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Nucleus accumbens core and shell inactivation differentially affects impulsive behaviours in rats

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ABSTRACT

Impulsivity is a multifactorial phenomenon, determined by deficits in decision-making (impulsive choice) and impulse control (impulsive action). Recent findings indicate that impulsive behaviour is not only top-down controlled by cortical areas, but also modulated at subcortical level. The nucleus accumbens (NAc) might be a key substrate in cortico-limbic-striatal circuits involved in impulsive behaviour. Dissociable effects of the NAc subregions in various behavioural paradigms point to a potential functional distinction between NAc core and shell concerning different types of impulsivity. The present study used reversible inactivation of the rats' NAc core and shell via bilateral microinfusion of the $GABA_A$ receptor agonist muscimol (0.05 μg/0.3 μl) and fluorophore-conjugated muscimol (FCM, 0.27 μg/0.3 μl) in order to study their contribution to different aspects of impulse control in a 5-choice serial reaction time task (5-CSRTT) and impulsive choice in a delay-based decision-making T-maze task. Acute inactivation of NAc core as well as shell by muscimol increased impulsive choice, with higher impairments of the rats' waiting capacity in the T-maze following core injections compared to shell. Intra-NAc shell infusion of muscimol also induced specific impulse control deficits in the 5-CSRTT, while deactivation of the core caused severe general impairments in task performance. FCM did not affect animal behaviour. Our findings reveal clear involvement of NAc shell in both forms of impulsivity. Both subareas play a key role in the regulation of impulsive decision-making, but show functional dichotomy regarding impulse control with the core being more implicated in motivational and motor aspects.

1. Introduction

Impulsivity is a behavioural phenomenon that both adversely and beneficially affects living conditions (Eysenck and Eysenck, 1977). From a theoretical point of view, impulsive behaviour results from the relation between an incentive (impulsive drive) and an inhibitory dimension (impulse control) (Herpertz and Sass, 1997). Impulse control is described as an active inhibitory mechanism, which modulates an internally or externally driven prepotent desire for a primary (food) or secondary (money) reinforcer. Rapid, conditioned reactions are transiently suppressed so that slower cognitive patterns can guide behaviour (Eagle and Baunez, 2010; Winstanley et al., 2006). Dysfunctional impulse control (e.g., acting prematurely without foresight) is referred to as impulsive action or motor impulsivity (Brunner and Hen, 1997; Dalley et al., 2011) and is often measured in the 5-choice serial reaction time task (5-CSRTT) in rats, which was modelled after its human analogues, the continuous performance test of attention and Leonard's five choice serial reaction time task (Carli et al., 1983; Muir et al., 1996; Robbins, 2002). As a multifactorial phenomenon, impulsivity is generally distinguished into impulsive action and impulsive choice (Evenden, 1999b; Pattij and Vanderschuren, 2008; Winstanley et al., 2006). The dominant behavioural model to assess impulsive decision-making in both humans and rodents is the delay-discounting task, where impulsive tendencies are reflected in the preference for a small immediate over a larger-but-delayed reward due to delay aversion and reduced waiting capacity (Broos et al., 2012; de Wit, 2009; Moeller et al., 2001; Swann et al., 2002). High levels of impulsivity are expressed in many psychiatric disorders, involving attention-deficit/hyperactivity disorder (ADHD), antisocial personality disorder, borderline personality disorder, schizophrenia, drug abuse and other forms of addiction (de Wit, 2009; Evenden, 1999a; Herpertz and Sass, 1997). Functional magnetic resonance imaging (fMRI) studies in ADHD individuals suggest a contribution of corticostriatal circuitry to impulse control disorders, including the nucleus accumbens (NAc) as part of the ventral striatum (Costa Dias et al., 2012; Jupp et al., 2013). Moreover, previous studies associated the NAc with impulsive cocaine-, alcohol- and food-seeking (Kalivas and Volkow, 2005; Koob, 1992; LaLumiere et al., 2012).

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The NAc is implicated in decision-making (Assadi et al., 2009; Day et al., 2011; de Visser et al., 2011) and anticipation of reward in humans, other primates and rats (Cromwell and Schultz, 2003; Knutson et al., 2001; Martin and Ono, 2000; Rademacher et al., 2013). Human studies found activation of the NAc during performance in delay-discounting tasks (Ballard and Knutson, 2009; Hariri et al., 2006; McClure et al., 2004; Wittmann et al., 2007) and a negative correlation between striatal dopamine D2/3 receptors and impulsive choice or action (Ghahremani et al., 2012; Lee et al., 2009). Such a reduced D2/3 receptor availability in the NAc was also observed in a 5-CSRTT study of impulsive rats (Dalley et al., 2007).

