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Nucleus accumbens and impulsivity

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ABSTRACT

The multifaceted concept of impulsivity implies that different impulsivity aspects, mediated by different neural processes, influence behavior at different levels. The nucleus accumbens (NAc) is a key component of the neural processes regulating impulsivity. In this review, we discuss the findings of lesion studies in animals and functional imaging studies in humans focusing on the role of the NAc in impulsivity. Evidence supports that the extent and pattern of involvement of the NAc, and its subregions, the core and the shell, vary among different facets of impulsivity. Data from imaging studies reviewed in this article suggest the involvement of the ventral striatum/NAc in impulsive choice. Findings of animal studies indicate that lesions of the NAc core subregion facilitated impulsivity in tasks involving intertemporal choice, and promoted a risk-averse, less impulsive, tendency in tasks involving options with probability differences. Modification of neurotransmitter activity, especially of dopamine, which is proposed to underlie the changes observed in functional imaging studies, has been shown to influence afferent input pattern in the NAc and the generation of the behavioral output. Parameters of behavioral tasks reflecting response inhibition function are altered by neurochemical interventions and local electrical stimulation in both the core and the shell subregions. *In toto*, NAc's pattern of neuronal activity, either genetically determined or acquired, has a critical impact on the interindividual variation in the expression of impulsivity. Nevertheless, the NAc is not the only substrate responsible for impulsivity and it is not involved in each facet of impulsivity to the same extent.

Contents

Abbreviations: 5-HT, 5-hydroxytryptamine; 5CSRT, five-choice serial reaction time; ADHD, attention deficit and hyperactivity disorder; DBS, deep brain stimulation; DRL, differential reinforcement of low rates; fMRI, functional magnetic resonance imaging; GABA, gamma-aminobutyric acid; LI, latent inhibition; MSN, medium-sized spiny neurons; NAc, nucleus accumbens; RT, reaction time; SSRT, stop-signal reaction time; VTA, ventral tegmental area.

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1. Introduction

Making choices and acting accordingly are basic daily life activities for both humans and animals. The quality of these activities is critical for adaptation and survival. Impulsive features directly influence the quality of the decisions and actions (Zermatten et al., 2005; Franken et al., 2008). Impulsivity has been defined as the inability to wait, a tendency to act without forethought, insensitivity to consequences, preference for immediate over delayed gratification, inability to inhibit inappropriate behavior, the tendency to engage in risky behavior, and the desire to seek out novel sensations (Mitchell, 2004; Reynolds et al., 2006). Impulsivity has been a difficult term to define; part of this complexity arises from the fact that different areas of science (psychiatry, psychology and neuroscience), as well as lay people, have used it with a wide range of connotations (Evenden, 1999d). Impulsive acts often have deleterious consequences, although we all act impulsively with varying degree and frequency. Besides being part of healthy behavior, impulsivity is one of the core symptoms of various disruptive behaviors and psychiatric disorders such as drug abuse, attention deficit and hyperactivity disorder (ADHD), bipolar disorder, obsessive compulsive disorder, aggression, suicide, pathological gambling, trichotillomania, intermittent explosive disorder, self-injurious behavior, and kleptomania (Kisa et al., 2005; Swann et al., 2001).

Research on impulsivity, using a wide range of methods both in humans and animals, has attempted to define the main neuronal elements involved in the development and expression of impulsivity. The current concept of impulsivity emphasizes its multifaceted nature (Evenden, 1999d). This means that there are different cognitive and behavioral features covered by the term (Congdon and Canli, 2005; Evenden, 1999a; Reynolds et al., 2006). This conceptualization makes it unlikely that a single common biological mechanism underlies all features of impulsivity. In the last years, a growing amount of evidence support a frontostriatal regulation of impulsive behavior (Bechara and Van Der Linden, 2005; Chambers and Potenza, 2003; Dalley et al., 2008), and within this frontostriatal circuit, the nucleus accumbens (NAc) has been shown to be a key structure (Dalley et al., 2007). For instance, lesions of the NAc in rats produce profound changes in specific facets of impulsivity (Bezzina et al., 2007; Cardinal et al., 2001; Eagle and Robbins, 2003b; Pothuizen et al., 2005).

The NAc has been extensively studied with anatomical, electrophysiological, pharmacological and behavioral methods because of its possible role in the pathophysiology of psychiatric disorders (Mogenson et al., 1980; Stevens, 1973). The NAc receives information both from limbic structures, which are critical for affective processing, as well as motor structures which coordinate motor performance. Therefore, the NAc is proposed to be critical in integrating motivational information to modulate behavior. In the last decades, more and more data has become available on the involvement of the NAc in reward, motivation, and affective disorders (Nestler and Carlezon, 2006; Robbins and Everitt, 1996). The NAc has been implicated in the neurobiology of decision making; not only in motivation and salience attribution, but also in action selection (Berridge and Robinson, 1998; Ernst and Paulus, 2005; Nicola, 2007).

A multitude of behavioral measures and models of different features of impulsivity have been proposed (Monterosso and Ainslie, 1999; Winstanley et al., 2006). The elucidation of underlying neurobiological mechanisms regulating each impulsive feature, and application of the multifaceted conceptualization of impulsivity to models of psychopathology may improve strategies of intervention and treatment in impulsivity related disruptive behaviors and disorders.

2. Nucleus accumbens

Before reviewing the evidence on the involvement of the NAc in impulsive behavior, we will review some anatomical facts. Following a brief description of the regional anatomy, we will deal with the intrinsic organization and connections of the NAc.

2.1. The nucleus accumbens as part of the ventral striatum

The NAc is generally considered the nuclear mass ventral and slightly medial to the head of the caudate nucleus in the basal forebrain, just dorsal to the caudal gyri of the orbitofrontal cortex in humans (Fig. 1) and dorsal to the olfactory tubercle in rats (Fig. 2). The NAc forms the main part of the so-called ventral striatum. The ventral striatum is primarily characterized by its strong inputs from limbic structures such as the amygdala, hippocampus, midline thalamus and certain regions of the prefrontal cortex, as well as from the mesolimbic dopamine system originating in the ventral tegmental area (VTA; A10 cell group). The term 'ventral striatum' was first introduced by Heimer and Wilson (1975) to distinguish it from the dorsally located caudate–putamen, i.e. the dorsal striatum. Heimer and Wilson (1975) emphasized the parallel between the dorsal and ventral striatum with respect to cortical, thalamic and dopaminergic afferent connections, and pallidal efferent projections. Whereas the dorsal striatum receives cortical inputs from the neocortex, in particular sensory and motor cortical areas, the ventral striatum collects cortical afferents from allocortical areas, including the hippocampus, as well as frontal and temporal association cortices. The dorsal striatum is projected upon by the nigrostriatal system; the ventral striatum receives its dopaminergic fibers from the ventral tegmental area. While the dorsal striatum projects to the globus pallidus, Heimer and Wilson (1975) identified an area in the basal forebrain, at that time still indicated as the substantia innominata, that receives strong inputs from the ventral striatum

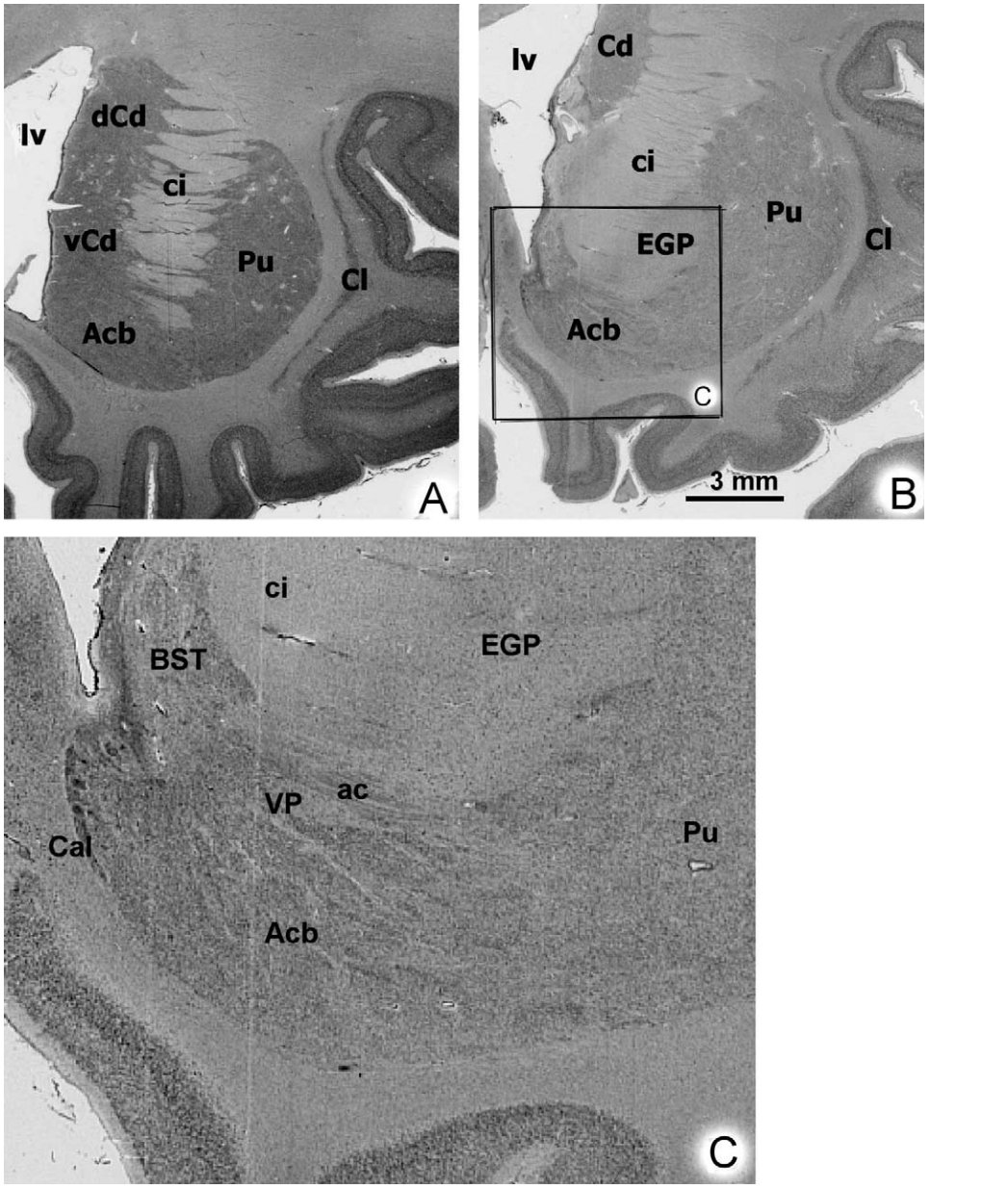

Fig. 1. Photomicrographs of two coronal sections through the rostral part of the human striatum, including the nucleus accumbens. The sections have been stained with a silver Nissl staining to show the cytoarchitecture. (A) Section through the rostral part of the nucleus accumbens, (B) section though its caudal part. The rectangle in (B) shows the area which is enlarged in (C). *Abbreviations*: ac, anterior commissure; Acb, nucleus accumbens; BST, bed nucleus of the stria terminalis; Cai, major island of Calleja; Cd, caudate nucleus; ci, internal capsule; Cl, claustrum; dCd, dorsal part of Cd; EGP, ecxternal segment of the globus pallidus; lv, lateral ventricle; Pu, putamen; vCd, ventral part of Cd; VP, ventral pallidum. Courtesy Prof.dr. H.B.M. Uylings.

and that has cytoarchitectonic characteristics very similar to the dorsally adjacent globus pallidus. They named this area within the substantia innominata the ventral pallidum and in this way identified a dorsal and a ventral striatopallidal system (Heimer, 2003).

It must be realized that the NAc forms an integral part of the ventral striatum but that the ventral, limbic-innervated striatum is larger than the NAc alone. In addition to the NAc, the ventral striatum includes the striatal elements of the olfactory tubercle, ventral and medial parts of the caudate–putamen complex, as well as caudal areas of the caudate–putamen located dorsal to the amygdala (Fudge and Haber, 2002; Heimer and Wilson, 1975). However, since by far the most functional and behavioral studies in the context of impulsivity have been concerned with the NAc, the following paragraphs will primarily deal with the structure and connections of this part of the ventral striatum.

Whereas it is now generally accepted that the NAc forms an integral part of the striatum, in the past it has also been considered to be closely associated with the septum or the olfactory system (Herrick, 1926; Meynert, 1872). In the course of history, the nucleus has also been indicated as the nucleus accumbens septi (Ariens Kappers and Theunissen, 1908; Meynert, 1872) in an attempt to combine different views, but in the past decades this term has disappeared. Clear-cut borders of the NAc can only partly be identified. Thus, the medial and ventral borders of the NAc with the lateral septal nuclei and the olfactory tubercle, respectively, are undisputable. However, dorsal, lateral and rostral borders with the caudate nucleus and putamen are much more difficult to establish. In fact, not only the cytoarchitecture but also immunohistochemical and connectional characteristics support the idea that there are no sharp boundaries between the NAc and the rest of the striatum. Rather, there are gradual transitions between the ventral,

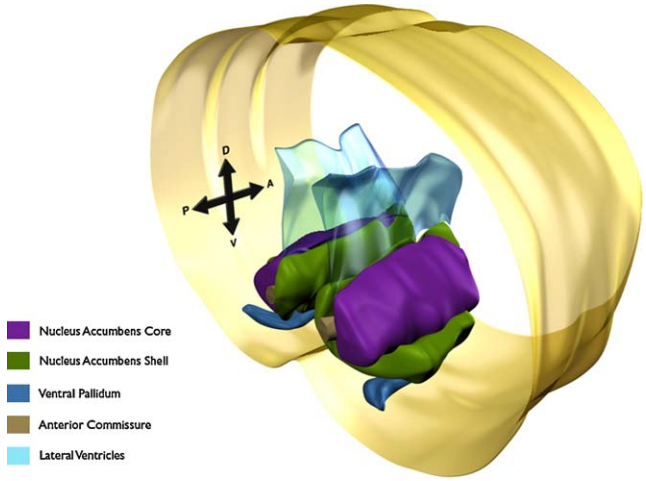

Fig. 2. The regional anatomy of the rat nucleus accumbens. The structures are respresented in different colors.

limbic-innervated striatum, including the NAc, and the dorsal, sensorimotor-innervated striatum (Voorn et al., 2004). Finally, the caudal border of the NAc with the bed nucleus of the stria terminalis is likewise rather a gradual transition than a sharp demarcation, the bed nucleus having clear striatal-like cytoarchitectonic characteristics (Alheid and Heimer, 1988). Heimer and colleagues have argued that the most caudal and medial parts of the NAc (i.e. the caudomedial shell [see below]) form a rostral extension of the so-called extended amygdala in view of its similarity in structure and connections with the bed nucleus of the stria terminalis (Alheid and Heimer, 1988; Heimer and Van Hoesen, 2006).

