The neuropsychiatry of impulsivity

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Purpose of review

Impulsive symptoms occur across neuropsychiatric disorders, with important ramifications for everyday functioning and quality of life. This article considers recent developments in the neuropsychological assessment of impulsivity with a focus on the ability to suppress motor responses (response inhibition).

Recent findings

Using objective tests, response inhibition deficits were identified in several neuropsychiatric conditions associated with impulsivity, namely attention deficit hyperactivity disorder, trichotillomania, obsessive–compulsive disorder, and chronic substance abuse. Deficits were also found in unaffected first-degree relatives of attention deficit hyperactivity disorder and obsessive–compulsive disorder patients. Evidence from patients with focal brain lesions and from healthy volunteers using functional MRI and transcranial stimulation implicated the right inferior frontal gyrus in response inhibition. Pharmacological manipulations of the serotonin system had no detectable behavioural effects on response inhibition, whereas manipulations of the noradrenaline system did.

Summary

Neuropsychological assessment shows great promise in the investigation of impulsivity and its brain substrates. These results support a key role for response inhibition, a function linked to the right inferior frontal gyrus, in the manifestation of impulsivity. Measures of response inhibition will contribute to the search for psychiatric endophenotypes, novel treatments, and more optimal diagnostic classification systems for neuropsychiatric disorders.

Keywords

impulse, inhibition, noradrenaline, serotonin, spectrum

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Abbreviations

ADHD	attention deficit hyperactivity disorder
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders version IV
OCD	obsessive–compulsive disorder
RIFG	right inferior frontal gyrus

Introduction

The term 'impulsivity' encompasses a multitude of behaviours or responses that are poorly conceived, premature, inappropriate, and that frequently result in unwanted or deleterious outcomes [1]. We all engage from time to time in impulsive acts, such as blurting out critical comments without thinking, or buying expensive items on the spur of the moment. In the Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV) several neuropsychiatric disorders are either classified as impulse control conditions or encompass impulsive symptoms in the diagnostic criteria, including attention deficit hyperactivity disorder (ADHD), trichotillomania (repetitive hair-pulling), and substance abuse. These extreme pathological manifestations of impulsivity impair quality of life and everyday functioning, and as such represent important targets for treatment intervention [2,3]. This article considers the advantages of investigating impulsivity using objective neuropsychological tests, and discusses recent findings in relation to response inhibition. Methods of assessment are described, followed by findings in patient and relative studies. The neural and neurochemical substrates of response inhibition are considered on the basis of human and animal work. Finally, these data are integrated in relation to their clinical implications, and future research directions.

Investigating impulsivity: advantages of neuropsychological assessment

Although impulsive symptoms can be described from a 'top-level' syndromic perspective, and this is central to the formal diagnosis of neuropsychiatric disorders in DSM-IV, it is important to question whether impulsivity can be more objectively quantified, and related to underlying brain function. Self-report questionnaires have also been developed to measure aspects of impulsivity, including the Barratt Impulsiveness Scale (BIS-10) [4,5] and the Eysenck Personality Questionnaire [6]. Typically, volunteers are asked to rate the extent to which particular items describe their long-term personality traits, e.g. 'I act on

impulse'. Measures such as these are difficult to relate to underlying neurobiological substrates, are not suitable for repeated administration, and were generally developed for assessing lifetime traits in healthy volunteers rather than in patients [2,3]. They may also be susceptible to bias from low self-awareness in some patient groups [7]. By contrast, objective computerized cognitive assessment can be linked to underlying neural substrates by examining behavioural performance in patients with focal brain lesions, and by using techniques such as neuroimaging [8••] and transcranial magnetic stimulation [9]. By using selective pharmacological agents and amino-acid manipulations, the role of neurochemical systems in the control of cognitive functions can be probed. For many neuropsychological tests, equivalent versions have been developed in the animal literature, which permits the finer fractionation of frontostriatal mechanisms underpinning cognition [10,11].

