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Brain γ-aminobutyric acid: a neglected role in impulsivity

Dave J. Hayes,[1,2,3,7] Bianca Jupp,[3,7] Steve J. Sawiak,[3,4] Emiliano Merlo,[3,7] Daniele Caprioli[5] and Jeffrey W. Dalley[3,6,7]

[1]Toronto Western Research Institute, Toronto Western Hospital and Division of Neurosurgery, University of Toronto, Toronto, ON, Canada
[2]Mind, Brain Imaging and Neuroethics, Institute of Mental Health Research, University of Ottawa, Ottawa, ON, Canada
[3]Behavioural and Clinical Neuroscience Institute, University of Cambridge, Cambridge, UK
[4]Wolfson Brain Imaging Centre, Department of Clinical Neurosciences, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK
[5]National Institute on Drug Abuse, Baltimore, MD, USA
[6]Department of Psychiatry, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK
[7]Department of Psychology, University of Cambridge, Cambridge CB2 3EB, UK

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Abstract

The investigation of impulsivity as a core marker of several major neuropsychiatric disorders has been greatly influenced by the therapeutic efficacy of drugs that block the reuptake of dopamine and noradrenaline in the brain. As a result, research into the neural mechanisms of impulsivity has focused on the catecholamine systems as the loci responsible for the expression of impulsive behaviour and the primary mechanism of action of clinically effective drugs for attention-deficit hyperactivity disorder (ADHD). However, abnormalities in the catecholamine systems alone are unlikely to account for the full diversity and complexity of impulsivity subtypes, nor can they fully explain co-morbid brain disorders such as drug addiction. Here we review the lesser-studied role of γ-aminobutyric acid (GABA) in impulsivity, a major target of the dopaminergic and noradrenergic systems in the prefrontal cortex and striatum, and consider how abnormalities in this inhibitory neurotransmitter might contribute to several forms of impulsive behaviour in humans and experimental animals. Our analysis reveals several promising leads for future research that may help inform the development of new therapies for disorders of impulse control.

Introduction

Impulsivity is characterised behaviourally by rapid actions and decisions without foresight as well as impaired inhibition of motor responses (Evenden, 1999; Moeller *et al.*, 2001; Pattij *et al.*, 2007; Dalley *et al.*, 2011). Impulsivity is often assessed by paradigms that measure premature responding for future rewards and by impulsive decision-making where subjects preferentially choose small immediate rewards over large delayed rewards. Both highly impulsive healthy subjects and those with psychiatric disorders perform less well on decision-making tasks, particularly those involving value-associations to rewarding or aversive stimuli (Franken *et al.*, 2008; Chamorro *et al.*, 2012). Evidence in humans and other animals suggests that impulsivity is frequently co-morbid with, and may even precede, several major disorders including drug addiction (e.g. Verdejo-Garcia *et al.*, 2008; Nigg, 2013). Collectively, these and other findings support the notion that understanding the neural and psychological mechanisms of impulsive behaviour will be important for improving mental health and wellbeing (Sahakian *et al.*, 2010; Insel *et al.*, 2012).

Correspondence: Dr Jeffrey W. Dalley, [7]Department of Psychology, as above.
E-mail: jwd20@cam.ac.uk

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Research in this field has profited from the use of paradigms that assess broadly similar forms of impulsivity in rodents, non-human primates and humans (Winstanley *et al.*, 2006; Dalley *et al.*, 2011). In experimental animals, different aspects of impulsivity can be measured using computerised behavioural paradigms to assess actions that are premature, mistimed or difficult to suppress, and by delay-discounting tasks, in which subjects are trained to choose between small immediate rewards and larger but delayed rewards (Dalley & Roiser, 2012). In broad terms, impulsivity tasks can be divided into those that assess 'waiting' and 'stopping' impulsivity (see Fig. 1, adapted from Dalley *et al.*, 2011). Analogous paradigms in humans include variants of the five-choice serial reaction time task (5-CSRTT) used widely to assess premature responding in rodents (Robbins, 2002; Voon *et al.*, 2013), impulsive choice for immediate rewards versus delayed rewards, and both go/no-go and stop-signal reaction time (SSRT) paradigms to assess response inhibition and action cancellation (Winstanley, 2011; Bari & Robbins, 2013). In addition, self-report questionnaires such as the Barratt Impulsiveness Scale are widely used in humans but their precise relationship to more objective behavioural measurements of impulsivity is not always clear (Dalley & Roiser, 2012).

For various reasons research into the neural mechanisms of impulsivity has focused on the monoamine systems, including especially

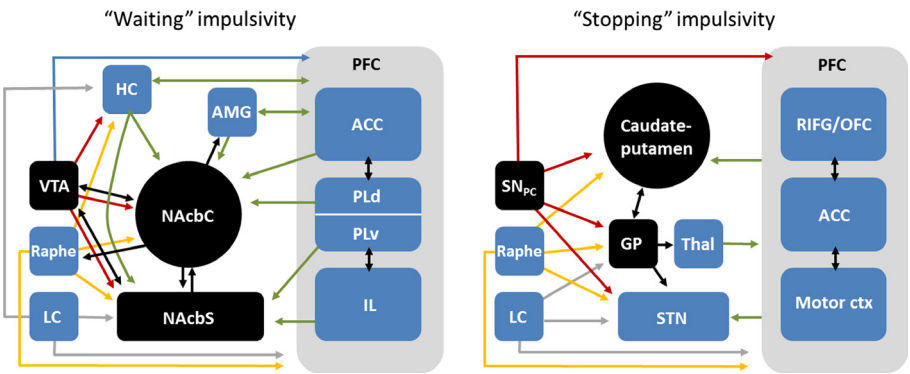

FIG. 1. Simplified schematic diagram of circuitry underlying waiting and stopping impulsivity (based on Dalley *et al.*, 2011). Brain regions containing a large pool of intrinsic GABA-containing neurons are shaded in black whereas inhibitory GABAergic projections are shown by the black arrows. Although GABAergic interneurons are found in virtually all brain regions, only those that significantly contribute to impulsivity are shown. The diagrams also show glutamatergic (green), noradrenergic (grey), dopaminergic (red) and serotonergic (orange) projections. ACC, anterior cingulate cortex; AMG, amygdala; GABA, gamma-aminobutyric acid; GP, globus pallidus; HC, hippocampus; IL, infralimbic cortex; LC, locus coeruleus; Motor ctx, motor cortices including premotor, supplementary motor, and frontal eye fields; NAc core, nucleus accumbens core; NAc shell, nucleus accumbens shell; PFC, prefrontal cortex; PLd/v, prelimbic cortex, dorsal and ventral divisions; RIFG/OFC, rostral inferior frontal gyrus/orbitofrontal cortex; SNpc substantia nigra pars compacta; STN, subthalamic nucleus; Thal, thalamus; VTA, ventral tegmental area.