In rats, the NAc forms the most rostral and ventral extension of the striatum. However, in humans the head of the caudate nucleus has expanded so much in conjunction with the expansion of the prefrontal cortex that the NAc has been 'pushed' in caudal direction (Meredith et al., 1996). In fact, unlike the situation in rats, the human NAc has extensive caudal finger-like extensions into the basal forebrain (Heimer et al., 1999).

2.2. Shell and core of the nucleus accumbens

Whereas the boundaries of the NAc with the rest of the striatum are difficult to establish on the basis of cytoarchitectonic and immunohistochemical criteria, within the nucleus there is a clear distinction between the so-called shell and core subregions (Fig. 3). Shell and core were first described on the basis of the differential distribution of cholecystokinin-immunoreactivity (Zaborszky et al., 1985). Later studies showed that various other neurochemical substances, neurotransmitters and receptors show differential distribution patterns in the outer medial, ventral and lateral shell versus the more dorsally and centrally located core of the NAc (Jongen-Relo et al., 1994; Voorn et al., 1989; Zahm and Brog, 1992). The most well-established marker for shell and core in the NAc of rats is the calcium binding protein calbindin-D_{28K} (Jongen-Relo et al., 1994; Zahm and Brog, 1992). The core, like the dorsally adjacent caudate–putamen exhibits strong immunoreactivity for calbindin, while the shell shows low to absent immunoreactivity for this protein. Although in humans calbindin-immunoreactivity has also been used to demarcate shell and core (Meredith et al., 1996), the differential distribution of mu-opioid receptors also clearly marks the two main subregions in the human NAc (Voorn et al., 1996) (Fig. 3). Since the recognition of a shell and core in the NAc, these two subregions and their differential contribution to various functional aspects of the nucleus have played a major role in the ongoing research into

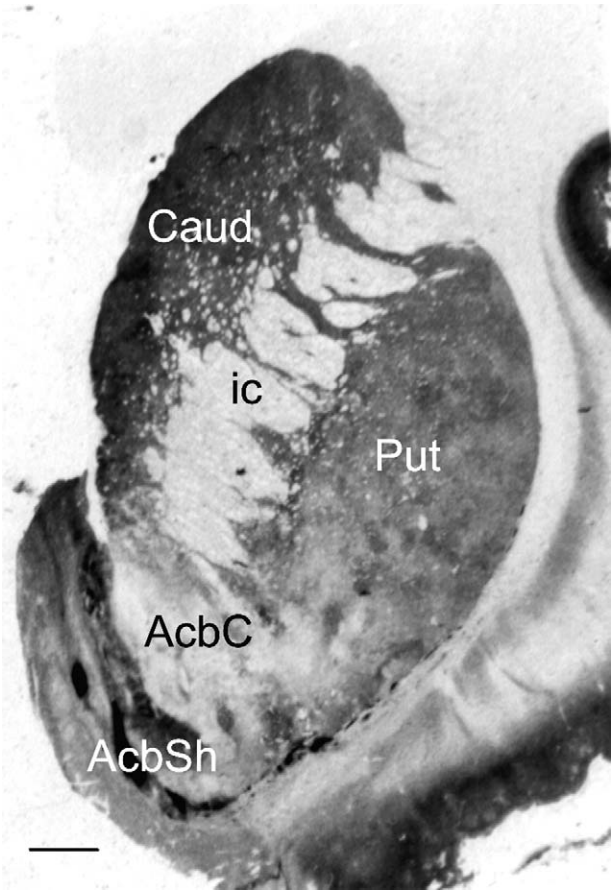

Fig. 3. Frontal section through the rostral part of the human striatum illustrating the pattern of mu-opioid receptor binding (for details see Voorn et al., 1996). Note the differences in binding between the accumbens shell (AcbSh) and core (AcbC), and the caudate nucleus (Caud) and putamen (Put), ic, internal capsule. Bar represents 5 mm. Courtesy dr. P. Voorn.

the functional-anatomical aspects of the NAc (Di Chiara, 2002; Nicola, 2007; Parkinson et al., 1999; Pothuizen et al., 2005; Zahm, 2000).

In general, the cytoarchitectonic and chemoarchitectonic features of the dorsal and ventral striatum are very similar, justifying the concept of the striatum as a functional-anatomical unit. Yet, the NAc in the ventral striatum contains a greater diversity of neurotransmitters and neuroactive peptides than the dorsal striatum. The principal neurons of the NAc are medium-sized, densely spiny projection neurons (MSN) that form more than 95% of the total population. The population of MSN largely falls apart into two subgroups, namely MSN containing GABA (gamma-aminobutyric acid) and the neuropeptides substance P and dynorphin, and MSN containing GABA and enkephalin as neurotransmitters/modulators. Interneurons in the NAc, like the dorsal striatum, encompass cholinergic and a variety GABAergic interneurons, the latter co-storing various neuropeptides (Meredith, 1999). As indicated above, calbindin is a well-accepted marker for differentiating the outer, crescent-shaped shell and the inner core subregion in a variety of species (Groenewegen et al., 1996; Meredith et al., 1996; Zahm and Brog, 1992). Using calbindin as well as other markers, NAc shell and core subregions appear to have a very heterogeneous composition. Thus, the core shows inhomogeneities that resemble the patch-matrix patterns in the dorsal striatum (Graybiel, 1990; Groenewegen et al., 1996; Voorn et al., 1989; Zahm and Brog, 1992). Cytoarchitectonically the core is very homogeneous. The shell subregion, however, exhibits clusters of cells, some of which contain cells with immature characteristics

(Heimer et al., 1999; Herkenham et al., 1984; Jongen-Relo et al., 1994). The shell further exhibits strong inhomogeneities in the distribution of various neurochemical substances and neurotransmitter receptors, among which mu-opioid receptors (Fig. 3) and dopamine D1 and D2 receptors (Berendse and Richfield, 1993; Voorn et al., 1996). Finally, the shell of the NAc contains the highest concentration of dopamine D3 receptors in the brain (Joyce and Gurevich, 1999; Schwartz et al., 2000).

2.3. Afferent and efferent connections of shell and core

Like in the dorsal striatum, cerebral cortical fibers form the main source of glutamatergic inputs into the NAc. Cortical inputs originate mainly in the medial orbitofrontal, anterior cingulate and medial parahippocampal cortical areas (Ferry et al., 2000; Groenewegen et al., 1996; Kunishio and Haber, 1994; Zahm and Brog, 1992). Moreover, the midline and intralaminar thalamic nuclei, the amygdala and the hippocampal formation supply the NAc with excitatory fibers (Berendse and Groenewegen, 1990; Brog et al., 1993; Groenewegen et al., 1987). Extrinsic inhibitory GABAergic projections stem from the ventral pallidum (Bolam et al., 2000; Groenewegen et al., 1993). Dopamine fibers reaching the NAc originate in the VTA and medial part of the substantia nigra pars compacta; serotonergic input stem from the dorsal raphe nucleus. Efferent fibers of the NAc as a whole reach the ventral pallidum, the medial part of the globus pallidus and the dorsomedial part of the substantia nigra pars reticulata. In addition, NAc fibers project to basal forebrain and mesencephalic areas that cannot be considered 'classical' basal ganglia targets. These regions include the lateral preoptic area and lateral hypothalamus, as well as the region of the pedunculopontine nucleus in the caudal mesencephalic regions (Groenewegen et al., 1993, 1996; Groenewegen and Russchen, 1984; Heimer et al., 1991).

Although not exclusive, there are considerable differences in the input–output characteristics between the shell and core subregions (Fig. 4). More specifically, the core subregion receives afferents primarily from dorsal regions of the medial prefrontal cortex, including the dorsal prelimbic and anterior cingulate areas, as well as from the parahippocampal cortex, the caudal midline and rostral intralaminar thalamic nuclei, and the anterior part of the basolateral amygdaloid nucleus (Berendse et al., 1992; Berendse and Groenewegen, 1990; Brog et al., 1993; Wright et al., 1996). The outputs of the core parallel the dorsal striatal projections by sending fibers to the dorsal, subcommissural part of the ventral pallidum, that must be considered a ventral extension of the external segment of the globus pallidus, the medial part of the internal segment of the globus pallidus (entopeduncular nucleus in rats) and the dorsomedial part of the substantia nigra pars reticulate (Deniau et al., 1994; Haber et al., 1990; Heimer et al., 1991). Interestingly, the subcommissural ventral pallidum is reciprocally connected with the dorsomedial part of the subthalamic nucleus (Groenewegen and Berendse, 1990). The medial parts of the internal globus pallidus and substantia nigra project to the ventromedial and mediodorsal thalamic nuclei. These thalamic nuclei are in reciprocal connection with the medial and agranular insular prefrontal areas that, in turn, project to the core of the NAc. In this way, the core of the NAc constitutes the striatal way station in one of the 'limbic' basal ganglia-thalamocortical circuits (Alexander et al., 1990; Ferry et al., 2000; Groenewegen et al., 1993, 1996; Zahm and Brog, 1992).

The shell receives cortical inputs from the more ventrally located medial prefrontal areas, including the infralimbic and ventral prelimbic areas (Berendse et al., 1992; Brog et al., 1993; Heidbreder and Groenewegen, 2003). Thalamic inputs arrive from the midline paraventricular thalamic nucleus (Berendse and Groenewegen, 1990) and amygdaloid projections to the NAc shell originate in posterior parts of the basolateral amygdaloid nucleus (Wright et al., 1996). The subiculum and CA1 regions of the hippocampal formation also primarily target the shell of the NAc (Groenewegen et al., 1987). Dopaminergic inputs form part of the so-called mesolimbic dopamine system originating in the ventral tegmental area (VTA; recent review: Ikemoto, 2007) and serotonergic inputs from the dorsal raphe. Finally, the caudomedial shell receives a considerable noradrenergic input, most likely stemming from noradrenergic cell groups in the caudal brainstem (Berridge et al., 1997). This makes the caudomedial shell a rather unique striatal area since the noradrenergic fibers are virtually absent from the rest of the striatum. Outputs of the shell target the ventral and medial parts of the ventral pallidum and adjacent lateral preoptic area (Groenewegen et al., 1993). Shell projections further reach the lateral hypothalamus, the dopaminergic cell groups in the VTA and dorsal tier of the substantia nigra pars compacta and, more caudally in the mesencephalon, the region of the pedunculopontine nucleus. Through the ventral pallidum, the shell forms a

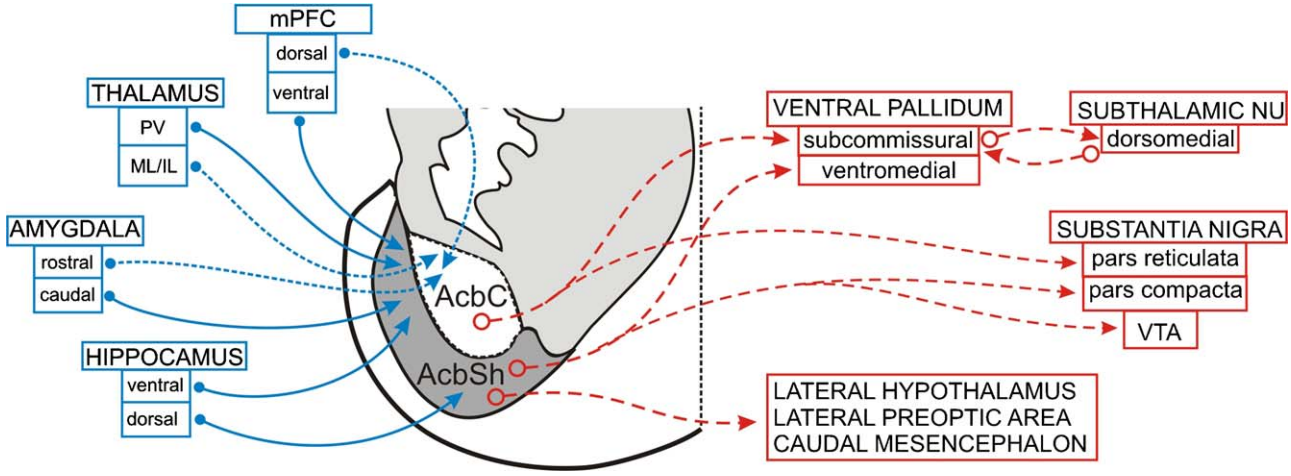

Fig. 4. Schematic drawing of the inputs and outputs of the shell (AcbSh) and core (AcbC) of the nucleus accumbens (see also Fig. 3). Dopaminergic, serotonergic, and noradrenergic inputs have been omitted from the drawing. Note that virtually all structures (left hand side of the scheme), although via different subdivisions or subnuclei, project to both shell and core. This also holds true for the outputs of both subdivisions (right hand side of the scheme), but it must be noted that there are also main differences. Both shell and core reach pallidal and nigral area, albeit different parts of these basal ganglia structures. The shell, in addition projects to preoptic and hypothalamic areas and the caudal mesencephalon. *Abbreviations*: ML/IL, midline and intralaminar thalamic nuclei; mPFC, medial prefrontal cortex; PV, paraventricular thalamic nucleus; VTA, ventral tegmental area.

way station in a re-entrant 'limbic' basal ganglia-thalamocortical circuit that also entertains the mediodorsal thalamic nucleus and medial prefrontal areas (Groenewegen et al., 1999a, 1996; Zahm and Brog, 1992). It is further of interest to note that, via the projections to the VTA and adjacent substantia nigra pars compacta, the shell possibly influences the dopaminergic inputs to other parts of the striatum. In this way, the shell projections to the dopaminergic neuronal cell groups in the ventral mesencephalon form a neuronal substrate for the integration of activity in various basal ganglia-thalamocortical circuits (Belin and Everitt, 2008; Groenewegen et al., 2003; Haber et al., 2000; Nauta et al., 1978).

