Fotedar, S., Blankner, J.G., Pekar, J.J., Denckla, M.B., Mostofsky, S.H., 2008. Functional magnetic resonance imaging evidence for abnormalities in response selection in attention deficit hyperactivity disorder: differences in activation associated with response inhibition but not habitual motor response. Journal of Cognitive Neuroscience 20, 478–493.
Swainson, R., Cunnington, R., Jackson, G., Rorden, C., Peters, A., Morris, P., Jackson, S., 2003. Cognitive control mechanisms revealed by ERP and fMRI: Evidence from repeated task-switching. Journal of Cognitive Neuroscience 15, 785–799.
Swanson, J., Oosterlaan, J., Murias, M., Schuck, S., Flodman, P., Spence, M.A., Wasdell, M., Ding, Y., Chi, H.-C., Smith, M., Mann, M., Carlson, C., Kennedy, J.L., Sergeant, J.A., Leung, P., Zhang, Y.-P., Sadeh, A., Chen, C., Whalen, C.K., Babb, K.A., Moyzis, R., Posner, M.I., 2000. Attention deficit/hyperactivity disorder children with a 7-repeat allele of the dopamine receptor D4 gene have extreme behavior but normal performance on critical neuropsychological tests of attention. PNAS 97, 4754–4759.
Tamm, L., Menon, V., Ringel, J., Reiss, A.L., 2004. Event-related FMRI evidence of frontotemporal involvement in aberrant response inhibition and task switching in attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry 43, 1430–1440.
Tannock, R., Schachar, R., Logan, G., 1995. Methylphenidate and cognitive flexibility: dissociated dose effects in hyperactive children. Journal of Abnormal Child Psychology 23, 235–266.
Tarter, R.E., Kirisci, L., Mezzich, A., Cornelius, J.R., Pajer, K., Vanyukov, M., Gardner, W., Blackson, T., Clark, D., 2003. Neurobehavioral disinhibition in childhood predicts early age at onset of substance use disorder. American Journal of Psychiatry 160, 1078–1085.
Teicher, M.H., Anderson, C.M., Polcari, A., Glod, C.A., Maas, L.C., Renshaw, P.F., 2000. Functional deficits in basal ganglia of children with attention-deficit/hyperactivity disorder shown with functional magnetic resonance imaging relaxometry. Nature Medicine 6, 470–473.
Tseng, J., Kolb, P., Raskind, M., Miller, M., 1997. Estrogen regulates galanin but not tyrosine hydroxylase gene expression in the rat locus ceruleus. Brain Research. Molecular Brain Research 50, 100–106.
Vaidya, C.J., Austin, G., Kirkorian, G., Ridlehuber, H.W., Desmond, J.E., Glover, G.H., Gabrieli, J.D., 1998. Selective effects of methylphenidate in attention deficit hyperactivity disorder: a functional magnetic resonance study. Proceedings of the National Academy of Sciences of the United States of America 95, 14494–14499.
van den Wildenberg, W.P.M., van Boxtel, G.J.M., van der Molen, M.W., Bosch, D., Speelman, J., Brunia, C.H.M., 2006. Stimulation of the subthalamic region facilitates the selection and inhibition of motor responses in Parkinson's disease. Journal of Cognitive Neuroscience 18, 626–636.
VanNess, S.H., Owens, M.J., Kilts, C.D., 2005. The variable number of tandem repeats element in DAT1 regulates in vitro dopamine transporter density. BMC Genetics 6, 55.
Verbruggen, F., Liefooghe, B., Vandierendonck, A., 2004. The interaction between stop signal inhibition and distractor interference in the flanker and Stroop task. Acta Psychologica 116, 21–37.
Verbruggen, F., Logan, G., 2009. Models of response inhibition in the stop-signal and stop-change paradigms. Neuroscience and Biobehavioral Reviews 33, 647–661.
Verdejo-Garcia, A., Lawrence, A.J., Clark, L., 2008. Impulsivity as a vulnerability marker for substance-use disorders: Review of findings from high-risk research, problem gamblers and genetic association studies. Neuroscience and Biobehavioral Reviews 32, 777–810.
Volkow, N.D., Wang, G.J., Newcorn, J., Fowler, J.S., Telang, F., Solanto, M.V., Logan, J., Wong, C., Ma, Y., Swanson, J.M., 2006. Brain dopamine transporter levels in treatment and drug naive adults with ADHD. Neuroimage.
Voytek, B., 2006. Emergent basal ganglia pathology within computational models. Journal of Neuroscience 26, 7313–7318.
Wager, T.D., Sylvester, C.-Y.C., Lacey, S.C., Nee, D.E., Franklin, M., Jonides, J., 2005. Common and unique components of response inhibition revealed by fMRI. Neuroimage 27, 323–340.
Walker, R., Husain, M., Hodgson, T., Harrison, J., Kennard, C., 1998. Saccadic eye movement and working memory deficits following damage to human prefrontal cortex. Neuropsychologia 36, 1141–1159.
Walsh, V., Cowey, A., 2000. Transcranial magnetic stimulation and cognitive neuroscience. Nature Reviews Neuroscience 1, 73–79.
Waters, A.J., Shiffman, S., Sayette, M.A., Paty, J.A., Gwaltney, C.J., Balabanis, M.H., 2003. Attentional bias predicts outcome in smoking cessation. Health Psychology 22, 378–387.
Willcutt, E.G., Doyle, A.E., Nigg, J.T., Faraone, S.V., Pennington, B.F., 2005. Validity of the executive function theory of ADHD: A meta-analytic review. Biological Psychiatry.
Winterer, G., Goldman, D., 2003. Genetics of human prefrontal function. Brain Research Review 43, 134–163.
Winterer, G., Hariri, A.R., Goldman, D., Weinberger, D.R., 2005. Neuroimaging and Human Genetics. International Review of Neurobiology 67PB, 325–383.
Woolley, C., Weiland, N., McEwen, B., Schwartzkroin, P., 1997. Estradiol increases the sensitivity of hippocampal CA1 pyramidal cells to NMDA receptor-mediated synaptic input: correlation with dendritic spine density. Journal of Neuroscience 17, 848–859.
Wylie, S.A., Ridderinkhof, K.R., Eckerle, M.K., Manning, C.A., 2007. Inefficient response inhibition in individuals with mild cognitive impairment. Neuropsychologia 45, 1408–1419.
Xue, G., Aron, A.R., Poldrack, R.A., 2008. Common neural substrates for inhibition of spoken and manual responses. Cerebral Cortex 18, 1923–1932.
Yantis, S., Schwarzbach, J., Serences, J.T., Carlson, R.L., Steinmetz, M.A., Pekar, J.J., Courtney, S.M., 2002. Transient neural activity in human parietal cortex during spatial attention shifts. Nature Neuroscience 5, 995–1002.