serotonin (5-HT), dopamine (DA) and noradrenaline (NA). This relatively narrow focus of inquiry reflects in part the early influential work of Soubrié showing a role of 5-HT in behavioural inhibition (Soubrie, 1986), research in non-human primates demonstrating a relationship between 5-HT and impulsive aggression (Fairbanks *et al.*, 2001), and more generally by the therapeutic efficacy of drugs that block the uptake of DA and NA in the brain (Swanson *et al.*, 2006). Yet, despite this evidence, surprisingly little is known on how methylphenidate and other stimulant drugs so effectively diminish behavioural impulsiveness in patients with attention-deficit hyperactivity disorder (ADHD). Most parsimoniously, these compounds may correct an underlying deficiency in the brain NA and DA systems, a hypothesis for which there is empirical support (Ernst *et al.*, 1997; Volkow *et al.*, 2012), but in light of recent discoveries on the neural mechanisms of impulsivity (Boy *et al.*, 2011; Caprioli *et al.*, 2013b; Jupp *et al.*, 2013; Silveri *et al.*, 2013; Yang *et al.*, 2013) it is now timely to assess the contribution of emerging non-monoaminergic targets and mechanisms involved in the regulation of impulsivity. Here we discuss burgeoning evidence for a significant role of γ-amino butyric acid (GABA) in impulsivity which, remarkably, has received little attention compared with the biogenic amines. The paper is divided into three main sections. The first section provides a brief overview of GABA transmission together with a synopsis of the neural circuitry underlying impulsive behaviour. The sections that follow integrate direct and indirect lines of evidence for a role of GABA in impulsivity based on research in humans and experimental animals.

Corticostriatal GABA pathways

GABA is the major inhibitory neurotransmitter in the brain contributing to interneuronal microcircuits and longer-range signalling, notably within corticostriatal circuitry responsible for the selection and inhibition of motivated behaviour (Matsumoto *et al.*, 2003; Goubard *et al.*, 2011; Jelinek & Partridge, 2012; Paille *et al.*, 2013; Schuemann *et al.*, 2013). The inhibitory actions of GABA on neuronal function are mediated by two principal receptor subtypes. $GABA_A$ receptors are fast-acting ionotropic receptors responsible for the majority of immediate GABAergic responses. $GABA_A$ receptors comprise five subunits from a family of 19 homologous subunit gene products, whose composition contributes greatly to the variation in $GABA_A$ receptor function in different brain regions (see Olsen & Sieghart, 2009 for an in-depth review). $GABA_B$ receptors mediate slower G-protein-coupled receptor transmission and consist of two subtypes, $GABA_{B1}$ and $GABA_{B2}$, and a tetramer of auxiliary subunits whose composition provides variation in function (see Pinard *et al.*, 2010). $GABA_A$ and $GABA_B$ receptors have both been linked to impulsivity, addiction, mood disorders and value-related circuitry function (Rudolph & Knoflach, 2011).

GABAergic cells make up the majority of inhibitory interneurons in the brain and form key projections both within and between relevant cortical and subcortical regions involved in the regulation and expression of impulsivity. Although impulsivity is widely regarded as a multidimensional construct its assessment can be broadly categorised into 'waiting' and 'stopping' subtypes. The neural circuitry underlying these distinct forms of impulsivity are summarised in Fig. 1 and reviewed in Dalley *et al.* (2011). Recent findings indicate that GABAergic interneurons contribute in a fundamental way to disinhibitory control in many cortical areas, particularly in response to reward-related signals (Pi *et al.*, 2013). Subcortical regions such as the basal ganglia, including especially the nucleus accumbens (NAc), mainly comprise GABA-containing cells, with major projections to the thalamus, midbrain and brainstem (Groenewegen & Russchen, 1984; Haber *et al.*, 1990; Tepper *et al.*, 2007; Durieux *et al.*, 2011). In the rat, the major sub-regions of the NAc, the core and shell (NAc core and shell, respectively), are reciprocally interconnected via GABAergic neurons (van Dongen *et al.*, 2005), and GABAergic projections from the NAc target selectively GABA and DA cells in the ventral tegmental area (VTA) (Wolf *et al.*, 1978; Floresco *et al.*, 2003; Lammel *et al.*, 2011; Xia *et al.*, 2011).

While beyond the scope of this article, there is growing interest in the functional significance of long-range corticopetal and corticofugal GABAergic neurons (see Tamamaki & Tomioka, 2010; Caputi *et al.*, 2013 for review). Their distinct connectivity to both excitatory and other inhibitory neurons enable simultaneous local and cross-regional processing, notably targeting dendritic shafts where they play a major role in signal conduction (Harris & Kater, 1994), oscillatory activity (Jinno *et al.*, 2007; Melzer *et al.*, 2012) and the synchronization of many neurons across numerous brain regions (Benes & Berretta, 2001). GABA-dependent synchronization

depends on distinct electrical and chemical mechanisms (Freund, 2003; Pangratz-Fuehrer & Hestrin, 2011) and the precisely timed activation of $GABA_A$ receptor-mediated synaptic plasticity (Paille *et al.*, 2013; Schuemann *et al.*, 2013). Importantly, these mechanisms have been shown to be behaviourally relevant; for example, electrical self-stimulation in rats relies on the functional integrity of the mesolimbic GABAergic network (e.g. Lassen *et al.*, 2007; Hayes *et al.*, 2011). Moreover, EEG-based findings in humans support a major role for $GABA_A$ receptors in the functional connectivity of cortical networks (Fingelkurts *et al.*, 2004). Unfortunately, it is presently not possible to determine the differential impact of GABAergic transmission and interventions on local inter-neuronal and long-range GABAergic projections. Detailed morphological and electrophysiological studies can help in this assessment (e.g. Higo *et al.*, 2007), but no studies of this nature have been conducted in relation to impulsivity. However, as inter-neuronal and long-range GABAergic projection neurons can theoretically have opposite effects, the reader should consider this when interpreting the studies discussed below.