In describing the primary outputs of the NAc, it is clear that the nucleus reaches various targets, prominently including pallidal and nigral structures, but also preoptic, hypothalamic and caudal mesencephalic areas. Since the principal output neurons of the NAc are GABAergic, these projections most likely exert inhibitory influences on their targets. Interestingly, several of the target areas of the NAc are also reached by ventral pallidal fibers (Groenewegen et al., 1993) and since pallidal neurons are also GABAergic, the influence of NAc activity on structures such as the medial part of the internal globus pallidus, the VTA and medial substantia nigra pars compacta, the dorsomedial substantia nigra pars reticulata, the caudal mesencephalic areas and the lateral hypothalamus might be both inhibitory and disinhibitory. Like the dorsal striatopallidal/nigral system (Gerfen, 2004), the ventral striatopallidal/nigral system contains direct and indirect pathways (Groenewegen et al., 1996). The situation is, however, slightly more complex for the ventral striatum than for its dorsal counterpart. The core most clearly shows the direct/indirect organization of its outputs. In rats direct, substance P and dynorphin containing striatal projections reach the medial part of the entopeduncular nucleus and the dorsomedial part of the substantia nigra pars reticulata. The indirect pathway consists of the enkephalin-containing striatal projection fibers to the subcommissural part of the ventral pallidum. This part of the ventral pallidum is in reciprocal contact with the dorsomedial part of the subthalamic nucleus which in turn also projects to the medial part of the entopeduncular nucleus and the dorsomedial substantia nigra pars reticulata. (Groenewegen and Berendse, 1990). The latter two regions are thus under direct and indirect control of the NAc core and they project to the mediodorsal and ventromedial thalamic nuclei (Groenewegen et al., 1999b). While the subthalamic nucleus receives a direct projection from the medial prefrontal cortex, much like the 'hyperdirect' cortical pathways to the remainder of the subthalamic nucleus, the core of the NAc might be arranged in cortical – basal ganglia pathways much comparable with the dorsal striatum. This provides for neuronal mechanisms allowing suppression of unwanted and the facilitation of desired outputs (Mink, 1996; Redgrave et al., 1999). In particular, the subthalamic nucleus plays an important role in the mechanisms of suppression (Mink, 1996; Temel et al., 2005). The outputs of the NAc shell are differently organized in the sense that there is less clearly a direct and an indirect component. Fibers from the two groups of MSN of the shell, i.e. the enkephalin- and the dynorphin/substance P-containing, are intermingled in the medial and ventral parts of the ventral pallidum. This part of the ventral pallidum has no direct connections with the subthalamic nucleus, although projections have been found to the lateral hypothalamic area immediately adjacent to the subthalamic nucleus. In any case, the regulation of the outputs of the shell of the NAc seems to be differently organized than that of the NAc core and the dorsal striatum. It may lack the suppressive role of the subthalamic nucleus.

Based on the character of the afferents of the NAc, this part of the ventral striatum may be viewed as a site for integration of signals with emotional content (amygdala), contextual information (hippocampus), motivational significance (dopaminergic inputs), information about the state of arousal (midline thalamus) and executive/cognitive information (prefrontal cortex). The accumbens outputs, directly or via ventral pallidal and dopaminergic or non-dopaminergic nigral relays, lead to brain areas involved in basic functions such as feeding and drinking behavior (lateral hypothalamus), motivational behavior (VTA and nigral dopaminergic neurons), locomotor behavior (caudal mesencephalon) and more complex cognitive and executive functions (via medial thalamic nuclei to the prefrontal cortex).

3. Impulsivity

The definition and the structural components of impulsivity, as well as the methods of evaluating impulsivity have been extensively investigated. The most influential models of personality include impulsivity as a significant component, and frequently multiple dimensions of impulsivity were taken into consideration (Eysenck and Eysenck, 1977; Eysenck, 1985; Gray, 1981, 1987; Cloninger et al., 1993; Zuckerman et al., 1984; Dickman, 1990; McCrae and Costa, 1990). The research on human personality traits supports the multifaceted conceptualization of impulsivity, made up of several, independent facets with different degrees of relationship with personality traits and coupled to different aspects of behavior (Congdon and Canli, 2005; Evenden, 1999d; Reynolds et al., 2006). The structural components of impulsivity were further refined with the help of self-report questionnaires and scales (Barratt, 1993; Patton et al., 1995).

Studies focusing on the relationship between self-report inventories for impulsivity and tasks measuring impulsive behavior reported two main dimensions (Avila et al., 2004; Kindlon et al., 1995); impulsive action/disinhibition (inability to inhibit behavior) and impulsive choice/decision-making (preference for immediate over delayed rewards, even when the immediate reward is smaller). These dimensions are also referred by some authors as motor (behavioral) and cognitive impulsivity (White et al., 1994). Motor impulsivity was defined as failure to inhibit behavior, suppress a prepotent response, resulting in fast and inaccurate responding. Cognitive impulsivity was considered as distorted judgement of alternative outcomes, resulting in loss of reward on the long-term. Cognitive impulsivity, defined as the inability to delay gratification, is the opposite of self-control which is a function of factors controlling the choice of delayed reinforcers (Logue, 1988). Another form of impulsivity, not covered by the definition of cognitive impulsivity above, is reflection impulsivity. This term is used to describe the inability to collect and evaluate necessary information before reaching decisions (Kagan, 1966), although it has been used earlier in a broader sense covering all cognitive forms of impulsivity (Messer, 1976).

Evenden defined different aspects of impulsivity according to three components of behavior: preparation to respond, execution of the behavior, and assessment of outcome (Evenden, 1999d). Chambers and Potenza proposed a similar three-component model: (1) input: accumulation of external and internal sensory input into a general contextual frame; (2) processing: the representation, evaluation of behavioral response options, and selection among them; (3) output: the planning and execution of the behavioral response (Chambers and Potenza, 2003). The authors proposed two general circuits governing these processes. Concurrent and integrated activity of these neural circuits were accepted to be necessary for proper functioning. The primary circuit, which is a cortico-basal ganglia-thalamocortical projection system (Alexander et al., 1986; Masterman and Cummings, 1997; Temel et al., 2005), consists of parallel loops of neuronal projections from the prefrontal cortex, to the ventral striatum

(including the NAc), thalamus, and back to the cortex. This circuitry is predominantly influential in the processing component, and its activity directly affects motor output structures. Sensory cortices in association with afferent input from subcortical structures such as hypothalamus, amygdala, hippocampus, and brain stem provide the primary circuit with integrated, multimodal representation of the contextual frame. The second circuit mainly supplies the primary with autonomic, affective, motor, and memory information which is necessary for the proper shaping of the output.

In this review, we will discuss lesion studies in animals and functional imaging studies in humans reporting on the role of the NAc in impulsivity. Based on the diverse features of impulsivity reviewed above, research findings will be discussed in three groups, which are outlined below in Sections 3.1, 3.2 and 3.3. However, a strict distinction between the processes in each group, as well as between different facets of impulsivity, does not exist. This formulation is proposed for practical reasons. Indeed, frequently the tasks used for evaluation of these facets, either used in human or animal research, are not specific or limited to any of these components of behavior.

3.1. Attentional/reflection impulsivity

Various facets of impulsivity are involved in the assessment preceeding the behavioral response. The assessment involves the collection of external and internal sensory information, and fitting this information into a general contextual frame. In this stage, impulsivity can be displayed by not taking all relevant information into account before making a decision. This form of impulsivity, referred as reflection impulsivity (Clark et al., 2005), has been measured using the matching familiar figures test in humans (Kagan, 1966). Evenden suggested the application of a discrimination task using unreliable visual stimuli for the assessment of reflection impulsivity (Evenden, 1999b,c).

Reaction time tests are frequently used in the assessment of this tendency. Reaction time (RT) is traditionally accepted as a reflection of the cognitive processes preceding a motor behavior (Blokland, 1998). RT is defined as the time interval between the stimulus presentation and the initiation of the motor response. This duration may be a rough indicator of the overall cognitive evaluation process: the collection of task-relevant information, cognitive evaluation of this information, evaluation of response options and selection among them. These processes are practically inseparable in behavioral tasks in animals. RT has been assessed in various models of operant chambers, such as Skinner boxes. RT tasks can either be simple (e.g. one cue-one respond) or complex involving choices (e.g. multiple cues-choices) (Blokland et al., 2005). Choice RT involves the process of response selection in addition to cognitive evaluation of the stimulus and the context. However, in each condition, the RT is a product of multiple functions. Nevertheless, a diminution of accuracy and a left centered RT distribution (shorter reaction time) can be the indicator of the deficiency or omission of cognitive evaluation, as well as the tendency to avoid the burden of collecting task-relevant information may be responsible for its shortening.

In addition, the failure in resistance to interference influences the assessment. The ability to ignore information that is irrelevant to the execution of a response (either cognitive or motor) is termed as interference control or resistance to interference (Barkley, 1997; Nigg, 2000). The construct of interference control encompasses both resistance to distractor interference and resistance to proactive interference (Friedman and Miyake, 2004). Resistance to distractor interference is the ability to resist interference by external information which is available simultaneously with the target information, but not related with the task. Resistance to a proactive interference is the ability to resist intrusion of information which is irrelevant to the present task, but the memory of relevance exists due to earlier experience with the task. These forms of interferences can be assessed with Stroop's test and Wisconsin Card Sorting Test.

Lack of perseverance facet of impulsivity is related to the ability to remain focused on a task (Whiteside and Lynam, 2001). Gay and associates (2008) have reported on a strong relationship between the lack of perseverance facet of impulsivity and increased difficulty in the resistance to a proactive interference. Impairment in these forms of cognitive inhibition influences behavior throughout its course, not only the assessment.

Difficulties in focusing attention and easy distractibility are also discussed as a feature of impulsivity in earlier models as the attentional impulsiveness (Patton et al., 1995; Dickman, 1990). Attentional functions, which are necessary for selective and continuous processing of environmental and internal stimuli, are assessed with various paradigms and tasks, such as five-choice serial reaction time (5CSRT) task. The 5CSRT task has been designed with the purpose of studying sustained and divided attention for rats (Winstanley et al., 2006). During the 5CSRT task, the animal is expected to respond to one of the five adjacent response apertures after the light stimulus above one of the apertures has been turned on (Robbins, 2002). There is an intertrial interval during which animals are expected not to respond. Correct responses are awarded by food pellets. Errors of ommission (failure in responding within a predetermined time limit), and errors of commission (responding in an aperture in which the stimulus is not presented) are punished with a time-out period. Response accuracy is calculated as a measure of sustained spatial attention. Errors of ommission are accepted as a reflection of failure in selective attention, and errors of commission reflect inattentiveness.

3.2. Impulsive choice

When selection of a response (or a set of responses) is necessary among several alternatives with different outcomes, impulsive choice produces a failure in net overall maximization of consequences. This form of impulsivity may be based on the deficiency in forethought and failure in reflecting on long-term consequences before engaging in an act. Disproportionate representations of the outcome alternatives with different degrees of delay, probability and risk, hinder the individual's ability to respond in his best interence, blurring his capacity to reflect on long-term consequences of his behavior (Chambers and Potenza, 2003). Individual's sensitivity to risk associated with a behavioral response option may promote the selection of options regardless of the probable cost, in some cases facilitating his preference against the overall benefit, or even leading to detrimental consequences. This deficiency in forethought corresponds to the narrow impulsivity dimension of Eysenck's model, and non-planning impulsivity of Barratt's theory, and the lack of premeditation facet of impulsivity (Eysenck and Eysenck, 1977; Patton et al., 1995; Whiteside and Lynam, 2001).

In addition, the selection of a response option may be misguided by an abnormally low threshold for the enactment of a certain motivated drive or disproportional priority of a motivated drive (Chambers and Potenza, 2003). Individual's tendency may be based on two different aspects: a tendency to prefer and to be pleased by exciting activities, and openness to experimenting new activities that may or may not be dangerous. Resulting pattern of choice may be related to another impulsivity facet: the sensation seeking (Cloninger et al., 1993; Eysenck, 1985; Zuckerman et al., 1984).

The evaluation of response options includes the cognitive and emotional assessment of the stimulus/outcome considering various features, such as the valence (positive or negative),

salience (intensity, magnitude), and also probability (certainty), and timing (delay) depending on the availability of the outcome, relative values and number of options to select from, previous experience with these options and their outcomes, and external and internal context in which the decisions are made (Ernst and Paulus, 2005). In addition to this integral representation of the outcome, the strength of the association between the action/outcome-predicting-stimulus and the outcome has to be considered. This latter representation is built on earlier experience, thus involves learning and memory functions. Therefore, individual differences in these processes may have an impact on the expression of impulsivity.

In humans, impulsive choice is studied with various decision-making and gambling tasks which include options with differences in time of delivery, probability, risk and uncertainty. Impulsive choice is frequently based on anomalous processing of actual incentive values due to individual differences in outcome assessment (Evenden, 1999a). Discounting processes are involved with the evaluation of response options with regard to differences in the delay of delivery of the outcome, or in probabilities of delivery (Cardinal, 2006; Ho et al., 1999). Temporal and probability discounting functions regulate the subjective value of the outcome in these conditions. According to the model developed by Ho and associates (Ho et al., 1999), each individual has different discounting functions with regard to delay, certainty and magnitude of the reinforcement. Models of temporal and probability discounting are the most frequently applied paradigms in the research on impulsive choice in humans and animals (Winstanley et al., 2006).

The discounting of the reinforcer value as the delay in the presentation of the reinforcer increases, is called temporal discounting. Delay discounting paradigms are constructed over the concept of temporal discounting. The subject chooses between two rewards – one larger but delayed, the other smaller but immediate (Monterosso and Ainslie, 1999). The tendency to choose the more immediate but smaller alternative is considered impulsive and is also referred as failure to tolerate delay of reinforcement (Logue, 1988). In delay discounting paradigms, the magnitude difference between choices is increased – the large reward is increased, until this is repeatedly preferred, then the delay for the larger reward is introduced and gradually increased, until there is no certain preference between the two rewards. Then temporal discounting function of the organism is calculated and the indifference point is evaluated, e.g. the ratio cost/benefit is equivalent among the conditions: the lower this point, the more the subject is sensitive to delay (Ho et al., 1999). However, in the majority of the studies with fixed-scheduled delay discounting paradigm, the proportion of times the small and immediate choice is preferred is considered to be the index of impulsivity, not the actual indifference point (Cardinal et al., 2001; Dellu-Hagedorn, 2006; Pothuizen et al., 2005; Robinson et al., 2009; Winstanley et al., 2006).

The discounting of the reinforcer value as the probability of the reinforcer delivery decreases, is called probability discounting. In probability discounting paradigms, impulsive choice is defined as a tendency to choose a less probable reinforcement resulting in overall economically inconvenient gratification (Cardinal, 2006). Therefore, it is crucial to define whether the shift from certain to an uncertain option is economically convenient or not. This border is not as clear cut as it is for temporal discounting. With certain size differences between rewards, it is more plausible for the organism to choose the smaller reward which is more certain.