Several potentially dissociable cognitive domains relating to impulsivity have been described in the literature. These include the ability to collect and evaluate information before reaching decisions ('reflection'), the ability to opt for larger delayed rewards over smaller more immediate rewards ('deferment of reward') and the ability to suppress motor responses that have been rendered prepotent ('response inhibition') [12–14,15•,16]. The focus of the present paper is on this latter function, response inhibition, which has been implicated in the manifestation of motor impulsivity in a number of neuropsychiatric disorders, notably ADHD.

Measurement of response inhibition

Response inhibition is assessed with go/no-go and stop-signal paradigms. On go/no-go tasks, volunteers are instructed to make speeded motor responses on go trials (e.g. horizontal lines appearing on-screen) but to withhold responses on no-go trials (e.g. vertical lines). By including more go than no-go trials, responses are rendered prepotent. Motor impulsivity is assessed in terms of the number of inappropriate motor responses to no-go stimuli, referred to as commission errors. Stop-signal paradigms differ from go/no-go tests in that they measure the ability to inhibit already-activated motor responses [14]. As can be seen in Figure 1, volunteers make speeded motor responses to directional arrows appearing on-screen. On a subset of trials, a stop-signal (e.g. auditory tone) occurs after presentation of the go stimulus. By varying the time between go stimulus presentation and the stop-signal, such paradigms provide a sensitive estimate of the time taken for the brain to inhibit responses. This is referred to as the stop-signal reaction time, which is the key measure of motor impulsivity [12,14]. An equivalent stop-signal paradigm for use in rats has also been developed with success [17–20].

Figure 1 An example stop-signal paradigm [12,14]
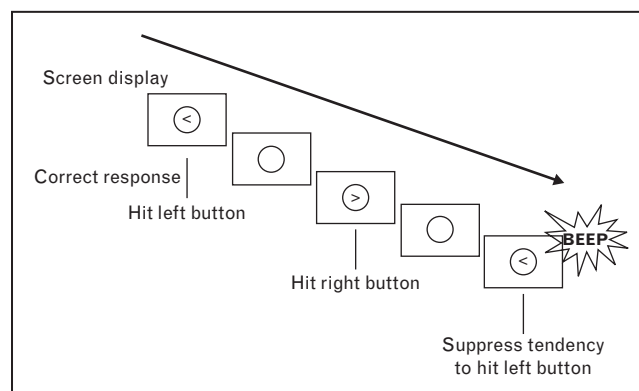
Patients or volunteers view single arrows appearing on-screen and make speeded motor responses depending on the direction of each arrow. On 25% of trials, a stop-signal (e.g. auditory beep) occurs, signalling that the individual should attempt to suppress their just-activated motor response. By varying the time between the presentation of the go stimulus and the occurrence of the auditory stop-signal, this task provides a sensitive estimate of the time taken by the brain to suppress prepotent motor responses, the stop-signal reaction time.

Impaired response inhibition in patients with dysregulated impulse control

Response inhibition deficits have been found in several neuropsychiatric conditions linked to problems suppressing inappropriate impulsive behaviour. ADHD is regarded by many as an archetypal disorder of impulsivity. Children with ADHD undertake behaviour described as impulsive in DSM-IV, such as hitting out at other children, initiating fights, or running into danger [21•]. Into adulthood, ADHD is associated with impulsive phenomena such as increased criminality and substance abuse [22–24]. ADHD has a profound negative impact on school and work performance. Behavioural deficits in response inhibition represent one of the most consistent neuropsychological findings in children and adults with ADHD [25,26].

Trichotillomania is an atypical impulse control disorder according to DSM-IV, in which patients undertake repetitive damaging hair-pulling that leads to debilitating and noticeable hair loss [27]. The investigation of impulsivity in this condition is important as little is known about the brain basis of the symptoms and there are no established pharmacological treatment algorithms [28]. Chamberlain *et al.* [29••] reported impairments in response inhibition in patients with trichotillomania, the magnitude of which correlated significantly with subjective ratings of hair-pulling severity. Patients with obsessive–compulsive disorder (OCD), which shares overlap with trichotillomania in terms of phenomenology and likely genetic underpinnings [28,30,31••], also showed impaired response inhibition compared with controls [29••,32]. Similar

impairments for OCD patients were also identified by Penades and colleagues [33•].