Direct evidence for GABA in impulsivity

This section considers studies in healthy humans and animals, respectively, which putatively assess non-pathological forms of impulsive behaviour. These include research on trait impulsivity in humans using psychometric measures and studies in animals stratified according to low- and high-impulsivity subgroups.

GABA and impulsivity in humans

Pharmacological interventions that target GABA receptors modulate disorders of impulse control (e.g. Brady *et al.*, 1998), and recent studies in healthy humans indicate that GABA may also play a role in regulating non-pathological forms of impulsivity. Levels of GABA in cerebrospinal fluid showed a positive correlation with psychometric measures of impulsivity, but not aggression, in healthy people (Lee *et al.*, 2009). In another study, acutely administered benzodiazepines, which enhance inhibitory $GABA_A$ receptor function, increased impulsivity and risky decision-making behaviour (Deakin *et al.*, 2004; Lane *et al.*, 2005). Lee *et al.* (2011) showed that an index of $GABA_B$ receptor function, the level of circulating growth hormone in response to the $GABA_B$ receptor agonist baclofen, negatively correlated with psychometric measures of cognitive, but not motor, impulsivity. These studies suggest that, while $GABA_A$ receptor activation is related to increased measures of impulsivity, $GABA_B$ receptor stimulation may have opposing effects.

In a recent magnetic resonance spectroscopy (MRS) study, levels of GABA were reportedly decreased in the right dorsolateral prefrontal cortex (PFC) of high-impulsive, healthy men (Boy *et al.*, 2011). In contrast, GABA levels in the inferior frontal, anterior cingulate, parietal and supplementary motor cortices did not correlate with impulsivity, although earlier findings from this group showed that reduced GABA in the supplementary motor cortex predicted reduced subconscious, but not inhibitory, motor control (Boy *et al.*, 2010). While these results suggest that higher relative concentrations of GABA in the dorsolateral PFC reflect reduced impulsiveness, it is unknown how these findings relate to synaptic GABAergic transmission (Stagg *et al.*, 2011; Mullins *et al.*, 2012). Moreover, although a correlation was found between the psychometric measure of 'urgency' and GABA levels there was no correlation with respect to performance on an SSRT task, suggesting that GABA levels in the dorsolateral PFC may be more closely related to cognitive rather than motor impulsivity. A second, related study showed that the GABA/creatine ratio in the anterior cingulate cortex, but not the parieto-occipital cortex, was lower in individuals expressing both increased psychometrically determined impulsivity and impaired response inhibition on a go/no-go task (Silveri *et al.*, 2013). This relationship was particularly marked in 12- to 14-year-old adolescent males compared with 18- to 24-year-old males. Notably, impulsivity did not co-vary with other neurochemicals and metabolites, including glutamate and glutamine, suggesting a rather selective impairment of cortical GABA function in certain forms of impulsivity.

The findings reviewed above underscore the complexity of the GABAergic systems and demonstrate that systemic-level findings will probably not translate directly to those at the sub-regional or cellular levels. Additionally, it is important to note several methodological and conceptual issues related to neuroimaging data. For instance, although a recent MRS study found no change in GABA levels in the PFC of impulsive subjects (Mon *et al.*, 2012), contrary to the study by Boy *et al.* (2011), these subjects were alcohol dependent, making a direct comparison between studies challenging. Moreover, the acquisition, analysis and interpretation of MRS data, particularly related to GABA, which requires additional preprocessing steps, has many challenges and is still evolving as a reliable technique for probing brain neurochemistry (Bogner *et al.*, 2010; Dou *et al.*, 2013). Finally, it is not entirely clear how MRS data relate to the fMRI blood oxygen level-dependent signal (Northoff *et al.*, 2007; Hayes & Huxtable, 2012; Duncan *et al.*, 2014).

GABA and impulsivity in animals

One of the earliest studies investigating the role of GABA in impulsivity assessed the effects of vigabatrin, an anti-epileptic drug that inhibits the catabolism of GABA by irreversibly inhibiting GABA transaminase, thereby increasing the level of GABA in the brain (Mazurkiewicz *et al.*, 1992). When given systemically, vigabatrin had no effect on premature responding on a 5-CSRTT, a result reminiscent of recent findings showing diazepam, a $GABA_A$ receptor agonist, to have no overall effect to reduce or increase impulsivity, but rather to reduce the separation in impulsivity between trait low- and high-impulsive rats (Molander *et al.*, 2011). In contrast, a study in mice found that diazepam increased impulsivity on the 5-CSRTT (Oliver *et al.*, 2009) whilst studies in humans showed that benzodiazepines generally disinhibit behavior, possibly by reducing the threshold for a response (Deakin *et al.*, 2004; Acheson *et al.*, 2006).

While further research is needed to elucidate the effects of systemically administered GABAergic compounds on delay-discounting impulsivity and SSRT, interventions that specifically target the PFC robustly affect impulsive responding on the 5-CSRTT. For example, infusions of muscimol, a $GABA_A$ receptor agonist, directly into the medial PFC strongly increased premature responding without affecting other behavioural measures (Paine *et al.*, 2011; Murphy *et al.*, 2012). By contrast, the $GABA_A$ receptor antagonist bicuculline reduced premature responding, suggesting a bidirectional modulation of impulsivity by PFC GABA (Murphy *et al.*, 2012). Interestingly, bicuculline also blocked the increase in impulsivity produced by local infusions of the NMDA receptor antagonist R-CPP, implying a putative opposing interaction between NMDA and $GABA_A$ receptors in gating pyramidal cell output in the PFC. Thus, the modulation of at least one form of impulsivity appears to depend on $GABA_A$ receptor function in the PFC, a view supported by recent autoradiography findings in selected highly impulsive rats (Jupp *et al.*, 2013).