3.3. Response inhibition

Impulsivity can be expressed in the form of execution of a response inappropriately, i.e. failure to withold a behavioral action or premature responding. Impulsivity in this form is widely accepted as a dysfuntion in response inhibition (Aron et al., 2003). Response inhibition, rather than a unitary construct, has been proposed to consist of two forms: action restraint and action cancellation (Schachar et al., 2007). The former is related with the inhibition of a response before the beginning of an action, and the latter involves inhibition of an action during execution. Indeed, in all its forms, response inhibition is far from being an isolated process, since it is closely related to the attending and processing of various stimuli in relation to the context, selecting an appropriate response, and executing a motor behavior counteracting the pre-planned action (Eagle et al., 2008). Failure in response inhibition corresponds to the urgency dimension of impulsivity (Whiteside and Lynam, 2001), as well as the motor impulsiveness in Barratt's model of impulsivity (Patton et al., 1995)

Response inhibition is frequently assessed with go/nogo and stop-signal tasks (Logan et al., 1984). In go/nogo tasks, the subjects are expected to execute responses on go trials, but not on no-go trials. Pre-response selection of an action strategy, whether to go or not to go, is required in line with the different classes of stimuli presented. In the stop-signal reaction time (SSRT) task, the subjects perform a motor response to a "go" stimulus, but in some trials a "stop" signal is presented, after the initiation of the "go" response (Robbins, 2002). Subjects are expected to inhibit the "go" response. The responses following the successive signals are evaluated, in terms of go-trial accuracy, mean reaction time, and inhibition function. The delay between the "go" and "stop" signal has an influence on the efficiency of the inhibition, and this is examined among variable durations of delays between the two signals. This design allows the elimination of the pre-response decision-making step involved in the go/nogo tasks. Go/nogo tasks measure action restraint, whereas SSRT tasks measure action cancellation forms of response inhibiton (Chevrier et al., 2007). An exception for this dissociation is the inclusion of the zero-delay condition into the SSRT task, where the go and the stop signals are presented together, then both action restraint and action cancellation can be evaluated in a single framework (Eagle and Robbins, 2003a).

The 5CSRT task has some parameters which can be used to evaluate impulsivity, although the task has been designed with the purpose of studying sustained and divided attention for rats (Winstanley et al., 2006). At least two types of inhibitory functions are assessed in the 5CSRT task (Dalley et al., 2004). Premature responses (responses during intertrial interval) are indicators of failure in inhibition of preparatory response, and it is an index of impulsive action. Perseverative responses (responses at the apertures after the presentation of the target) correspond to a failure in disengaging from a response; and it is proposed to reflect compulsive over-responding.

Another operant task assessing inappropriate responding as a feature of impulsive behavior is the differential reinforcement for low rates of responding (DRL) task (Dalley et al., 2008). DRL task has long been accepted as a measure of impulsivity features related to the execution of an action (Evenden, 1999d; Monterosso and Ainslie, 1999). DRL requires withholding response for a fixed period of time in order to obtain reward. In this task the subject is expected to space consecutive responses by a specified interval of time (Evenden, 1999a), such as in the DRL-72 s, pressing the lever with an interval of 72 s is rewarded only. Premature responding in DRL task reflects a failure of action restraint, as in the 5CSRT task.

4. Nucleus accumbens and impulsivity

Lesions due to various reasons (e.g. tumour, ischemia) have contributed significantly to our understanding of the function of various brain regions. However, this is not the case for the NAc. In animal models, a substantial amount of data has become available

Table 1
Overview of studies which have investigated the effects of experimental lesions of the NAc on behavioral task parameters in animal models.

Lesion	Task	Effect*	Notes	Reference
Reaction time tests				
NAc (core + shell)	9 Holes Box	–	No effect on reaction time and anticipatory errors	Bowman and Brown (1998)
NAc core	5CSRT test	–/+	No effect on reaction time, accuracy and omission errors; increased premature responses (not significantly), and perseverative responses (significantly) only after failed trials	Christakou et al. (2004)
NAc core	5CSRT/FC test	–	No effect on reaction time, accuracy, omission errors, premature and perseverative responses	Murphy et al. (2008)
NAc shell	5CSRT/FC test	–	No effect on reaction time, accuracy, omission errors, premature and perseverative responses	Murphy et al. (2008)
SSRT				
NAc core	SSRT	–	No effect on go-reaction time, go-trial accuracy and SSRT	Eagle and Robbins (2003b)
DRL				
NAc (core + shell)	DRL	+	Increased mean lever presses per reward earned	Reading and Dunnett (1995)
NAc core	DRL	+	Increased mean lever presses per reward earned	Pothuizen et al. (2005)
NAc shell	DRL	–	No effect	Pothuizen et al. (2005)
Temporal discounting tasks				
NAc core	Delayed reinforcement choice task	+	Decreased mean percentage preference for large-delayed reinforcer	Cardinal et al. (2001)
NAc core	Delayed reinforcement choice task	+	Decreased mean percentage preference for delayed-certain reinforcer	Pothuizen et al. (2005)
NAc shell	Delayed reinforcement choice task	–	No effect	Pothuizen et al. (2005)
NAc (core + shell)	Adjusting amount schedule	–/+	No effect on indifference point with a constant delay duration; increased indifference point and flattened temporal discounting curve when delay duration changed across sessions	Acheson et al. (2006)
NAc core	Progressive delay schedule	+	Steepened temporal discounting	Bezzina et al. (2007)
NAc core	Adjusting-delay schedule	+	Increased preference for smaller-immediate reinforcer	da Costa Araujo et al. (2009)
Probability discounting tasks				
NAc core	Probabilistic choice task	+	Increased indifference point, decreased mean percentage preference for large-uncertain reinforcer	Cardinal and Howes (2005)
NAc (core + shell)	Adjusting amount schedule	–/+	No significant effect, but a tendency to discount more	Acheson et al. (2006)

Abbreviations: 5CSRT, five-choice serial reaction time; DRL, differential reinforcement of low rates; NAc, nucleus accumbens; SSRT, stop-signal reaction time.
* +, effect; –, no effect; –/+, statistically non-significant effect or effect under certain conditions.

by experimental lesions, electrical stimulation and application of pharmacological agents. In humans, the role of the NAc in impulsivity has predominantly been investigated by neuroimaging studies. In this section, we will review and discuss the effects of NAc lesions on the performance in behavioral tasks related to impulsivity. Subsequently, we will present an overview of the neuroimaging findings in humans.

4.1. Effects of nucleus accumbens lesions on impulsivity

The vast majority of studies in which the function of the NAc in impulsivity has been investigated are lesion studies in animal models (Table 1).

4.1.1. Attentional/reflection impulsivity

Resistance to interference either by irrelevant stimuli or by earlier associations which are not valid in the present conditions is a form of cognitive inhibition (Barkley, 1997). Failure in this form of inhibition may lead to a failure to focus attention and easy distractibility. In rats it has been shown that lesions of the NAc core and shell had no effect on accuracy or rates of omission errors in the 5CSRT task (Cole and Robbins, 1989). However, increased interference due to enhancement of attention to background stimuli has been reported in cats and mice with NAc lesions (Ammassari-Teule et al., 2000; Montaron and Fabre-Thorpe, 1996). In addition, distinguishable effects of NAc core and shell lesions in some attention-related tasks, such as prepulse inhibition and latent inhibition have been reported (Jongen-Relo et al., 2002). Latent inhibition (LI) is a form of salience learning in which repeated nonreinforced preexposure to a neutral stimulus reduces the stimulus' subsequent associability (Lubow and Moore, 1959). Therefore an intact LI renders the animal's ability to prevent distraction by insignificant stimuli, whereas inhibition of LI may facilitate cognitive and behavioral switching, enhancing adaptation to new environmental circumstances (Weiner, 1990; Weiner and Feldon, 1997). It has been shown that LI remained intact following entire NAc or core lesions, but impaired by NAc shell lesions (Jongen-Relo et al., 2002; Pothuizen et al., 2005; Tai et al., 1995; Weiner et al., 1996, 1999). These findings suggest that the NAc core is mediating the switching, facilitating flexible responding in rats (Gal et al., 2005). This flexibility may serve adaptation, however, when it is excessive, it may lead to distractor interference.

Indeed, a marked role played by the core subregion in flexibility is supported by evidence from studies investigating executive functions. Set shifting, changing a behavioral strategy when necessary (e.g. shift from matching to nonmatching rule in a behavioral task), has been shown to be impaired with lesions of the NAc (Dunnett, 1990; Reading and Dunnett, 1991). NAc core lesions have been shown to impair set shifting, whereas lesions restricted to the shell had no affect (Floresco et al., 2006). So the core subregion is thought to facilitate the acquisition and maintenance of novel behavioral strategy, this way rendering the subject the flexibility necessary for adaptation.

Reaction time, which has been assumed as a reflection of cognitive processes preceding a behavioral response, has not been shown to be significantly different in rats with NAc lesions (not

selective to the core or the shell) from control rats in assessments with 9 Holes Boxes operant chambers (Brown and Bowman, 1995). In accordance with these findings, selective NAc core lesions had no significant effect on the RT in the 5CSRT task (Christakou et al., 2004) and in the stop-signal RT test (Christakou et al., 2004; Eagle and Robbins, 2003b). However, since multiple cognitive processes underlie the RT, these findings should not be interpreted as the absence of an effect of NAc lesions on cognitive processes preceding the execution of the behavioral response.

As a conclusion, findings reviewed above imply that the NAc is involved in attentional processes. The lack of influence on errors of omission, accuracy, and RT supports that NAc lesions do not interfere with the collection of task-relevant information. However, NAc core and shell are shown to exhibit opposing effects on the flexibility of the allocation of attentional resources. Yet, lesion studies in rats provide no evidence of NAc involvement in impulsive reflection.

Attention to stimulus features, and flexibility in the allocation of cognitive resources among stimuli and tasks are processes regulated by subregions of the prefrontal cortex (Dalley et al., 2004). The courses of sensory processing and attention are known to be influenced by the significance of the stimulus (Vuilleumier, 2005). The significance of a stimulus is determined by its integral representation with respect to a multitude of features. The involvement of the NAc as an element of the frontrostriatal circuits in these functions will be discussed in further detail in the next section.

4.1.2. Impulsive choice

The selection of an action in response to stimuli is guided by the assessment of each alternative stimulus, outcome of responding to this stimulus, and the cost of responding. This evaluation influences the pattern and direction of behavioral output. NAc, due to its position between limbic and motor structures, is proposed to be responsible to integrate a variety of information to modulate behavior (Mogenson et al., 1980). In this section, we will review the involvement of NAc with the construction of affective and motivational representation of alternative response options, and choice among them.

4.1.2.1. The involvement of the NAc in incentive salience attribution, hedonic processing, and valence coding. Incentive salience attribution: Incentive salience attribution is the process where the neural representation of a stimulus (or outcome) is transformed into an object of attraction with the incorporation of motivational features, leading to approach behavior (Berridge and Robinson, 1998). The incentive salience hypothesis proposes two closely interrelated, but dissociable psychological components which involve different neural substrates in reward-related processes: liking and wanting (Kalivas and Volkow, 2005; Robinson and Berridge, 2000). The former corresponds to the hedonic impact of the reward, which is the affective component of a reward; whereas the latter is related with the incentive salience attributed to it. There is strong evidence supporting the view that the dopaminergic system, especially within NAc, plays a central role in assigning incentive salience, rather than in hedonic assessment (Berridge, 2007; Berridge and Robinson, 1998).

Stimuli and events may acquire salience through learning. Both stimulus-response and response-outcome associations can be learned in rats with NAc lesion (Cardinal et al., 2002a). Through a detailed analysis of research findings in rats, Yin and associates concluded that the NAc is neither necessary nor sufficient for instrumental learning (Yin et al., 2008). Interestingly, learning and execution of instrumental responding involving delayed reinforcement were impaired in rats with NAc core lesions, whereas learning was not influenced in the case of immediate delivery (Cardinal and Cheung, 2005). These findings suggest that the NAc core is involved in both learning and execution of reinforcement of actions when the outcome is delayed. Furthermore, the sensitivity of rats to instrumental contingency degradation was not changed with selective lesions of the NAc core and shell, whereas, the sensitivity to outcome devaluation was reduced following core lesions, but was not changed following shell lesions (Corbit et al., 2001). Similarly, there is evidence suggesting the involvement of NAc core in Pavlovian conditioning, through which stimuli can gain incentive salience, in studies investigating lesion effects on Pavlovian autoshaping and Pavlovian-instrumental transfer (Cardinal et al., 2002b; Parkinson et al., 2000).

Dissociation of "wanting" into two separate components has also been proposed: appetite to consume and working to obtain the reward (Salamone and Correa, 2002; Salamone et al., 2003, 2007). The latter component refers to the tendency to work for motivational stimulus and the activation required to employ instrumental actions despite of the constraints and effort-related burden associated with it. Based on a series of experiments, Salamone and associates emphasized the significant role played by the NAc in decision-making involving effort-related assessment of behavioral options (Salamone et al., 2007). The dopaminergic activity in the NAc core subregion was shown to be significantly influential (Nowend et al., 2001; Sokolowski and Salamone, 1998). Recently, the disconnection of the anterior cingulate cortex and the NAc core in rats was found to impair effort-based decision-making, and reduce the preference of high-effort option (Hauber and Sommer, 2009).

These findings provide significant evidence on the involvement of the NAc, especially the core subdivision, in the acquisition of motivational value (incentive salience) through different forms of learning. In a recent review of research findings on reward-related learning, it was proposed that the dorsal striatum was required for learning and expression of instrumental responses, whereas NAc contributed significantly to the motivational regulation of instrumental performance, in addition to its role in acquisition and expression of responding in Pavlovian conditioning (Yin et al., 2008). The authors also proposed a distinct pattern of involvement for mesolimbic and nigrostriatal dopaminergic systems in the regulation of these learning processes. The NAc may influence the activity in both systems via its projections to the two main sources of dopamine, the VTA and substantia nigra pars compacta (see Section 2.3). The NAc does not execute these processes alone but functions as a component of brain circuits which include cortical and subcortical structures such as the prefrontal cortex and amygdala (Balleine and Killcross, 2006; Dalley et al., 2004).