Impulsivity is also a feature of substance dependence according to DSM-IV. Symptoms include putting oneself into danger, recurrent legal problems, and persisting substance use despite worsening behaviours. Monterosso and co-workers [34] found stop-signal response inhibition deficits in 5–7-day abstinent chronic methamphetamine abusers (free from other current axis-I diagnoses), compared with non-user controls. The authors indicated that further research was needed to evaluate whether these deficits preceded substance abuse (i.e. represented a risk factor) or rather arose as a result of the damaging effect of chemical abuse on corticosubcortical circuitry.

Impaired response inhibition as a candidate endophenotype

In the context of cognitive neuroscience, the term 'endophenotype' refers to intermediate markers of brain dysfunction that may be of utility in elucidating the aetiological basis of neuropsychiatric disorders [35,36••]. Computerized measures of cognition hold great potential in the search for these intermediate measures [14,36••,37]. Operational criteria for an endophenotype include: (1) that the marker be associated with an illness within the population; (2) that it be heritable; (3) that is be 'trait' (i.e. capable of existing to some degree in the absence of clinically significant symptoms); and (4) that it be present with unexpectedly high frequency in unaffected relatives [38,39]. The search for psychiatric endophenotypes is still in its infancy, and only a handful of studies have investigated cognition, including response inhibition, in the unaffected relatives of patients to date.

In a study by Schachar and colleagues [40], ADHD patients and their siblings (7–16 years of age) were assessed on the stop-signal task. In comparison with control subjects, affected siblings, unaffected siblings, and patient probands all showed response inhibition deficits. In a study of children with ADHD and their siblings conducted by Waldman and colleagues [41••], the validity of several potential executive function endophenotypes was evaluated. Their data suggested greater impairments compared with controls in ADHD probands and their unaffected siblings for all executive function measures examined, including response inhibition. Impaired response inhibition fulfilled more criteria for validity as an endophenotype than the other measures of executive functioning. Elsewhere, in a recent study by Chamberlain et al. [32], OCD patients with no co-morbid diagnoses and their unaffected first-degree relatives were compared with individuals with no known family history of OCD on the stop-signal paradigm. Both patients and their unaffected relatives showed response inhibition deficits compared with controls.

Neural substrates of response inhibition

Multiple functional neuroimaging studies in healthy volunteers have implicated the right prefrontal cortex, especially the right inferior frontal gyrus (RIFG), in response inhibition [14]. Furthermore, Aron and colleagues [42,43] reported that patients with damage to the right prefrontal cortex showed lengthened stop-signal reaction times compared with healthy controls, whereas patients with left hemisphere lesions did not. The volume of damage to the RIFG correlated significantly with the magnitude of the stop-signal impairment. Consistent with a key role for the RIFG in response inhibition, Chambers et al. [44••] reported that disruption of this region using transcranial magnetic stimulation impaired response inhibition in healthy volunteers. By contrast, disruption of the right middle frontal gyrus and right angular gyrus had no effect on response inhibition. In a seminal study by Rubia et al. [45], a stop-signal paradigm was adapted for neuroimaging purposes and was deployed in medication-naive adolescents with ADHD. ADHD patients showed abnormally reduced brain activation in the RIFG during successful motor response inhibition (Figure 2), which correlated with behavioural ADHD scores.

Recent work suggests that the subthalamic nucleus, a region in the basal ganglia, may also be involved in aspects of response inhibition. Lesions to midbrain regions including the subthalamic nucleus lead to stop-signal impairment in rodents (D.M. Eagle, T.W. Robbins, personal communication). Aron and Poldrack [46••] identified significant activation in the RIFG and subthalamic nucleus in healthy human volunteers during successful stopping, using functional MRI. Activation was greater in individuals with superior stopping capacity. The authors speculated that the RIFG may exert top-down effects on inhibition via connections to the subthalamic nucleus, and are presently following up these findings using diffusion tensor imaging, to assess white matter tract connectivity between brain regions [47].