More circumstantial evidence for a role of GABA in impulsivity comes from research in GABA transporter 1-knockout mice, which show elevated GABA levels and function in the PFC (Yu *et al.*, 2013), and increased impulsivity (Yang *et al.*, 2013). However, the measure of impulsivity used in this study was slightly unusual; knockout mice entered a shock-paired compartment previously paired with reward more quickly, and this was accompanied by hyperactivity, impaired memory, ataxia and exaggerated novelty responding (Yang *et al.*, 2013; Yu *et al.*, 2013). In other research, acute suppression of GABA synthesis in the PFC had no effect on impulsivity and attention but strongly increased locomotor activity (Asinof & Paine, 2013). These findings support a role for PFC GABA in at least two endophenotypes of ADHD (hyperactivity and impulsivity) but this role is evidently complex and one that very probably also involves downstream effects on sub-cortical structures such as the NAc (Basar *et al.*, 2010; Dalley *et al.*, 2011).

In a recent study we found that trait-like impulsivity on the 5-CSRTT is associated with highly localised structural and neuronal abnormalities in the NAc core (Caprioli *et al.*, 2013a). Specifically, we established that high impulsivity on this task is accompanied by a significant reduction in grey-matter density, assessed using high-resolution *in vivo* magnetic resonance, which was linked to a reduced expression of dendrite spine markers and glutamate decarboxylase (GAD), the rate-limiting enzyme for GABA synthesis. These abnormalities were present exclusively in the NAc core and mainly in the left hemisphere although smaller reductions in GAD were also noted in the right NAc core. Importantly, a functional reduction in $GAD_{65/67}$ in low-impulsive rats, effected by intra-NAc core infusions of antisense oligodeoxynucleotides, significantly increased their impulsive responses without affecting locomotor activity or other variables on the 5-CSRTT. These data substantiate previous findings of a critical role of the NAc core in certain forms of impulsivity, especially those involving the suppression of responding for future or delayed rewards (e.g. Cardinal *et al.*, 2001; Pothuizen *et al.*, 2005). They also demonstrate a potentially important involvement of medium spiny GABAergic neurons in impulsivity putatively mediated by underlying abnormalities in the regulation of dendritic spines (see Fig. 2). Although this hypothesis requires further direct evidence to objectively quantify dendrite spine density in extreme low- and high-impulsive rats, these results may have relevance to the mechanism of action of stimulant drugs in ADHD, which increase the density of spines on medium spiny GABAergic neurons, especially in the NAc core (Ferrario *et al.*, 2005).

Recent research in our laboratory indicates that highly impulsive rats exhibit decreased $GABA_A$ receptor binding in the anterior cingulate cortex compared with low-impulsive rats, with no differences in DA receptors, μ-opioid receptors or the 5-HT transporter in this region (Jupp *et al.*, 2013). Inverse relationships were noted, however, between impulsive behaviour and the DA transporter and $D_{2/3}$ receptors in the left NAc shell, and for D_1 receptors in the left NAc core. By contrast, no differences were observed for $GABA_A$ receptors in either NAc sub-region. Although this appears at odds with the results noted above, it is worth noting two things. Firstly, the autoradiography study found no abnormalities in benzodiazepine-sensitive $GABA_A$ receptor binding in the NAc. However, benzodiazepine-insensitive $GABA_A$ receptor subunits expressed in this region may have a differential role to play in impulsivity and related behaviours (Nie *et al.*, 2011). Secondly, altered GABA transmission

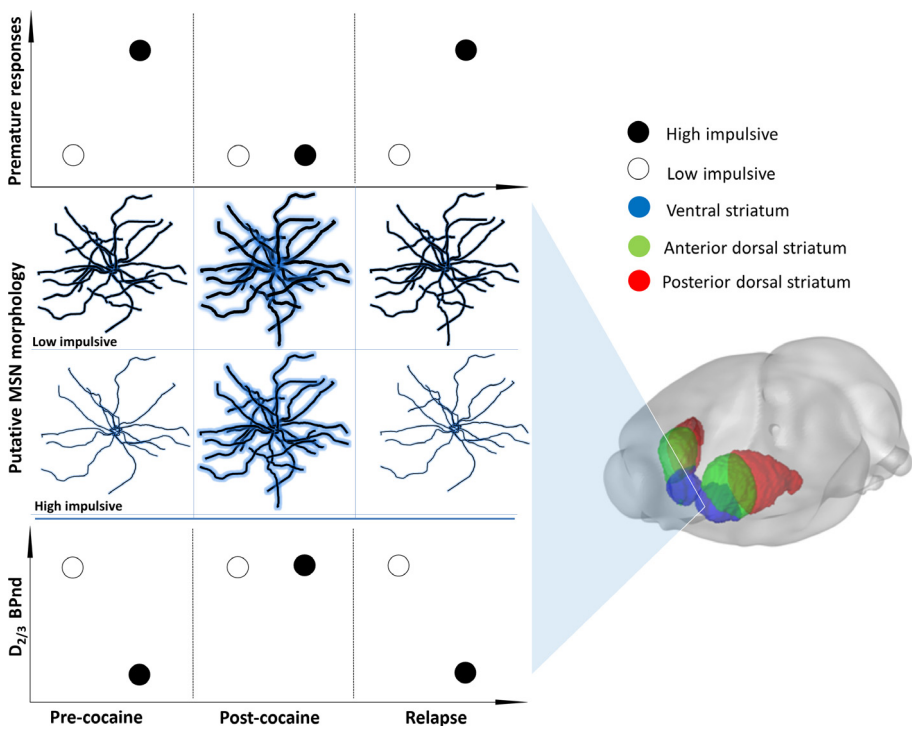

FIG. 2. Hypothetical relationship between impulsivity on the 5-CSRTT, assessed by the number of premature responses in high- and low-impulsive rats (Dalley *et al.*, 2007), and the density and function of dendritic spines on GABAergic medium spiny neurons (MSN) in the ventral striatum. Highly impulsive rats putatively show a reduced density of dendritic spines on MSNs in the ventral striatum, an abnormality that may be corrected by the psychostimulant drug cocaine, leading in turn to a reduction in impulsivity. Extended withdrawal from cocaine hypothetically enhances risk for relapse in high-impulsive rats by two, possibly independent, mechanisms within the ventral striatum: (i) a return of diminished MSN spine density and function; and (ii) a reduction in $D_{2/3}$ receptor availability. Based on Caprioli *et al.* (2013a,b). $D_{2/3}$ BPnd refers to non-displaceable binding potential measured using positron emission tomography.

in the NAc may have led to compensatory changes in receptor density in downstream structures, but not within the NAc itself.