Hedonic processing: Hedonic evaluation of the outcome, which is the second major components of reward-related processes, is proposed to employ specific neural structures including the NAc shell and ventral pallidum (Berridge and Robinson, 2003). Opioid hedonic hotspot, where local mu-opioid receptor agonist injections trigger responses identified as reactions arising from 'liking', was found in the rostral and dorsal one-quarter of the medial NAc shell (Pecina and Berridge, 2005). In this experiment, all other parts of the NAc, including the core subdivision, failed to elicit similar responses. Moreover, recent research findings, which implicate the opioid system in incentive salience ('wanting') as well, led to the suggestion that opioid neurotransmission exhibited an anatomically dissociable role in reward-related processes: the hedonic hot spot in the shell was mainly responsible for hedonic assessment, whereas incentive salience attribution function was diffusely distributed throughout the NAc (Pecina, 2008).

Valence coding: Distinguishing between positive (appetitive/reward) and negative (stress/defense) motivational features of outcome alternatives requires the evaluation of the response options with regard to their valence. The NAc is known to be involved in

responding to a wide range of unconditioned stimuli, both aversive and appetitive in nature (Kelley and Berridge, 2002). Moreover, the NAc is involved in conditioning to aversive events (Salamone, 1994; Schoenbaum and Setlow, 2003; Setlow et al., 2003). There is evidence for a subregion-specific involvement of the NAc in valence evaluation; dissociable effects of NAc core and shell lesions with respect to the pattern of conditioning to stimuli in appetitive and aversive procedures have been reported (Cassaday et al., 2005; Sellings et al., 2008). Early findings suggested that the processes involving aversion were related to alterations in dopamine levels in the NAc shell (Deutch and Cameron, 1992; Fenu et al., 2001). Glutamatergic and GABAergic modulations of the local microcircuitry in subregions of the shell, but not the core, were found to have anatomically distinct effects on positive and negative motivation, indicating a rostrocaudal grading in bivalent responding (Reynolds and Berridge, 2002, 2003). This modulation was shown to be influenced by the local dopaminergic activity; dopamine antagonist blocked the behavioral effects of glutamatergic modulation (Faure et al., 2008). These findings suggest that the assessment of valence requires different subregions of the NAc, and that the mesolimbic dopaminergic system significantly modulates this process, probably through modification of afferent glutamatergic input to the NAc (from prefrontal cortex, hippocampus, and amygdala).

In summary, through their connections with cortical and subcortical structures, the core and the shell subdivisions exhibit a significant influence on the evaluation of valence and salience. The shell appears to be predominantly involved in the assessment of valence (positive/negative), as well as unconditioned responses. The core, on the other hand, has a significant contribution to the assignment of motivational salience through learning processes, which have important influence on instrumental performance, both in conditioned preparatory responses and goal-directed actions. A subregion of the shell is critical in hedonic evaluation. Overall, these findings identify a key role for the NAc in the assessment of response choices.

In addition to guiding the selection among multiple options, these assessments assist in directing the attentional resources appropriately. These assessments and selection processes involve cortico-basal ganglia networks and they are strongly influenced by other neural structures, such as the amygdala and hippocampus as well. Strong evidence suggests that the neurochemical modulation of afferent projections of the NAc regulates the function of these networks (Goto and Grace, 2008; Kelley and Berridge, 2002). This conclusion fits to the earlier proposal of primary and secondary motivation circuits by Chambers and Potenza (2003) that the frontostriatal circuit is dominant in this component of decision making, and it depends on additional information provided by other subcortical structures.

4.1.2.2. Temporal discounting. The initial finding indicating the involvement of the NAc on impulsive choice was obtained by Cardinal and co-workers who reported that bilateral lesions of the NAc core, but not of the anterior cingulate cortex or medial prefrontal cortex, resulted in more impulsive choices in a temporal discounting paradigm, delayed reinforcement choice task (Cardinal et al., 2001). Before surgery, all rats exhibited a within-session shift in preference from the large to small reinforcer as the delay for the larger reinforcer increased. After the surgery, though all groups exhibited a similar shift in preference with increasing delay, the percentage of choice of the small (immediate reinforcer) was significantly higher through the entire session in rats with NAc core lesions compared to sham-operated animals. The core lesions were found to increase impulsive choice; the effect was described as an "intolerance to delay".

Pothuizen and associates studied the effects of NAc lesions in a modified version of the delayed reinforcement choice task (Pothuizen et al., 2005). The authors evaluated the effect of increasing delay in the preference between reinforcers of different certainties, i.e. immediate-uncertain and delayed-certain, with identical amounts. They found that not all delay durations, but a delay of 20 s in reinforcer delivery resulted in a progressively increased choice of immediate-uncertain reinforcer by NAc core lesions. Thus, the NAc core lesions were found to decrease the choice of delayed alternative, whereas NAc shell lesions had no influence on choice. These results may be considered as an extension of earlier finding (Cardinal et al., 2001); however, the differences in certainty among response options in this version of the task has to be kept in mind.

However, NAc lesions in rats, not restricted to the core or the shell, were reported to have no effect on temporal discounting in an adjusting amount procedure (Acheson et al., 2006). Rats were given a choice between a delayed constant volume of water and an immediate adjusted amount of water. Magnitude of adjusting reinforcement was increased when delayed alternative was chosen, and decreased after a choice of immediate adjusted alternative. The point where the adjusted alternative was chosen with the same frequency as the delayed alternative was termed as the indifference point. It was found that there was no significant effect of NAc lesions on the indifference point when the rats were tested on discounting with a constant delay of reinforcement delivery. In the second phase of the study, temporal and probability discounting curves were derived through changing the length of delay in the reinforcement delivery among the sessions. The NAc lesioned rats were found to have flatter temporal discounting curves than the sham group (i.e. making less impulsive choices) only when the delay was changed between sessions. The authors argued that the NAc lesions impaired learning or adapting to changes in delay reinforcement but did not affect tolerance to delays.

The findings of Acheson et al. (2006) are not in line with the earlier results of Cardinal et al. (2001). However, there are important differences between those two studies which should be considered. First of all, lesions in the study by Cardinal and colleagues were restricted to the core subregion of the NAc, whereas in the study of Acheson and colleagues lesions included the entire NAc. Even though there is some evidence that the lesions of the shell subregion do not affect impulsive choice in temporal and probability discounting procedures (Pothuizen et al., 2005), it seems unlikely that the difference in results are due to the inclusion of the NAc core in the lesion site. Lesions of the entire NAc may have different consequences than the summation of the effects of lesions in one of these two structures. The second important difference is the procedure to measure impulsive choice, as described above. Finally, there are some differences in the reinforcement protocols, for example the delay durations introduced before reinforcement were shorter (1–8 s) in the study of Acheson et al. (2006), compared to delay durations ranging between 10 and 60 s in the study by Cardinal et al. (2001), and 20 s in the study of Pothuizen et al. (2005).

Bezzina and colleagues studied the effects of quinolinic acid-induced lesions of the NAc core on delayed reinforcement using a quantitative analysis (Bezzina et al., 2007). The authors applied a progressive delay schedule, with an approach based on the multiplicative hyperbolic model of intertemporal choice (Ho et al., 1999) which permits discriminating the influence of delay discounting and the effects of sensitivity to reinforcer magnitude. Indifference functions of the rats were derived from the sessions in which the rats with NAc core and sham lesions were expected to choose between two levers associated with large or small amount of reinforcer with different delay durations. Delay durations were changed stepwise in geometrical manner in both levers enabling the generation of accurate discounting curves. The indifference

functions derived from the response plots of the rats in each group have several parameters. A change in the slope of the function implies a change in magnitude sensitivity, whereas, the intercept of the function is influenced jointly by delay discounting and magnitude sensitivity. The slope of the linear indifference function is not different between the sham and core-lesioned animals. However, the intercept of the indifference function was significantly lower in the NAc core-lesioned subjects than the intercept in the sham group. A selective effect of a lesion on this parameter is an indicator of higher rate of delay discounting, i.e. higher impulsive choice in the NAc core-lesioned subjects. This finding is in line with the results of Cardinal and colleagues (Cardinal et al., 2001). With further analysis of the preferences, it was shown that discrimination of within-session changes in delay of the delivery of the large reinforcer was less precise in animals with NAc core lesions. Thus, this finding is supporting the results of Acheson and colleagues (Acheson et al., 2006). However, Bezzina and colleagues have shown that the difference between core lesioned and sham rats in high rate of delay discounting cannot be explained solely on grounds of discrimination failure (Acheson et al., 2006; Bezzina et al., 2007). The authors concluded that higher rates of delay discounting and failure in discrimination of changes in delay both influence impulsive choice in rats with NAc core lesions (Bezzina et al., 2007). Moreover, in a recent study using a adjusting-delay approach lesions restricted to the core part of the NAc did not modify discrimination of delay changes, but altered intertemporal choice behavior increasing the choice of immediate reinforcement (da Costa Araujo et al., 2009).

4.1.2.3. Probability discounting. The NAc core lesions were reported to influence behavior in a probability discounting task (Cardinal and Howes, 2005). Rats had to choose between a small-certain reinforcer ($p = 1$) and a larger reinforcer with varying probability (p between 0.0625 and 1) within discrete trials. Preoperatively, with decreasing probability, the choice of the larger reward was decreasing in all rats. Postoperatively, after a transient indifference, there was a stable preference for a small-certain reward in core-lesioned animals, compared to control subjects. This was accepted as an indication of increased probability discounting in rats with NAc core lesions. It was also shown that rats in both groups discriminated the large reinforcer from the small reinforcer, and also the certain large reinforcer from the uncertain large reinforcer. These results were interpreted as NAc core lesions making the animals "risk aversive". The authors proposed a role for the NAc core in promoting the selection of and attributing salience to uncertain rewards.

However, in a delayed reinforcement choice task in which delayed choice was associated with higher degree of uncertainty, Pothuizen and associates found increased preference of the immediate-uncertain reinforcer in rats with NAc core lesions (Pothuizen et al., 2005). Even though this may seem contradictory to the findings of Cardinal and Howes, it should be kept in mind that the delayed reinforcement choice task used by Pothuizen and associates included temporal discounting (Cardinal and Howes, 2005; Pothuizen et al., 2005).

Acheson and colleagues reported that the NAc lesions, including both subregions, did not affect the indifference points and probability discounting curves when the rats were tested in a discounting task with a fixed probability of reinforcement (p between 0.1 and 1.0) using the adjusting amount procedure (Acheson et al., 2006). Also, no significant effects were found when rats trained with a fixed probability ($p = 0.4$) were challenged with acute changes in probability ($p = 0.2$, 0.4 or 0.7). The authors reported a tendency for NAc lesioned rats to discount more, although this was not found to be statistically significant. These findings are not confirming the earlier report on increased probability discounting (Cardinal and Cheung, 2005). The differences in the lesion site, the protocol and the procedure of measuring impulsive choice with probability discounting between these two reports should be considered when comparing these results (see Section 4.1.2.2).

Two major possible confounding factors in the studies about impulsive choice reviewed above are the altered sensitivity to the magnitude of the reinforcer, and motivational state of the subject (e.g. food deprived). Lesions of the NAc core or entire NAc were not found to impair the rats' ability to discriminate reward size; therefore did not influence instantaneous reinforcer value (Cardinal and Cheung, 2005; Cardinal and Howes, 2005). As for the motivational state, satiety itself was not found to be a determinant of increased impulsive choice following NAc core lesions (Cardinal and Howes, 2005; Cardinal et al., 2001).

Altogether, evidence reviewed above suggest that the NAc core is a component of the brain circuitry engaged with temporal discounting function and loss of structural integrity promotes impulsive choice in rats. Although there is less consistent evidence, the NAc core is involved in probability discounting, and limited evidence suggest that lesions of the NAc core promote less impulsive choices. This issue warrants further investigation with recently developed animal models of gambling (Madden et al., 2007; van den Bos et al., 2006). Nevertheless, the NAc core is proposed to contribute to reinforcement and choice of temporally distant and uncertain rewards. The principal role of the NAc core, compared to the NAc shell, in these reinforcement paradigms is in accordance with the findings on its contribution to the motivational features in instrumental performance as discussed earlier (see Section 4.1.2.1). The role of the NAc shell is not extensively investigated in these paradigms, however in one study lesions restricted to the NAc shell failed to show a significant influence (Pothuizen et al., 2005). The role of the NAc in choice involving delayed and uncertain aversive outcomes still requires further elucidation.

4.1.3. Response inhibition

Impulsivity may be expressed as an individual's failure in initiating a response with appropriate timing, inhibiting a prepotent response when it is inappropriate, and inhibiting competing responses or responses which lose their priority. SSRT tasks were used in research on response inhibition in humans and rodents (Eagle and Robbins, 2003a,b; Herrmann et al., 2003; Logan et al., 1984; Winstanley et al., 2006). Patients with basal ganglia lesions were reported to have deficits in response inhibition (Rieger et al., 2003). However, there is no report on effects of selective NAc lesions. The striatal involvement in response inhibition was supported with a lesion study in rats, where lesions of the mediodorsal striatum were shown to result in impairment of inhibitory function (Eagle and Robbins, 2003a). However, selective lesion of the NAc core had no effect on SSRT task performance (as measured by the inhibition function), and all the secondary parameters of this task, i.e. go-trial accuracy or mean reaction time (Eagle and Robbins, 2003b).

Although the assessment of inhibitory functions with SSRT failed to support the involvement of NAc, in other tasks there are findings suggesting otherwise. Christakou and associates have shown that bilateral lesions of the NAc core resulted in increase in parameters of the 5CSRT task reflecting failure in inhibitory control of responding, such as perseverative behavior, and to a lesser extent (not statistically significant) premature response (Christakou et al., 2004). Lesions disconnecting the medial prefrontal cortex from the NAc core resulted in a similar pattern of increased disinhibition in rats as well, supporting a frontostriatal network in inhibitory regulation. However, the failure in inhibition was only observed in trials which followed failed trials. In a recent study,

these findings were not replicated (Murphy et al., 2008). Neither core nor shell lesions were found to result in an increase in premature or perseverative responses; even in trials following failed ones. Nevertheless, this latter work provided evidence on dissociative involvement of the subdivisions of NAc in response inhibition. Lesions of NAc core potentiated, whereas lesions of NAc shell attenuated the effect of systemic administration of amphetamine, which increased premature responses (Murphy et al., 2008).