Neurochemical modulation of response inhibition

Serotonin has traditionally been assumed to be critically involved in impulsivity [48]. Reduced quantities of serotonin metabolites have been found in the cerebrospinal fluid of individuals who committed suicide, and in violent offenders [49–51]. Tyano et al. [52] recently reported correlations between low plasma serotonin levels and measures of violence/suicidal behaviour in suicide attempters. Certainly animal data support a role for serotonin in aspects of impulsivity [53]. There is, however, little evidence to support the use of serotonin-based medications in the treatment of core impulsive motor behaviour in ADHD. By contrast, psychostimulants such as methylphenidate has a confirmed track record of efficacy [54], and act to increase extracellular levels of

Figure 2 Medication-naive adolescents with attention deficit hyperactivity disorder showed abnormally reduced activation in the right inferior frontal gyrus during successful versus unsuccessful response inhibition [45]

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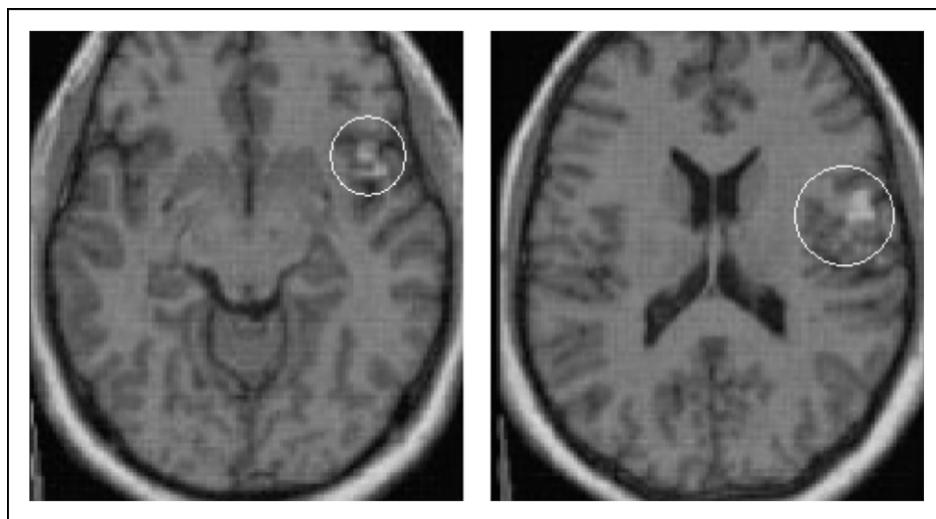
noradrenaline and dopamine, by preventing reuptake via transporter blockade and triggering release [55]. Other drugs with efficacy in the treatment of ADHD, namely atomoxetine (a selective noradrenaline reuptake inhibitor) and modafinil (a wake-promoting agent), also exert important effects on noradrenergic or dopaminergic transmission [56,57]. Atomoxetine increased free levels of prefrontal noradrenaline and dopamine but not serotonin when given systemically to rats [56,58]. Although the mechanisms of action of modafinil are incompletely understood, its behavioural effects in animals were counteracted by alpha-1 noradrenergic receptor antagonism [59]. It thus appears that despite a traditional focus on serotonin, other neurochemicals are involved in modulating aspects of impulsivity.

Several studies in healthy volunteers have suggested a limited role for serotonin in motor impulsivity, assessed with stop-signal tests. Clark *et al.* [60*] assessed the effects of central serotonin depletion, using the tryptophan depletion technique, on stop-signal performance in healthy volunteers. They found no evidence for the effects of this manipulation on response inhibition. In other healthy volunteer studies, Chamberlain *et al.* [61] likewise found that administration of the serotonin 1A receptor agonist buspirone had no effect on response inhibition with the same paradigm; nor did administration of the selective serotonin reuptake inhibitor citalopram have any effect [62**]. These findings do not refute the likely involvement of serotonin in other forms of impulsivity. As noted previously, there is evidence for a relationship between low brain serotonin levels and behavioural facets of impulsivity such as suicidality [52] and aggression [63].