As an interim summary, the few human and animal studies published to date suggest that GABAergic mechanisms in frontostriatal brain circuits may underlie certain forms of impulsive behavior. A summary of these studies is given in Table 1 together with a related regional overview in Table 2. We next consider the closely related concepts of motor inhibition, decision-making and value-related processing, coupled with clinical studies in neuropsychiatric populations, which further associate GABA-related mechanisms with impulsivity.

Indirect evidence for GABA in impulsivity

Work over several years now has implicated GABA neurotransmission in processes closely related to impulsivity. Although these studies assess behaviours that are intimately related to impulsivity, making them potentially informative, they nonetheless do not include explicit measures of this construct. Thus any conclusions related to such findings should be considered with additional caution. This section is divided into three sections: (i) studies related to motor inhibition and decision making, which overlap with 'stopping' and 'waiting' impulsivity (see Fig. 1); (ii) studies pertaining to value-related processing which explore how the evaluation of stimuli can impact behavioual choice outcomes; and (iii) studies involving disorders of impulse control.

Motor inhibition and decision making

Transcranial magnetic stimulation of the primary motor cortex in humans was found to modulate inhibition of fast motor responses, an effect that relied, in part, on $GABA_B$ receptor-related processes (van den Wildenberg *et al.*, 2010). Further, a prior study using subdural electrocorticography in four epileptic subjects found that SSRTs reflected increased GABA inhibition in primary motor cortex (Swann *et al.*, 2009). In rats, transient inhibition of the prelimbic (PL) PFC by a locally administered cocktail of $GABA_{A/B}$ receptor agonists increased instrumental lever-press responding for food, an outcome putatively reflecting impaired response inhibition (Jonkman *et al.*, 2009). Consistent with this finding, intra-PL, but not intra-premotor, injections of the $GABA_A$ receptor agonist muscimol increased premature responding and response time variability in a simple reaction-time task in rats (Narayanan *et al.*, 2006; Smith *et al.*, 2010). These findings have been corroborated by studies in non-human primates. Thus, select inactivation of the lateral PFC resulted in increased errors on no-go trials, with no effect on go trials, in a go/no-go saccade task (Kuwajima & Sawaguchi, 2007). Interestingly, lateral PFC injections of bicuculline in monkeys trained on a go/no-go task induced involuntary forelimb movements not seen in task-naïve subjects, suggesting that GABA circuits may tonically inhibit movement in a learned context-dependent manner (Oishi & Kubota, 1990).

Further insight can be drawn from a recent landmark study implicating striatal GABAergic medium spiny neurons in a related form of inhibitory motor control. In this study, mutants with a deletion of the synaptic scaffolding protein *Sapap3* not only showed excessive grooming behaviour but also exhibited greatly enhanced activity of putative medium spiny neurons in the dorsal striatum (Burguiere *et al.*, 2013). Intriguingly, optogenetic stimulation of the lateral orbitofrontal cortex (OFC) and its terminals in the dorsal striatum both reversed the inappropriate behaviour and moderated medium spiny neuron activity in the *Sapap3* mutants. Such results encourage the hypothesis that analogous mechanisms may be recruited during the expression of inappropriate impulsive behaviours that depend on inputs from the PFC to the ventral striatum, including the NAc (Dalley *et al.*, 2011). This view is also consistent with evidence discussed above of GABAergic dysfunction in highly impulsive rats, putatively targeting medium spiny neuron spine density and function (Caprioli *et al.*, 2013b), but the precise impact of this abnormality on medium spiny neuron neurophysiology requires further detailed research.

Studies using risk-choice and delay-discounting tasks provide additional evidence for an involvement of GABA in impulsivity. For example, the benzodiazepine and functional $GABA_A$ receptor agonist alprazolam was found to increase risk-taking behaviour in humans (Lane *et al.*, 2005), while an fMRI study reported reduced activity in the amygdala and medial PFC and increased activity in the insula following lorazepam administration (Arce *et al.*, 2006). Animal studies generally support these findings and strengthen the evidence for an involvement of GABA in select regions, particularly the NAc, OFC, medial PFC and basolateral amygdala. Thus, inactivation of the NAc in rats by local injections of $GABA_{A/B}$ receptor agonists resulted in a reduced bias toward large-magnitude rewards (Stopper & Floresco, 2011). Based on this work it was concluded that the NAc shell plays a major role in magnitude-based choice whereas the NAc core plays a role in processing time delays prior to decision-making. This conclusion is certainly consistent with neurobiological evidence implicating a role for the NAc core in waiting impulsivity and expression of premature motor responses (Cardinal *et al.*, 2001; Pezze *et al.*, 2007; Caprioli *et al.*, 2013b).

GABA also influences delay-discounting impulsivity at a frontal cortical level. Thus, inactivation of the PL cortex by microinjected $GABA_{A/B}$ receptor agonists was found to alter impulsive choice in an apparently context-dependent manner (St Onge & Floresco, 2010). Specifically, PL cortex inactivation increased risky choice when large-reward probability was initially high and subsequently fell, but decreased risky choice when reward probability increased over the session. In addition, it was shown that OFC inactivation led to increased and decreased risky choice in naturally low- and high-impulsive rats, respectively (Zeeb *et al.*, 2010). Importantly, the most prominent effects were noted when the delay between the choice and reward delivery was bridged by a cue in low-impulsive, but not high-impulsive, rats. In rats not stratified by high and low impulsivity, inactivation of the basolateral amygdala led to risk aversion and reduced preference for large rewards, but only on trials requiring relatively more effort (Ghods-Sharifi *et al.*, 2009). Moreover, knockout mice in which the β3 subunit of $GABA_A$ receptors on DA cells was deleted showed superior reward-related, but not aversion-related, learning, as well as a clear preference for risky vs. certain choices (Parker *et al.*, 2011). This intriguing set of findings suggests that encoding of reward probability may partly depend on GABAergic inputs to DA neurons.