The dissociation in the roles of the NAc core and shell subdivisions in premature responding was recently confirmed with electrical stimulation in rats (Sesia et al., 2008). Deep brain stimulation (DBS) has been developed as an alternative for ablative procedures and has proven to have critical advantages such as being reversible, the stimulation can be switched off, and adjustable, the stimulation parameters can be adjusted (Temel and Visser-Vandewalle, 2006; Temel et al., 2004; Wichmann and Delong, 2006). Sesia and associates applied DBS selectively to the NAc core and shell subregions, and investigated the effects of stimulation in a RT test (Sesia et al., 2008). They evaluated premature responses, and reengagement during the intertrial intervals. It was shown that premature responses increased with stimulation of NAc shell. NAc core stimulation decreased premature responses, although lesions of the same structure were earlier reported to increase these responses (Christakou et al., 2004). However, this type of difference between the effects of stimulation and ablative lesions is frequently reported, and is proposed to derive from the underlying mechanism of action of DBS (Liu et al., 2008).

Pothuizen and colleagues applied the DRL task with fixed periods of 4, 8, 12, 18 s in rats with selective lesions of the NAc core and shell (Pothuizen et al., 2005). The mean number of responses per reward was calculated for each group for each session. In the DRL-18, rats with NAc core lesions had significantly higher mean number of responses per reward compared to both control rats, and rats with shell lesion. The performance of NAc shell lesioned animals was not different from control subjects. Rats with bilateral nonrestrictive lesions of the ventral striatum (including, but not limited to the NAc) were earlier reported to show increased disinhibition of response in the DRL (Reading and Dunnett, 1995).

Findings reviewed above, suggest a task dependent involvement of the NAc core in response inhibition. Although the evidence is not sufficient to reach sound conclusion, the core lesion can be proposed to hinder response inhibition in tasks of action restraint, such as 5CSRT and DRL tasks.

4.2. Functional imaging findings on the role of the NAc in impulsivity

Neuroimaging studies related to impulsivity mostly investigate the signal activity pattern in different brain regions during different stages of behavioral tasks related to decision making: reward anticipation following the presentation of the stimuli, selection of an action and reward delivery. However, these processes are not absolutely temporally discrete, and sometimes participate in behavior simultaneously. Nevertheless, in recent years manipulations in study designs enabled the evaluation of each process with a higher degree of selectivity. In addition, there are problems with the definition of the anatomical borders of the region of interest. Thus, some of the imaging studies reviewed below studied the activity levels in the ventral striatum, which includes the NAc but is not limited to it.

The neurophysiological processes responsible for the changes observed in functional neuroimaging methods have critical importance in the interpretation of these findings. It has been proposed that fMRI measures integrated activity of large pools of neurons within the regions of interest determined by the researcher (Logothetis, 2003). The signal activity is suggested to arise mainly from postsynaptic processes, reflecting the afferent projection activity to the region of interest. Recently, it was proposed that dopamine release mediated changes in postsynaptic membrane potentials in the NAc, via occupation of postsynaptic dopamine D1 receptors, underlied increased signal activity measured by the fMRI (Knutson and Gibbs, 2007). With regards to the neurochemical modulation of the afferent input activity of the NAc (see Section 4.3), the proposed association between the activity in imaging studies and dopamine activity in the NAc merits further investigation.

In following sections, we will review the findings on signal activity changes in the ventral striatum during decision-making behavior in humans. Following a brief review of the changes in activity related to varying features of the stimulus and associated outcome, imaging findings on the selection process will be presented. The majority of the studies reviewed here involved functional magnetic resonance imaging (fMRI) in healthy volunteers, unless mentioned otherwise.

4.2.1. Resistance to interference

Tasks which require inhibition of proactive interference, such as the Stroop's, have been investigated in humans with functional imaging, revealing distinct functional neuronal systems involving various cortical regions (Egner and Hirsch, 2005; Jonides and Nee, 2006; Liu et al., 2004; Melcher and Gruber, 2009; Nee et al., 2007). Some studies with emotional variants of the Stroop task in disorders with varying degrees of relationship with impulsivity, such as obsessive compulsive disorder, drug abuse, mood and personality disorders, have reported changes in the activity of frontostriatal circuits as well as the amygdala and hippocampus (Brewer et al., 2008; Malhi et al., 2005; Mitterschiffthaler et al., 2008; van den Heuvel et al., 2005; Wingenfeld et al., 2008). However, there is no report of altered ventral striatal activity related with resistance to proactive interference function.

A similar form of interference is related with the influence of earlier stimulus-response associations on acquisition of new associations depending on new circumstances. Resolution of this interference requires set shifting ability. Human imaging studies during tasks requiring cognitive set shifting, such as the Wisconsin Card Sorting Test, implicate frontostriatal circuits in this function (Monchi et al., 2001; Shafritz et al., 2005; Smith et al., 2004). Although different regions of the dorsal striatum are involved in this process, there is no evidence of altered activity in the ventral striatum.

4.2.2. Representation of valence and salience

Anticipation of reward, monetary as well as taste, and anticipation of aversive outcome, such as pain, have been reported to recruit ventral striatum in humans (Breiter et al., 2001; Knutson et al., 2001a,b). The role of the NAc in coding valence of both appetitive and aversive stimuli has been confirmed recently (Levita et al., 2009). The authors showed that both classes of stimuli activated the NAc, in a pattern that is distinguished from perceptual processes. However, there is evidence suggesting that dissociable patterns of neural activity, including differential involvement of the NAc, represent gain and loss related predictions. These studies suggest that the NAc is involved with gain anticipation, whereas loss related activity is observed in other structures, such as the amygdala, insula and some specific cortical regions (Liu et al., 2007; Yacubian et al., 2006).

The association of NAc activity with stimuli, not discriminating between positive and negative valence, led to the suggestion that the ventral striatal activity could be related to the salience of the stimulus (or event) rather than representing the valence (Jensen et al., 2007). The representation of the degree of salience by ventral

striatal activity has been suggested in earlier studies (Zink et al., 2004, 2006). However, a recent event-related fMRI experiment with neuroimaging coupled to a variant of monetary incentive delay (MID) task, in which valence and salience were manipulated independently, provided evidence indicating that the NAc activity was correlated with both valence and salience in healthy volunteers (Cooper and Knutson, 2008). In MID task, the subjects are presented with a cue which informs on the potential monetary gain or loss of varying magnitudes, in some forms also on the certainty of the gain or loss (Knutson et al., 2000). Following a brief period of anticipation, the subject responds to a target, in order to obtain feedback. This task provides a mean of evaluating reward anticipation and delivery separately via imaging methods.

These findings support the involvement of the ventral striatum/NAc in the evaluation of the response-relevant stimuli (cues), and in encoding of the valence and salience of the outcome. However, the pattern of valence coding in the NAc is still not clear considering the contradicting results obtained in studies comparing gain versus loss predictions in monetary tasks and these comparing appetitive versus aversive stimuli.

Findings of functional MRI during reward delivery are conflicting; there are reports of increased activity or absence of variation in activity in the ventral striatum (Breiter et al., 2001; Delgado et al., 2005; Knutson et al., 2001a,b; Liu et al., 2007). This controversy becomes explicable in the light of the findings of research which have shown that the activity level of the ventral striatum depended on the learning status of the subject as well as the phase of the reward process (Heekeren et al., 2007; O'Doherty et al., 2003). As learning proceeds, activity associated with the reward delivery shifts in time to shape activity associated with the reward predicting stimulus. Through evaluation of the prediction error, which refers to the difference between expected and actual outcome, subjects are believed to predict reward based on earlier experience, and adopt reward expectations with changes in reward contingency (Sutton, 1988). Initially unexpected reward delivery results in a positive prediction error, with successive experiences with the stimulus-reward contingency, the activity related to reward prediction error shifts to stimulus onset, rather than delivery. The prediction error influences action selection; the propensity to perform that action is modified according to the outcome. Prediction error representation has been repeatedly shown in fMRI experiments to involve the ventral striatum/NAc activity in various tasks in humans (Bray and O'Doherty, 2007; Breiter et al., 2001; Liu et al., 2007; Rodriguez et al., 2006; Rolls et al., 2008; Ullsperger and von Cramon, 2003). However, there is a recent report which failed to show a correlation between gain prediction error and the NAc, but with mesial prefrontal cortex activity (Knutson and Wimmer, 2007). O'Doherty and colleagues have reported a shift in the ventral striatum activity as the learning proceeded, from the reward delivery back to the presentation of the stimulus which became reward predicting through experience, supporting the role of the ventral striatum in reward reinforcement learning (O'Doherty et al., 2003). These findings on the representation of prediction error support the contribution of the activity in the ventral striatum/NAc in outcome evaluation.

The neuronal activity related with outcome prediction is elicited with the presentation of the stimulus and preceeds the action selection. Research on dorsal striatal activity, both by functional imaging and electrophysiology, revealed that premovement firing in striatal neurons facilitates the movement for which its firing is selective, and this firing is enhanced when this movement has been learned to result in reward (Nicola, 2007). The role of the striatum in this process was proposed to have a heterogenous pattern; a correlation with prediction error was shown mainly in the ventral striatum and caudate, whereas stimulus-action-dependent reward prediction was mainly correlated with putamen activity (Haruno and Kawato, 2006a,b). A recent model of cortico-basal ganglia networks emphasized the orbitofrontal-ventral striatal loop in object-based value representations and target selection, in addition to other loops specialized for context, space and movement-based representations (Samejima and Doya, 2007). It was proposed that the medial prefrontal cortex is functional in monitoring different levels of prediction errors and coordinating multiple value representations.

As a conclusion, functional neuroimaging studies in humans suggest that the ventral striatum is involved in reinforcement learning and assessment of outcome-predicting stimuli with regards to the valence and salience. Although the translation of NAc activity during outcome anticipation to the selection and execution processes is not clear, the subjective differences in representation of these features are expected to contribute to variations in behavioral output. Thus, it is tempting to suggest that the dysfunction in the ventral striatum is related to impulsive behavioral output. This link will be discussed in further detail in light of the imaging findings focusing on the selection phase in choices under different conditions in the following sections.

4.2.3. Choice involving temporal differences

During reward anticipation, the expected value of the outcome was found to be correlated with the activity of ventral striatum/NAc, as well as subdivisions of prefrontal cortex (Knutson and Cooper, 2005; McClure et al., 2004; Smith et al., 2009; Yacubian et al., 2006). In the presence of delays in outcome-delivery, the subjective value of the outcome is the product of the interaction between objective value of the outcome and the subject's delay discounting function. The ventral striatal activity was held responsible for tracking the representation of delayed monetary reward's subjective discounted value in one study (Kable and Glimcher, 2007), objective value in others (Luhmann et al., 2008). In a recent imaging study during a temporal discounting task, impulsive individuals showed diminished NAc activation to the magnitude of future reward (Ballard and Knutson, 2009).

Findings of some fMRI studies in healthy individuals on ventral striatal activity during selection among response options with temporal differences in delivery, provided evidence suggesting that separate neural systems mediate the selection of immediate and delayed options (see Table 2). The selection among choices with temporal differences in outcome-delivery of monetary reward, as well as primary rewards such as juice or water, was consistently associated with increased activities in in the lateral prefrontal and orbitofrontal cortices (McClure et al., 2004). The selection involving immediate reward option disproportionately increased the signal activity in the ventral striatum, medial prefrontal and medial orbitofrontal cortices, which were proposed to represent the 'impulsive' system. The selection of delayed option was associated with comparatively higher activities in the lateral prefrontal and lateral orbitofrontal cortices. Based on these findings, the authors proposed that the balance between these systems was influential in choice of delayed versus immediate reward choice (McClure et al., 2004). Interestingly, the selection of the immediate option was associated with increased activity in fMRI during a monetary decision-making task in a number of structures including the ventral striatum, only when it was gain-related (Xu et al., 2009). These findings support the significance of the ventral striatum in the selection of immediate outcome option, especially when it is gain-related.

Yet, some studies failed to show a correlation between ventral striatal activity and the selection of immediate outcome (Boettiger et al., 2007; Luhmann et al., 2008), even though intertemporal decision-making was shown to be associated with increased ventral striatal activity (Luhmann et al., 2008). Recently, the governing role of the dorsolateral prefrontal cortex in the selection

Table 2
Overview of studies which have evaluated the changes in striatal activity assessed with fMRI during tasks of decision-making involving choices with differences in time, probability, risk and uncertainty of the outcome.

Task	Signal activity in striatum	Reference
Choice involving temporal differences of the outcome		
Monetary decision-making task	Increased ventral striatal activity with decisions involving immediate outcome; Choice of immediate outcome associated with a trend of greater activity in the ventral striatum	McClure et al. (2004)
Decision-making with primary rewards (juice/water)	Increased ventral striatal activity with decisions involving immediate outcome; Choice of immediate outcome associated with a trend of greater activity in ventral striatum	McClure et al. (2007)
Monetary delay discounting task	No change in striatal activity with choice of both immediate and delayed outcome	Boettiger et al. (2007)
Gambling task involving temporal differences in outcome	Increased striatal (caudate) activity with decisions including intertemporal differences; No significant change in striatal activity associated with choice of immediate outcome	Weber and Huettel (2008)
Delay discounting task	Increased activity in caudate/putamen with choices of shorter delays; Caudate activity correlates with discounting for all delays	Wittmann et al. (2007)
Intertemporal choice task	Increased striatal activity associated with choice, greater with the choice of large outcome both in immediate and delay conditions	Luhmann et al. (2008)
Monetary decision-making task involving temporal differences in outcome both as gain or loss	No change in striatum with decisions involving intertemporal gain choices; choice of immediate outcome associated with increased activity in ventral striatum; Increased activity in dorsal striatum with decisions involving intertemporal loss choices; no change with choice of immediate outcome	Xu et al. (2009)
Choice involving probability, risk, uncertainty		
Event prediction test	Increased ventral striatal activity in decisions involving probability differences	Volz et al. (2005)
Gambling task involving probability differences in outcome	No change with decisions including probability differences; Higher ventral striatal activity predicted choice of low-probability option	Weber and Huettel (2008)
Financial decision-making task	Increased activity in NAc predicted switching to risk-seeking choices	Kuhnen and Knutson (2005)
Risk-taking task	Increased ventral striatal activity associated with the selection of high-reward/risk option	Matthews et al. (2004)
Wheel of fortune task	Increased ventral striatal activity associated with the selection of high-reward/risk option	Ernst et al. (2004)
Wheel of fortune task	No change in ventral striatal activity with the selection of low-probability/high-reward option compared to high-probability/low-reward option	Smith et al. (2009)
Iowa Gambling Task	No change in striatal activity with the selection of disadvantageous decks compared to advantageous decks	Fukui et al. (2005)
Iowa Gambling Task	Increased activity in caudate during anticipation, which was not different between decks; No change in striatal activity during outcome experiencing	Lin et al. (2008)

of the delayed option was supported by the finding that increased activity in this region was the only significant predictor of this preference (Weber and Huettel, 2008). In this fMRI study intertemporal decision-making in healthy individuals was shown to be associated with increased recruitment of the dorsolateral prefrontal cortex, posterior cingulate cortex, and striatum (specifically the caudate nucleus). These findings disagree with the assumption that regions including ventral striatum and medial prefrontal cortex are elements of a system promoting immediate choice (McClure et al., 2004). Rather, they provide support to the view that the ventral striatum/NAc is involved in the representation of expected value, although the selection of an option and following behavioral output is mediated via other frontostriatal circuits involving other parts of the striatum (Knutson et al., 2005; Samejima et al., 2005).