In contrast to these null stop-signal findings relating to serotonin, several studies reported beneficial effects of manipulating other neurochemical systems on response inhibition. Aron *et al.* [64] reported improvements in response inhibition in adults with ADHD after the administration of methylphenidate. Turner *et al.* [65] reported improvements in response inhibition after the administration of modafinil in adults with ADHD, and in healthy volunteers [66]. In the same study that reported no significant effect of the selective serotonin reuptake inhibitor citalopram on response inhibition in healthy volunteers, response inhibition was improved by the selective noradrenaline reuptake inhibitor atomoxetine (Figure 3) [62**]. Previously, Overtoom *et al.* [67] had reported beneficial effects of the less selective selective noradrenaline reuptake inhibitor desipramine in children with ADHD, but no effects of L-DOPA (with predominantly dopaminergic actions). More recently, atomoxetine was also found to improve response inhibition in adults with ADHD (Chamberlain *et al.*, in preparation). Findings from experimental animals support an emerging role for the noradrenaline system, in particular, in impulse control. Systemic dosing with atomoxetine in rats improved response inhibition on a stop-signal analogue, and reduced impulsive errors on the five-choice serial reaction time task [19,68**]. Modafinil and methylphenidate improved response inhibition in the rat stop-signal paradigm, and these effects were not blocked by concurrent dopamine receptor antagonism, nor was response inhibition affected by dopamine receptor antagonism *per se* [20]. Also, direct infusion of the alpha-2 adrenoceptor antagonist yohimbine into the prefrontal cortex of non-human primates impaired inhibitory control on a go/no-go paradigm, and was associated with increased locomotor hyperactivity [69,70,71**].

Figure 3 Atomoxetine (selective noradrenaline reuptake inhibitor) improved response inhibition in healthy volunteers whereas citalopram (selective serotonin reuptake inhibitor did not) [62••]
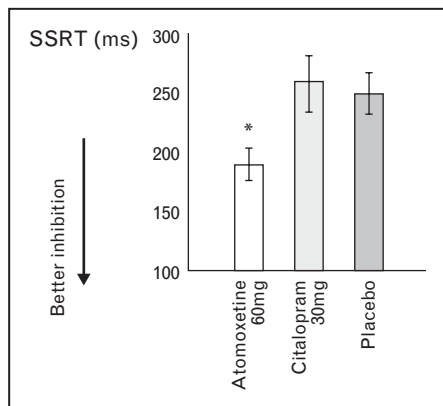
These findings, together with others, implicate a role for noradrenaline in certain forms of impulsivity. Reprinted with permission from *Science*. *$P < 0.05$ atomoxetine significantly improved response inhibition. SSRT, stop-signal reaction time.

Clinical implications

Findings to date indicate that response inhibition is subserved by a right-lateralized neural network encompassing the RIFG. Dysregulation of such circuitry probably belies response inhibition deficits manifested across several neuropsychiatric disorders associated with impulsivity. Drugs with noradrenergic actions (psychostimulants, atomoxetine, modafinil) show efficacy in the treatment of the impulsive features of ADHD, and were shown to improve response inhibition in several proof-of-concept studies in animals and humans. Consequentially, these drugs should be evaluated for other conditions associated with failures of impulse control in large-scale clinical trials. The identification of response inhibition deficits in unaffected relatives of OCD and ADHD patients demonstrates the likely utility of objective cognitive measures in the search for endophenotypes to help clarify genetic factors conferring susceptibility to these phenomenologically related disorders. Such measures may also help to identify those relatives 'at risk' who may require some form of clinical support.

Conclusion

Research so far has made important contributions to our understanding of the relationships between cognition, brain function (anatomical and chemical), and the impulsive features of neuropsychiatric disorders. Multidisciplinary neuroscience approaches, using tests of response inhibition and other cognitive functions relating to impulsivity, will improve our understanding of the aetiology of debilitating neuropsychiatric disorders, and help to optimize treatment approaches and future diagnostic classification systems.

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