Value-related processing

An implicit consideration in many decision-making paradigms, given their typical use of rewards and punishments as motivators, is the underlying function of value-related brain networks. Processing in these circuits contributes to the dynamic assessment of expected, perceived and/or remembered value. Alterations in the valuation of stimuli, particularly rewarding stimuli, are considered a fundamental component of impulsive decision-making (Ainslie, 1975; Fineberg *et al.*, 2010). For the present purposes, we consider this value-related processing simply in terms of the assessment of rewarding

TABLE 1. Summary of empirical evidence linking GABA neurotransmission with impulsivity

Impulsivity-related concept	Region	Method	Findings	Selected references
Direct evidence				
Choice/cognitive	Global	Psychometric; behavioural pharmacology	↑ CSF GABA; ↓ $GABA_BR$ function = ↑ Imp ↑ $GABA_AR$ function = ↑ Imp	Lee *et al.* (2009, 2011) Deakin *et al.* (2004) Lane *et al.* (2005)
	ACC	Psychometric; MRS	↓ GABA = ↑ Imp	Silveri *et al.* (2013)
	Right DLPFC	Psychometric; MRS	↑ GABA = ↓ Imp	Boy *et al.* (2011)
Response/motor	ACC	Psychometric; MRS	↓ GABA = ↑ Imp	Silveri *et al.* (2013)
		Rat 5-CSRTT; autoradiography	HI rats = ↓ $GABA_AR$ binding	Jupp *et al.* (2013)
	Left NAc core	Rat 5-CSRTT; MRI; western blot; psychopharmacology	↓ grey volume in HI = ↑ Imp HI rats = ↓ dendritic spine markers and GAD 65/67 ↓ functional GAD 65/67 of LI rats = ↑ Imp	Caprioli *et al.* (2013a)
	Lateral PFC/PL and/or medial PFC/IL	Rat 5-CSRTT; psychopharmacology	$GABA_AR$ activation = ↑ Imp $GABA_AR$ blockade = ↓ Imp; and blocks NMDAR antagonist-induced ↑ Imp	Paine *et al.* (2011) Murphy *et al.* (2012)
		Shock-paired compartment learning; electrophysiology; genetic knock-out	GABA transporter 1 knock-out mice = ↑ Imp; ↑ tonic PFC GABA currents	Yang *et al.* (2013) Yu *et al.* (2013)
Indirect evidence				
Motor inhibition	Primary motor cortex	Human behavioural; TMS; EMG	↑ Motor inhibition = ↑ speed of $GABA_BR$-related intracortical potentials	van den Wildenberg *et al.* (2010)
	Lateral PFC/PL	Human behavioural; ECG Rat reaction time task Monkey go/no-go task	↑ Motor inhibition = ↑ GABA inhibition $GABA_AR$ activation = ↓ Motor inhibition	Swann *et al.* (2009) Narayanan *et al.* (2006) Kuwajima & Sawaguchi (2007) Smith *et al.* (2010)
Decision making	Global	Behavioural pharmacology; fMRI	Benzodiazepine $GABA_AR$ activation = ↑ risk; ↑ insula BOLD, ↓ medial PFC and amygdala BOLD	Lane *et al.* (2005) Arce *et al.* (2006)
	Lateral PFC/PL	Rat risk; psychopharmacology	$GABA_{A/B}R$ activation = ↑ risk when reward probabilities decreased over time; ↓ risk with probability increases	St Onge & Floresco (2010)
	OFC	Rat risk; psychopharmacology	$GABA_{A/B}R$ activation = ↑ risk in LI rats ↓ risk in HI rats	Zeeb *et al.* (2010)
	NAc shell	Rat risk; psychopharmacology	$GABA_{A/B}R$ activation = ↓ risk for choices with greater long-term value (while NAc core appears involved in time delays before decision)	Stopper & Floresco (2011)
	BLA	Rat risk; psychopharmacology	$GABA_{A/B}R$ activation = ↓ risk and reduced large reward preference only in trials requiring high effort	Ghods-Sharifi *et al.* (2009)
Value processing	Global	Psychometric; behavioural; resting state fMRI; rat psychopharmacology	↑ Trait Imp = ↑ response to aversive stimuli ↑ Trait Imp = ↓ resting state functional connectivity between PFC and reward-related subcortical areas; ↑ resting state connectivity between value-related subcortical areas and sensorimotor cortex $GABA_A$ receptor α2/3 subunits required for benzodiazepine-enhanced electrical brain self-stimulation reward	Bjork *et al.* (1998) Davis *et al.* (2013) Reynolds *et al.* (2012)
	Sensorimotor; ventromedial PFC	Human fMRI-PET	↑ $GABA_AR$ binding = ↓ aversion-related BOLD activity in sensorimotor cortex	Hayes *et al.* (2013)
	PL/IL	Rat behaviour; psychopharmacology	↓ $GABA_AR$ activation = ↑ electrical brain self-stimulation reward	Paine *et al.* (2011)
	PL/NAc core	Rat behaviour; psychopharmacology	↑ $GABA_{A/B}R$ activation = ↓ cue- and methamphetamine-induced self-administration	Rocha & Kalivas (2010)
	IL/NAc shell		↑ $GABA_{A/B}R$ activation = ↓ methamphetamine-induced drug seeking	
	NAc shell	Rat behaviour; psychopharmacology	↑ $GABA_AR$ activation = ↓ electrical brain self-stimulation reward	Hayes *et al.* (2011)
	VTA	Rat behaviour; psychopharmacology	↑ $GABA_{A/B}R$ activation = ↓ electrical brain self-stimulation reward (no effect of NMDA or AMPA agonists)	Panagis & Kastellakis (2002)

TABLE 2. Summary of GABAergic function in highly impulsive individuals

Region	Direction of GABA transmission related to increased impulsivity	$GABA_A$ receptor activity/density related to increased impulsivity
Sensory cortex	↓	–
ACC, rat IL	↓	↓
Lateral PFC, rat PL	↓	–
Medial PFC, rat IL	–	↑
NAc core	↓	–
NAc shell	–	– (↓?)

This table provides an illustrative summary of the general direction of GABAergic activity in highly impulsive individuals. Data are based on empirical findings in humans and experimental animals (see Table 1). The symbol – denotes no, or too few, studies to allow speculation at this time. In general it can be seen that GABA transmission is reduced in individuals expressing high levels of impulsivity, in both cortical and sub-cortical brain regions.

and aversive stimuli. Value-related mechanisms can be somewhat separated from those involved in decision-making by including subjects not actively participating in a task (i.e. during passive exposure to stimuli) or in subjects performing well-trained tasks without a choice component (e.g. electrical brain self-stimulation). Value-related processing depends on GABAergic function in many brain regions that overlap with impulsivity and decision-making, supporting the need for future research in this area.