Hariri and colleagues investigated the ventral striatal signal activity with blood oxygenation level-dependent fMRI during feedbacks in a task involving positive and negative feedback with monetary reward in individuals whose delay discounting functions were derived by a different task applied in a separate session (Hariri et al., 2006). It was shown that individuals with higher ventral striatal activity associated with differential response to feedback covaried with the increased preference for smaller-immediate over larger delayed reward in a discounting task (Hariri et al., 2006). The individuals with the steepest temporal discounting, making more impulsive choices, showed largest magnitude of ventral striatum activation for monetary reward. In addition, individual discounting functions were found to be positively correlated with ventral striatal and medial prefrontal cortex activity, and negatively correlated with the activities in the dorsolateral prefrontal cortex and lateral orbitofrontal cortex. This diversity in the degree of correlations to discounting functions in different cortical areas supports the dissociable system activity proposed earlier (McClure et al., 2004). However, it should be noted that the activity signal related to discounting function in this study is assessed during feedback, instead of anticipation or selection (Hariri et al., 2006).

As a conclusion, there is convincing evidence showing that the magnitude of expected value is linked to the activity of the ventral striatum/NAc. Furthermore, there are findings implicating the

ventral striatum in the selection of immediate outcome, however, results are conflicting. Indeed, evidence on the correlation between ventral striatal activity and individual delay discounting functions, supports its involvement in intertemporal choices beyond the representation function (Hariri et al., 2006).

4.2.4. Choice involving probability, risk and uncertainty

Researchers have attempted to dissociate the neuronal representations of outcome probability and magnitude during reward anticipation using a probabilistic variant of the MID, in which cues indicated different levels of probability of the outcome, in addition to magnitude of gain and loss. The expected value (as a combined measure of magnitude and probability) was encoded by NAc activity (Knutson and Cooper, 2005). The probability of the outcome correlated with the activity in ventral striatum/NAc and medial prefrontal cortex (Preuschoff et al., 2006; Tobler et al., 2007; Yacubian et al., 2006), however not consistently (Knutson and Cooper, 2005; Smith et al., 2009). This discrepancy is proposed to be based on problems of temporal resolution, suggesting a time-limited representation of outcome probability in association with magnitude early in the anticipation period (Knutson and Bossaerts, 2007; Preuschoff et al., 2006). Nevertheless, these findings support the contribution of the ventral striatum/NAc to the neural representation of probability characteristic of an outcome. In addition, signal activity in NAc during reward anticipation in the probabilistic variant of the MID task was found to have a positive correlation with the subjects' scores in scales of novelty seeking and sensation seeking (Abler et al., 2006).

Risk and uncertainty are closely related with probability, however these concepts bear considerable differences. Risk is accepted as a measure of the unpredictability of the outcome, and it is proposed to be modelled as expected deviation from the expected outcome (Knutson and Bossaerts, 2007). Risk of an outcome refers to its variance; it is an inversely quadratic (inverted-U shaped) function of probability. Risk is maximal with a rewarding rate of 0.5, i.e. it is greatest at 50% probability. The changes observed with fMRI in the ventral striatal activity during anticipation plotted with different outcome probabilities indicated the representation of risk in the ventral striatum (Preuschoff et al., 2006). However, uncertainty refers to the variance of the probability distribution, and narrowing this variance renders the subject more confident on the rate of reward delivery (Tobler et al., 2007). It is not a characteristic of the decision-making context, unlike the probability and risk, rather it depends on the subject's quality of estimation, and it can be resolved by acquiring more data on response-outcome contingency (Rushworth and Behrens, 2008). This data acquisition process requires exploratory behavior, which is critical in the discovery of better reward options, but contains the risk of missing highly rewarded options. Neuroimaging studies on decision-making under uncertainty consistently failed to show alterations in ventral striatal activity (Volz et al., 2005; Daw et al., 2005; Abler et al., 2006; Tobler et al., 2007). To summarize, there is evidence on the contribution of the ventral striatum in risk anticipation, and no evidence related to uncertainty.

Findings reviewed until now were related to anticipation, broadly to the evaluation of outcome with regards to its probability, risk and uncertainty features. Increased activity in the ventral striatum during a decision-making task involving choices with different probabilities was reported in healthy volunteers (Volz et al., 2003). However, this study did not dissociate the anticipation and selection phases. The ventral striatal activity during selection among choices involving these features has been examined in several studies (Table 2). Greater activation during selection in the presence of probability variation, compared to delay and control conditions, was shown in the posterior parietal cortex, lateral prefrontal cortex, anterior cingulate cortex, insula, orbitofrontal cortex and posterior hippocampus (Weber and Huettel, 2008). But, no significant change in the ventral striatal activity was found. Nevertheless, increased activation in the ventral striatum, as well as in the insula, cingulate cortex, and ventrolateral prefrontal cortex, was shown to be the predictor of selection of riskier options (i.e. choice with lower probability).

Interestingly, event-related fMRI showed that higher NAc activation preceded switching to risk-seeking choices during a financial decision-making task (Kuhnen and Knutson, 2005), whereas higher insula activation preceded riskless choices. However, this study did not provide sufficient information on the translation of this risk anticipatory activity to the output of response selection. In financial decision-making tasks risk refers to the balance between potential gains and potential losses, therefore it is not only limited to the variance in the probability of the outcome, but also involves the magnitude. This underlies the distinction between risky and safe options in some gambling and decision-making tasks, such as the wheel of fortune task (Ernst et al., 2004). In this task a subject is asked to make decision between two choices of different magnitude and probability. In an fMRI study with the wheel of fortune task, the anticipation and selection were examined separately (Ernst et al., 2004). The selection phase recruited occipito-parietal, anterior cingulate and premotor cortical areas, whereas anticipation predominantly affected the ventral striatum. During anticipation no difference in the activity of the ventral striatum was observed between high-reward/risk and low-reward/risk conditions. During the selection phase, high-reward/risk conditions were associated with a greater signal activity in the ventral striatum, relative to low-reward/risk conditions. A similar increase in the ventral striatal activity was reported with selection of high-reward/high-risk options in a risk-taking task (Matthews et al., 2004). However, in a recent analysis of neuroimaging findings during wheel of fortune task, ventral striatal activity did not discriminate between the selection of a risky option (low-probability/high-reward) and a safe option (high-probability/low-reward) (Smith et al., 2009).

The Iowa Gambling Task (IGT) is one of the most frequently used tasks in the assessment of decision-making involving uncertainty, since explicit rules for gains and losses are not provided in the beginning of the task (Brand et al., 2006). This task requires the subjects to make choices among decks of cards which can be advantageous (immediate rewards but smaller long-term penalties) or disadvantageous (high immediate rewards followed by much higher long-term penalties) (Bechara, 2004; Bechara et al., 1994). Functional MRI during the selection phase of the IGT revealed that risky decision making was not associated with increased activity in the NAc, but with increased medial prefrontal cortex activity (Fukui et al., 2005). Striatal changes in the activity were not emphasized in earlier imaging studies with the IGT (Bolla et al., 2004). However, a recent report of brain activation mapping during different stages of the IGT in healthy subjects implicated the lentiform nucleus and insula in the anticipation, whereas the expression was dominated by a frontoparietal cortical network (Lin et al., 2008). Therefore, striatal activity is involved to a certain degree in some components of the IGT, but there is no evidence of ventral striatal involvement. Although initial trials in the IGT are accepted as decision-making under certainty, later trials represent decisions under risk (Brand et al., 2007), there is no imaging study investigating the influence of this dissociation on brain activity. Moreover, the IGT involves other high-level cognitive processes as well (Dunn et al., 2006), which may underlie the discrepancy between this finding and the earlier obtained with other risk-taking tasks. Nevertheless, there is no imaging evidence of ventral striatal involvement in decision-making under uncertainty, both in anticipation and selection processes.

Table 3
Overview of studies which have evaluated the changes in behavioral tasks of impulsivity with local modification of serotonin (5-HT, 5-hydroxytryptamine) receptor activity in the NAc.

Application	Site	Task	Effect on parameter*	Reference
5-HT depletion	NAc	5CSRT DRL-20	No change in premature response Response rate +	Fletcher et al. (2009)
5-HT2A antagonist 5-HT2C antagonist	NAc NAc	5CSRT 5CSRT	Premature response – Premature response +	Robinson et al. (2008)
5-HT2A/2C agonist	NAc core NAc shell	5CSRT 5CSRT	Premature response – Premature response –	Koskinen and Sirvio (2001)
5-HT1A agonist	NAc	Delay discounting	No change in impulsive choice	Winstanley et al. (2005b)

Abbreviations: 5CSRT, five-choice serial reaction time; 5-HT, 5-hydroxytryptamine; DRL, differential reinforcement of low rates; NAc, nucleus accumbens.
* +, increase; –, decrease.

To summarize, imaging findings on choice involving financial risk provide some evidence on the involvement of the ventral striatum/NAc in risk anticipation, however, its engagement in the selection requires further assessment. In those studies reporting a correlation between the signal activity in the ventral striatum/NAc and selection, increased activity tends to be related with impulsive choice (Ernst et al., 2004; Matthews et al., 2004).

4.2.5. Response inhibition

In imaging studies, response inhibition is usually assessed during a go/nogo task. Inhibition related activity is evaluated by comparing signal activation during no-go trials with that during go trials. Functional MRI studies in healthy individuals predominantly indicate the involvement of the frontal cortical regions and the anterior cingulate cortex in inhibition function (Chikazoe et al., 2007; Garavan et al., 2006; Nakata et al., 2008; Simmonds et al., 2008). However, connectivity analysis suggested that functional neural networks, probably including frontostriatal-thalamic projections, are responsible for response inhibition (Stevens et al., 2007). There are few neuroimaging studies indicating striatal involvement in response inhibition (Aron et al., 2003; Casey et al., 1997; Kelly et al., 2004). However, in an fMRI study of reponse inhibition in normal subjects, using a go/nogo task, no significant changes in striatal activity were found (Horn et al., 2003). Therefore, there is no imaging study which reports significant changes in the NAc activity associated with response inhibition.

4.3. Neurochemical modulation of the nucleus accumbens and its effects on impulsivity

Multiple neurotransmitter systems modulate the activity of the NAc. There is considerable heterogeneity in the anatomical distribution of projections, and receptor profiles in the subregions (see Section 2.3). Recent reviews provide a comprehensive picture of the neurochemical systems involved in impulsivity research (Cardinal, 2006; Dalley et al., 2008; Eagle et al., 2008; Winstanley et al., 2006). In this section, we will briefly review the role of serotonergic and dopaminergic systems in impulsive features related to the NAc.

Theories about the involvement of the serotonergic system in impulsive behavior are more than 20 years old (Soubrié, 1986). Modifications of local serotonergic activity in NAc influences impulsivity related parameters of behavioral tasks depending on the subregion of NAc, involved serotonin receptor subtype, and task (Table 3). There is strong evidence suggesting that the effects of serotonergic modifications on response inhibiton occur through its interaction with the dopaminergic system (Harrison et al., 1997; Koskinen and Sirvio, 2001). An interaction between the dopaminergic and serotonergic neurotransmission in the NAc has been reported in delay discounting paradigms as well (Winstanley et al., 2003, 2005b).

The NAc receives a rich dopaminergic innervation from the VTA and substantia nigra pars compacta, which are the source of dopamine for various brain areas (see Section 2.3). At the same time, the NAc projects to these areas as well. It is both a target and a potential regulator of the dopaminergic system. Studies on the effects of local modulation of dopamine receptor activity in NAc indicate major role of D1 receptor on reponse inhibition (Table 4), a finding in line with the results of systemic administration of dopamine receptor antagonist (van Gaalen et al., 2006).

The firing of dopaminergic neurons has been shown to quantitatively code the magnitude, probability, and the combination of these features of the outcome (Samejima et al., 2005; Satoh et al., 2003; Tobler et al., 2005). Therefore, this dopaminergic firing patterns may have a significant biasing effect in action selection, which involves in some conditions choice among options with

Table 4
Overview of studies which have evaluated the changes in behavioral tasks of impulsivity with local modification of dopamine (DA) receptor activity in the NAc.

Application	Site	Task	Effect on parameter*	Reference
Amphetamine	NAc	5CSRT	Premature response +	Cole and Robbins (1987)
DA depletion	NAc	5CSRT	Premature response – (transient)	Cole and Robbins (1989)
D-Amphetamine	NAc core NAc shell	5CSRT/FC	Premature response – Premature response +	Murphy et al. (2008)
D1 antagonist	NAc core NAc shell	5CSRT 5CSRT	Premature response – Premature response –	Pattij et al. (2006)
D2 antagonist	NAc core NAc shell	5CSRT 5CSRT	No change in premature response No change in premature response	
D1 agonist D2 agonist	NAc NAc	5CSRT 5CSRT	Premature response + No change in premature response	Pezze et al. (2007)
DA depletion	NAc	Delay discounting	No change in impulsive choice	Winstanley et al. (2005b)

Abbreviations: 5CSRT, five-choice serial reaction time; DA, dopamine; NAc, nucleus accumbens.
* +, increase; – decrease.

different temporal and probability characteristics. Dopamine in the NAc is proposed to have a regulatory role in the competition of behavioral output alternatives through direct and indirect output pathways, similar to the dorsal striatopallidal system (see Section 2.3) (Nicola, 2007). Through these output pathways, the NAc can inhibit or excite basal ganglia output neurons, which results in facilitation or suppression of behavior, respectively. Through an activity dependent coincidence detection mechanism involving interaction between glutamatergic afferents and dopaminergic activity in the NAc, dopaminergic activity strengthens the neural representation of certain behavioral output options (Floresco, 2007). This process leads to differences in cue-evoked firing patterns of NAc neurons. It was shown that dopamine enhanced the contrast between NAc neurons firing at different rates (Nicola et al., 2004). Furthermore, dopaminergic activity in NAc is not solely determined by dopaminergic projection neurons; the glutamatergic input from the hippocampus and basolateral amygdala to the NAc is known to facilitate the release of mesoaccumbens dopamine, through a glutamate depending mechanism within the NAc (Floresco et al., 2001).