For example, healthy individuals with higher trait impulsivity exhibited increased sensitivity to aversive stimuli (Bjork *et al.*, 1998), and a recent multimodal fMRI-PET study showed that increased $GABA_A$ receptor binding in ventromedial PFC and sensorimotor cortex predicted decreased aversion-related processing within sensorimotor cortex (Hayes *et al.*, 2013). Previous work has shown that activity within the sensorimotor cortex is related to the inhibition of motor responses (Tallet *et al.*, 2009; van den Wildenberg *et al.*, 2010). Impulsive individuals have reduced resting-state functional connectivity between PFC and value-relevant subcortical structures such as the NAc and amygdala, yet increased connectivity between similar subcortical structures and the sensorimotor cortex (Davis *et al.*, 2013). Moreover, a recent MRS study found reduced GABA concentrations in the sensorimotor cortex of children with ADHD compared with non-affected controls (Edden *et al.*, 2012). Speculatively, these results may also be related to findings in some ADHD subjects who preferentially choose immediate rather than delayed rewards in order to avoid the negative affective state produced by waiting (Sonuga-Barke *et al.*, 2010; Lemiere *et al.*, 2012), and together suggest that altered sensorimotor GABAergic signalling may be related to both impulsive and aversive processing.

GABAergic manipulations within a number of impulsivity-related brain regions in rats also affect value-related behaviours. For instance, $GABA_{A/B}$ receptor agonists injected into the PL cortex or NAc core abolished cue- and methamphetamine-induced reinstatement of self-administration behaviour, whereas injections into the infralimbic (IL) cortex or NAc shell reduced methamphetamine-induced drug-seeking (Rocha & Kalivas, 2010). Intra-PL/IL or NAc shell $GABA_A$ receptor blockade increased electrical self-stimulation reward behaviour whereas only NAc shell receptor stimulation decreased this behaviour (Hayes *et al.*, 2011; Paine *et al.*, 2011). Similarly, $GABA_A$ and $GABA_B$ (but not glutamatergic) receptor activation in the VTA reduced self-stimulation behaviour (Panagis & Kastellakis, 2002). Moreover, the use of knockout mice revealed that benzodiazepine-associated reward is dependent on the α2 and α3, but not α1, $GABA_A$ receptor subunits (Reynolds *et al.*, 2012). A number of studies have also found a clear link between changes in impulsivity and value-related processing in humans (Costa Dias *et al.*, 2013; Jimura *et al.*, 2013). Collectively, these data support the hypothesis that dysfunctional GABAergic systems may contribute to both value- and impulsivity-related brain function and behaviour.

Clinical disorders of impulsivity

While treatments focusing on ameliorating DSM-defined disorders have met with some success there has been increasing research in recent years on treating specific core symptoms, such as impulsivity, which are common to a number of neuropsychiatric disorders, including drug addiction and ADHD (Sahakian *et al.*, 2010; Insel *et al.*, 2012). Thus, elucidating the role of GABA in impulsivity may facilitate the search for effective new therapies for addiction and related disorders.

Although compulsive alcohol consumption is a hallmark of addiction, the initial stages of this disorder are thought to involve impulsive, repetitive, drug taking involving gradual decreases in $GABA_A$ receptor function (Koob, 2013). Trait impulsiveness is strongly predictive of future alcohol use (von Diemen *et al.*, 2008), and both response inhibition and trait impulsivity predict alcohol-related cue reactivity and relapse in alcohol-dependent subjects (Charney *et al.*, 2010; Papachristou *et al.*, 2013). In addition, alcohol dependence has been linked to variants of GABA receptor genes, particularly single-nucleotide polymorphisms of the *GABRA2* gene, which encode the α2 subunit of the $GABA_A$ receptor (Bierut *et al.*, 2010). Healthy subjects homozygous for the high-risk *GABRA2* allele show increased activation of the medial PFC in response to alcohol cues while heterozygotes show greater activity in the ventral tegmental area (Kareken *et al.*, 2010). Moreover, homozygotes were more likely to show symptoms of alcohol dependence, to have higher trait impulsivity, and exhibit increased activation of the insula during reward and loss anticipation on a monetary incentive delay task (Villafuerte *et al.*, 2012). Interestingly, α2 subunit-knockout mice showed increased sensitivity to the ataxic and sedative effects of alcohol, without effects on rewarding self-administration behaviour (Dixon *et al.*, 2012).

Unfortunately, the use of GABAergic compounds clinically, particularly those targeting the $GABA_A$ receptor, is restricted by adverse effects such as sedation and ataxia (e.g. Mehta & Ticku, 1999). However, positive allosteric modulators of the $GABA_B$ receptor, which modulate function only in the presence of endogenous GABA, appear more promising (Vlachou & Markou, 2010). While the $GABA_B$ receptor agonist baclofen holds some promise as a treatment for alcoholism (de Beaurepaire, 2012; Gorsane *et al.*, 2012), less encouraging findings have been reported in experimental animals. For example, although acute baclofen attenuates cue-induced reinstatement in alcohol-preferring rats (Maccioni *et al.*, 2008), repeated baclofen administration resulted in tolerance (Beveridge *et al.*, 2013). Nonetheless, direct injection of $GABA_{A/B}$ receptor agonists into the dorsal but not ventral PFC attenuated reinstatement of alcohol-seeking behaviour in rats (Willcocks & McNally, 2013). Similar effects were noted with $GABA_{A/B}$ receptor stimulation in the NAc shell (Millan *et al.*, 2010), consistent with evidence for an involvement of the NAc shell and NAc core in context- and cue-induced ethanol-seeking (Chaudhri *et al.*, 2010). Collectively, these findings encourage further research into the effectiveness of baclofen and other GABAergic compounds to prevent relapse, especially in drug-prone, highly impulsive subjects (Economidou *et al.*, 2009).

Contrary to studies in addiction, there is little evidence to date for a significant role of GABA in ADHD. Interestingly, however, a subset

of three young children with ADHD responded positively when treated with the indirect GABA agonist valproate but not when treated with methylphenidate (Miyazaki *et al.*, 2006). Anti-epileptic drugs, which act directly or indirectly to affect GABA transmission, are also effective in treating individuals with impulsive aggression (see Stanford *et al.*, 2009; for a summary of studies). Moreover, as noted above, GABA levels are reduced in the sensorimotor cortex of children with ADHD relative to age-matched controls (Edden *et al.*, 2012). In addition, the mechanism of action of ADHD therapies may in part involve GABAergic mechanisms. Thus, both methylphenidate and bupropion were found to significantly increase plasma levels of the endogenous neurosteroid dehydroepiandrosterone (DHEA) and its sulphate ester but not cortisol in young boys with ADHD (Maayan *et al.*, 2003; Lee *et al.*, 2008). As both neurosteroids have strong inhibitory effects on the $GABA_A$ receptor, it was concluded that this interaction may have been responsible for the therapeutic effects of methylphenidate. Evidence that methylphenidate alters GAD gene expression in the striatum and PFC of rats (Freese *et al.*, 2012) lends further support to the notion that GABAergic mechanisms may partly underlie the efficacy of psychostimulant drugs in ADHD.

Another promising line of ADHD research involves the control of PFC GABA transmission by DA D_4 receptors. Immunohistochemical studies have found that D_4 receptors are widely expressed in GABAergic interneurons and glutamatergic pyramidal cells in the PFC (Mrzljak *et al.*, 1996), where they are hypothesised to regulate the balance between glutamatergic excitation and GABAergic inhibition (Yuen & Yan, 2009). Polymorphic variants of the D_4 receptor are strongly linked to ADHD (LaHoste *et al.*, 1996; Rowe *et al.*, 1998), and research in animals supports a role for D_4 receptors in the expression of novelty-seeking, hyperactivity and impulsivity (Avale *et al.*, 2004; Bailey *et al.*, 2007). Drugs used to treat ADHD have been shown to restore PFC-dependent cognitive processes (Elliott *et al.*, 1997; Chamberlain *et al.*, 2007), putatively by restoring locally-deficient NA and DA (Ernst *et al.*, 1997). Such effects appear to depend on α_2 adrenoceptors and D_1 receptors (Arnsten & Dudley, 2005) and also, putatively, D_4 receptors which drive GABA-dependent gamma frequency network oscillations that correlate with attention (Furth *et al.*, 2013). GABAergic regulation by D_4 receptors appears to be driven by a dampening of excitatory synaptic strength in GABAergic interneurons leading to decreased GABAergic inhibition in the PFC (Yuen & Yan, 2009). Modulation of local-circuit PFC GABAergic activity by psychostimulant drugs may therefore, in part, underlie their cognitive enhancing effects in healthy volunteers and ADHD patients (Lauzon & Laviolette, 2010).

The strongest clinical links between GABA and impulsive behaviour are, at present, to addiction and ADHD. However, it is also worth briefly mentioning putative associations between GABA and other neuropsychiatric disorders such as impulsive aggression, depression and suicidality, each of which are tied to pathological impulsivity and involve putatively impaired functioning of the serotonergic systems (e.g. Lindstrom *et al.*, 2004; Coccaro *et al.*, 2010a,b). Notably, GABA is a major regulator of the anterior serotonergic raphe nuclei (e.g. Forchetti & Meek, 1981; Nishikawa & Scatton, 1985; Gocho *et al.*, 2013), and this may be an important contributory mechanism in these disorders. Indeed, antiepileptic drugs, which act through GABA-related mechanisms, are effective in impulsive aggression but interestingly not premeditated aggression (Stanford *et al.*, 2009). Moreover, genetic studies in suicide completers, with and without depression, have identified altered expression and epigenetic regulation of genes related to GABAergic neurotransmission in the PFC (Poulter *et al.*, 2008; Klempan *et al.*, 2009; Sequeira *et al.*, 2009). These interrelations may seem less surprising when one considers that depression combined with impulsivity and aggression is strongly correlated with completed suicides (Perroud *et al.*, 2011).

Concluding remarks

A putative role of GABA in impulsivity is supported by various lines of research, reviewed above, but the precise mechanisms involved remain poorly understood. Our intention in this article was to highlight the paucity of studies on GABA in the context of impulsivity, a surprising gap given the critical role of GABA both in synchronizing neuronal activity (Xu & Yao, 2010; Jocham *et al.*, 2012; Calhoon & O'Donnell, 2013) and in integrating afferent input at dopaminergic and glutamatergic synapses in the striatum (Kalivas & Volkow, 2005). However, new findings suggest that impaired inhibitory control and impulsivity may be caused, at least partly, by aberrant functioning of GABAergic medium spiny neurons in the striatum (Burguiere *et al.*, 2013; Caprioli *et al.*, 2013b).

Beyond the necessity to fill gaps at the molecular and cellular levels, higher level analyses are needed to elucidate the contribution of broader impulsivity networks and their distinct contribution to cognitive and motor impulsivity. For example, it is currently unclear which brain regions (e.g., NAc, medial and lateral PFC, cingulate cortex, insula, amygdala and sensory cortex) should be included in these networks, and the list is probably incomplete. Moreover, little research has been undertaken to explore how these networks interact with circuitry underpinning motor inhibition, decision making, value attribution and resting-state activity. In this regard, recent neuroimaging studies in humans have linked resting-state functional connectivity with trait impulsivity (Davis *et al.*, 2013) and value-related decision-making in healthy subjects (Li *et al.*, 2013) as well as individuals with ADHD (Costa Dias *et al.*, 2013).

In conclusion, the research findings reviewed herein advance the notion that GABAergic signalling in corticobasal ganglia networks is a key common pathway linking and coordinating inputs from a variety of neural structures and neurotransmitter systems. However, although studies in humans and experimental animals generally support a role of GABA in functional and pathological forms of impulsivity it is clear that substantial gaps exist in our knowledge. By addressing this shortfall, and continuing to link mechanism-based preclinical research with neuropsychological and neuroimaging studies in humans, new therapies may emerge to treat impulsivity in a range of clinical disorders.

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Abbreviations

5-CSRTT, five-choice serial reaction time task; 5-HT, serotonin; ADHD, attention-deficit hyperactivity disorder; DA, dopamine; GABA, γ-amino butyric acid; GAD, glutamate decarboxylase; IL, infralimbic; MRS, magnetic resonance spectroscopy; NAc, nucleus accumbens; NA, noradrenaline; OFC, orbitofrontal cortex; PFC, prefrontal cortex; PL, prelimbic; SSRT, stop-signal reaction time.

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