In addition, this biasing effect has been shown to rely on modulation of the neuronal activity of the NAc, as well as facilitation or attenuation of the afferent projections to the NAc. The firing of NAc neurons is known to be modulated by the afferent input, rendering them more or less excitable (reviewed in O'Donnell et al., 1999). Spike activity in NAc requires a strong excitatory afferent drive, as it is the case with coincidental excitation from different sources (O'Donnell and Grace, 1995). The presynaptic glutamatergic inputs, and the intrinsic electrophysiological state of the postsynaptic NAc neurons is proposed to be under significant influence of dopamine (Floresco, 2007). Indeed, recently it was shown that the input from the basolateral amygdala was required for dopamine to enhance the spike firing of NAc neurons in response to reward predicting stimuli (Ambroggi et al., 2008).

The influence of different corticolimbic afferents on NAc is also regulated by a biasing action of dopamine. Synaptic input from the hippocampus, prefrontal cortex and amygdala has been shown to compete, facilitate or attenuate input by a certain projection, through synaptic plasticity (Goto and Grace, 2008). Dopamine in the NAc was shown to have an important role in the attenuation and facilitation of the effect of the prefrontal cortical and hippocampal input, in a dopamine receptor subtype and dopamine release pattern specific manner (Goto and Grace, 2005).

Neurochemical modulation of the neuronal activity of the NAc and selection of its afferent connectivity with other cortical and subcortical structures is one of the essential determinants of goal-directed behavior. Plasticity in these interactions involving dopaminergic and glutamatergic projections is proposed to be responsible for age related changes in impulsive behavior (Ernst and Fudge, 2009; Hinshaw, 2003). Similarly, neuroplastic changes in these interactions have been implicated in development of addiction (Kalivas and Volkow, 2005).

Recent genetic research provided evidence on the significance of the dopaminergic system genes in individual variations in impulsivity (Congdon et al., 2008; Golimbet et al., 2007). In rats, a significant difference in dopamine D2/3 receptor availability in NAc was reported to be associated with impulsivity (Dalley et al., 2007). Interestingly, in a recent work, using imaging genetic approach, genetic variations in dopamine neurotransmission were found to significantly predict the variability in reward-related activity in the ventral striatum (Forbes et al., 2009).

In addition to the dopaminergic and serotonergic system, recent research emphasizes the role of noradrenergic system. Atomoxetine, a selective noradrenaline reuptake inhibitor, was reported to decrease diverse features of impulsivity assessed by different tasks in rats, such as the SSRT, 5CSRT tests and delay discounting task (Robinson et al., 2008). It is an effective treatment option for children and adults with ADHD (Adler et al., 2008; Prasad et al., 2007). Since the NAc shell subdivision is the only part of the striatum receiving noradrenergic projections (see Section 2.3), these findings may have an important impact in impulsivity research.

5. Discussion: nucleus accumbens and impulsivity

Impulsive acts and decisions are related to individual differences in the neural representations of stimuli/events (Chambers and Potenza, 2003). The NAc plays an important regulatory role in the neural representation of response options, as shown by functional neuroimaging studies in healthy individuals. Although some studies showed the involvement of the NAc in salience or valence representation, recent findings support the recruitment of the NAc in coding of both salience and valence (Cooper and Knutson, 2008). There is more consistent evidence on the representation of gain-related outcome in the NAc, rather than loss, in monetary decision-making tasks (Liu et al., 2007; Yacubian et al., 2006). However, changes in the NAc activity have been shown to be related to both appetitive and aversive stimuli (Levita et al., 2009). Animal studies support the involvement of the NAc core subdivision in the acquisition and expression of incentive salience, and the NAc shell subdivision in hedonic assessment and bivalent coding (Pecina and Berridge, 2005). The contribution of the NAc in these processes appears to rely on neurochemical modulation, especially by the dopaminergic, glutamatergic and opioid systems, rather than its structural integrity. Inappropriate representation of a behavioral option in action selection circuits may facilitate impulsive behavior. The NAc, as a key structure in the evaluation of stimuli/events, can contibute to the construction of improper representations either by genetically determined differences in its receptor profile, or by changes in its activity pattern in frontostriatal circuits acquired through various learning processes (Kalivas and Volkow, 2005; Dalley et al., 2007; Forbes et al., 2009).

The role of the NAc in impulsive preference among response options has been extensively studied with discounting paradigms. Research on impulsive choice provided strong evidence on the effects of the NAc core, but not of the shell, lesions on intertemporal decisions, rendering the subject more impulsive (Cardinal et al., 2001; Pothuizen et al., 2005; Bezzina et al., 2007; da Costa Araujo et al., 2009). The NAc core appears to promote the preference of the delayed reinforcement. Lesions restricted to the core were shown to impair instrumental learning in the case of delayed reinforcement (Cardinal and Cheung, 2005). Furthermore, there are fMRI findings suggesting that the discounted value of the outcome is represented by the NAc activity (Kable and Glimcher, 2007). Therefore, findings in lesion studies may be the result of the bridging provided by the core subdivision. However, there is more consistent imaging evidence indicating that the objective value of reinforcer is represented by the NAc activity (Luhmann et al., 2008). In addition, individual impulsive choice tendency was found to be related with the altered NAc activity in response to outcome magnitude (Hariri et al., 2006; Ballard and Knutson, 2009). More importantly, in spite of conflicting findings, the selection of immediate reinforcement has been repeatedly reported to be associated with increased activity in the ventral striatum (McClure et al., 2004). Thus, lesions of the NAc, especially the core subdivision, disrupts intertemporal decision-making leading to impulsive choice, and change in its signal activity, which probably represents an interplay of neurotransmitters influencing its afferent connectivity, is associated with impulsive choice.

Probability and risk, but not uncertainy, have been shown to be represented by ventral striatal activity (Preuschoff et al., 2006).

Imaging studies with various task have implied an association between increased ventral striatal activity and selection of less safe option (Ernst et al., 2004; Matthews et al., 2004; Kuhnen and Knutson, 2005; Weber and Huettel, 2008). However, there are also reports which failed to find this association (Fukui et al., 2005; Smith et al., 2009). Nevertheless, lesions of the NAc increased probability discounting, and NAc core lesions rendered rats risk-averse (Acheson et al., 2006; Cardinal and Howes, 2005). Therefore, the NAc, especially the core subdivision, is a part of the neural circuit regulating choice involving probability, and its activity promotes the selection of options which are less safe.

This dissociation in the role of the NAc in impulsive choice is in accordance with the multifaceted impulsivity concept. Temporal and probability discounting differences are proposed to underlie impulsive decision-making in some clinical and non-clinical conditions in humans (Bickel et al., 2007; Critchfield and Kollins, 2001; Holt et al., 2003; Reynolds et al., 2004; Yi et al., 2007). It is not certain whether temporal discounting and probability discounting reflect the same underlying process or different and dissociable processes (Cardinal, 2006). Findings of studies in human impulsive behavior suggest that temporal and probability discounting are dissociable processes, which do not essentially run in parallel (Deakin et al., 2004). Nevertheless, the NAc core appears to be a common neural substrate in the regulation of impulsive choice.

A voluminous literature on decision-making in humans provides imaging evidence of the involvement of a variety of brain structures in impulsive choice; different subregions of the human prefrontal cortex, cingulate cortex, insula, and the amygdala are the most prominent ones (Ernst and Paulus, 2005; Knutson and Bossaerts, 2007; Rushworth and Behrens, 2008). There are differences with regards to degree of involvement of these areas to impulsive choice, however a complete review of these relationships is beyond the scope of this article. However, these structures are known to either have direct anatomical connections to the NAc, or are indirectly connected (see Section 2.3). Therefore, alterations reported in the ventral striatum/NAc in functional neuroimaging studies should be interpreted in the context of these complex interactions. There is also evidence on the neurochemical modulation of the interaction between the NAc and these structures (see Section 4.3), which may have a significant role in shaping the behavioral outcome.

Lesions in the areas of the medial prefrontal cortex which are known to project to the NAc core, such as the prelimbic and infralimbic cortices, as well as lesions of the anterior cingulate cortex (ACC), were shown to have no influence on tolerance to delay in reward delivery (Cardinal et al., 2001; Rudebeck et al., 2006). However, orbitofrontal cortex (OFC) lesions in rats were reported to result in impulsive choice (Kheramin et al., 2002; Mobini et al., 2002; Rudebeck et al., 2006); but not consistently (Winstanley et al., 2004). Recently, the lesions disconnecting the OFC from the NAc core were found to result in higher delay discounting in rats (Bezzina et al., 2008). In addition, lesions of another input structure of the NAc, the basolateral amygdala, were found to promote impulsive choice in a delay discounting task (Winstanley et al., 2004). Interestingly, lesions of the STN, which is an important component of the cortico-basal ganglia-thalamocortical pathways and is functionally more influenced by the NAc core output than the shell (see Section 2.3), decreased impulsive choice (Winstanley et al., 2005a); therefore suggesting an 'indirect' pathway component in the data reviewed here. It would be relevant to investigate to which extent the role of the NAc core is expressed through its 'direct' or 'indirect' pathway projections.

There are fewer studies investigating probability discounting in rats. However, OFC lesions in rats promote the choice of the small-certain reinforcer instead of the large-uncertain (Mobini et al., 2002), steepening the probability discounting function (Kheramin et al., 2002), leading to risk-averse choice as it is the case for the NAc core lesions (Cardinal and Howes, 2005). The involvement of the anterior cingulate cortex in probability discounting is not studied in lesioned rats. However, rats with lesions of the ACC were shown to have impaired effort-based decision-making (Rudebeck et al., 2006), and recently a similar effect was observed with lesions disconnecting the NAc core and the ACC (Hauber and Sommer, 2009). With regards to the findings of the lesion studies in rats, the NAc core and OFC can be accepted as two common substrates of temporal and probability discounting with similar roles.

The assessment of outcome characteristics, such as valence and salience does not solely influence the behavioral preference, but also determines attentional priorities (Vuilleumier, 2005). Failure in focusing attention to the task (or predetermined goal) relevant stimuli and resisting to distracting stimuli and earlier associations, as well as failing to collect all necessary information results in reflection impulsivity. Although NAc is a component of frontos-triatal circuits involved in attention, NAc lesion studies have failed to show an effect. Also, imaging studies with tasks requiring resistance to interference reported no significant change in ventral striatal activity. Thus, the NAc is not directly linked with failure in these forms of cognitive inhibition (Barkley, 1997).

Inhibition of behavior, on the other hand, is influenced by lesions of the NAc core in a task dependent manner in rats: lesions increased premature responses in DRL (Pothuizen et al., 2005), increased or did not affect premature responses in the 5CSRT task (Christakou et al., 2004; Pothuizen et al., 2005), but had no influence on the SSRT performance (Eagle and Robbins, 2003b). The dissociation in these measures of inhibitory function was recently shown through application of multiple tasks in rats (Robinson et al., 2009). High impulsivity defined by premature responses in the 5CSRT task was not found to be correlated with impaired performance in the SSRT. Therefore, the authors proposed at least two distinct deficits, waiting versus stopping, in tasks measuring impulsivity in response inhibition, similar to the earlier proposal of action restraint versus action cancellation (Schachar et al., 2007). With this perspective, it is tempting to propose that the NAc core lesions leave action cancellation intact. However, the effect of lesions on action restraint is still unclear due to discrepancy in the results obtained in the 5CSRT tasks and the DRL. Lesions restricted to the shell have consistently spared response inhibition (Pothuizen et al., 2005; Murphy et al., 2008). In addition, no change in the ventral striatal activity was reported in an imaging study during a go/nogo task (Horn et al., 2003). Although these findings do not provide consistent evidence for the involvement of the NAc in response inhibition, there is evidence supporting its functional contribution. Both electrical stimulation (Sesia et al., 2008) and pharmacological modulation of the NAc and its subdivisions (Tables 3 and 4) influence premature responding.

Different patterns of involvement in tasks evaluating response inhibition can be seen in rats with prefrontal cortex lesions. There is strong evidence indicating that the structural integrity of the orbitofrontal cortex is required for the inhibition of behavior both before and during the execution of an action in stop-signal paradigms (Eagle et al., 2008; Eagle and Robbins, 2003a,b). However, the lesions of the infralimbic and prelimbic cortices were not found to impair the SSRT performance. Interestingly, failure in response inhibition in the 5CSRT task was reported in rats with lesions in areas that are the main source of cortical input to the NAc: ACC (Chudasama et al., 2003; Muir et al., 1996), infralimbic cortex (Chudasama et al., 2003), and prelimbic cortex (Christakou et al., 2004), but not with orbitofrontal cortex lesions (Chudasama et al., 2003) (see Section 2.3). Nevertheless, this pattern of distinguished involvement in different measures of inhibition is not observed in the case of the STN. STN lesions in rats were reported to increase premature responses consistently in

reaction time tests (Baunez et al., 2001, 1995), DRL-30 task (Uslaner and Robinson, 2006), and impair the SSRT performance (Eagle et al., 2008). *In toto*, dissociation in the neural substrates of these two forms of inhibitory functions indicates that lesions of both the NAc core and its prefrontal cortical sources of afferent projections facilitate premature responding. This suggests the existence of a frontostriatal circuit including the NAc core which is involved in the regulation of this type of inhibition.

6. Conclusion

The afferent and efferent connections of the NAc and the rich interplay of major neurotransmitter systems within it, makes the NAc a major determinant of behavioral output. The NAc functions as a key element of cortico-striatal circuits regulating cognitive and behavioral processes. NAc's pattern of neuronal activity, either genetically determined or acquired, has a critical impact on the interindividual variation in the expression of impulsivity. Dopamine facilitates the implementation of behavioral alternatives through modifying the strength of their neural representation. Furthermore, it has a strong impact on the selection of frontal-temporal-limbic input to the NAc, facilitating the generation of impulsive or non-impulsive behavior depending on the contingency. The NAc is not the only substrate responsible for impulsivity and it is not involved in each facet of impulsivity to the same extent. There is strong evidence supporting the involvement of the NAc core in impulsive choice, but only limited evidence supports the involvement of the NAc in response inhibition. But it has to be remarked that this feature has not been studied as extensively as impulsive choice. There is also no clear supporting evidence from imaging studies in humans. Probably, further investigations on response inhibition with experimental designs involving different affective states in humans and animals are required for clarification of the role of the NAc in the urgeny facet of impulsivity, which has a proposed association with failure in response inhibition.

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