As a critical element of the mesocorticolimbic system, the NAc is generally implicated in reward and motivation. The original concept of the NAc as a functional limbic–motor interface is still valid, but findings of the past two decades revealed much more differentiated insights indicating that the NAc should no longer be viewed in the sense of an anatomical entity (Groenewegen and Trimble, 2007; Heimer, 2003; Mogenson et al., 1980). On the basis of anatomical, neurochemical and electrophysiological criteria, the NAc in the rat brain is divided into distinct subterritories which are also present in the human brain: a dorsolateral core region surrounding the anterior commissure and a shell region that is situated ventromedially to the core (Meredith et al., 1996; Sokolowski and Salamone, 1998; Zaborszky et al., 1985). In rats, considerable differences exist in the input–output features of core and shell. In particular, the medial prefrontal cortex (mPFC) projects topographically to the NAc. Dorsal regions of the mPFC (anterior cingulate and dorsal prelimbic cortices) primarily innervate the core while the shell receives afferents from ventral parts of the mPFC, including ventral prelimbic and infralimbic cortices (Berendse et al., 1992; Brog et al., 1993; Heidbreder and Groenewegen, 2003). The efferents also contribute to the core–shell dichotomy. The core region sends fibres to the conventional basal ganglia circuitry, whereas shell projections extensively reach subcortical limbic structures (Heimer et al., 1991; Zahm and Brog, 1992).

These differences in connectivity suggest that the NAc subregions might also differ functionally (Corbit et al., 2001). Lesion studies and intracerebral pharmacological manipulations previously demonstrated that the NAc core and shell are differentially involved in goal-directed instrumental action (Corbit et al., 2001), Pavlovian–instrumental transfer (Corbit and Balleine, 2011; Saddoris et al., 2011), behavioural flexibility (Floresco et al., 2006), stress-, cue- or cocaine priming-induced reinstatement of drug- or food-seeking behaviour (Floresco et al., 2008; McFarland et al., 2004; Vassoler et al., 2013), working memory (Jongen-Relo et al., 2003), locomotor activity (Jongen-Relo et al., 2002; Pothuizen et al., 2005a; Robbins and Everitt, 1996), motivational behaviour (Bassareo et al., 2002; Stratford and Kelley, 1997) and attentional processes, like prepulse and latent inhibition (Jongen-Relo et al., 2002; Pothuizen et al., 2005a).

The functional dichotomy at the level of the NAc also holds true for impulsive behaviours. While there is strong evidence that core lesions promote impulsive choice (Bezzina et al., 2007, 2008a; Cardinal et al., 2001; da Costa et al., 2009; Pothuizen et al., 2005b), shell lesions do not (Pothuizen et al., 2005b). Additionally, rats' exposure to an adjusting-delay schedule in inter-temporal choice is associated with enhanced neuronal activity in the NAc core (da Costa et al., 2010). However, the effect of core lesions remains unclear due to discrepancy with other studies yielding no choice impulsivity (Acheson et al., 2006; Gill et al., 2010).

Regarding impulse control, accumbal DA depletions as well as excitotoxic lesions of the NAc shell lack an effect on anticipatory responding in response inhibition tasks (Cole and Robbins, 1989; Murphy et al., 2008; Pothuizen et al., 2005b), whereas accumbal 5-HT depletions and lesions of the core show impairments in 5-CSRTT and differential reinforcement for low rates of responding (DRL) tasks (Christakou et al., 2004; Fletcher et al., 2009; Pothuizen et al., 2005b). More insights are provided by recent pharmacological manipulations, highlighting a potential involvement of the shell. In both NAc core and shell, dopamine D_1-like and D_2-like receptors are involved in inhibitory response control (Pattij et al., 2007). Other findings support divergent roles of core and shell in regulating impulse control (Besson et al., 2010; Economidou et al., 2012; Sesia et al., 2008). DA function in the NAc varies between the subregions and further underlines the heterogeneity of core and shell. Impulsive action in the 5-CSRTT correlates with increased DA release due to reduced dopamine D2/3 receptor availability and higher D1 receptor mRNA expression in the shell, but decreased DA release caused by lower D1 receptor binding in the core (Diergaarde et al., 2008; Jupp et al., 2013; Simon et al., 2013).

The lesion technique was the most widely used method to investigate brain function, although carrying some drawbacks due to permanent destruction of brain tissue and a potential functional compensation by other brain areas. These shortcomings can be avoided using reversible acute inactivation procedures (Lomber, 1999). Up to now only a few studies investigated the role of NAc subregions in impulsivity using lesions or transient inactivation methods. Local microinfusion of the $GABA_A$ receptor agonist muscimol allows repeated reversible inactivation of distinct brain regions, and hence, within-subject designs with increased reliability (Lomber, 1999). Muscimol represents an appropriate inactivation tool, as $GABA_A$ receptors are widely distributed throughout the NAc located on medium-sized, spiny neurons (MSN) (Schwarzer et al., 2001). Muscimol selectively induces a rapid hyperpolarization lasting up to several hours on post-synaptic neurons via activation of $GABA_A$ receptors on the surface of local cell bodies without affecting fibres of passage, thereby allowing behavioural testing almost immediately after injection (Edeline et al., 2002; Heiss et al., 2010; Krupa et al., 1999; Martin and Ghez, 1999). In contrast, the lesion technique requires several days for the animals to recover, enabling the development of adaptive functions of remaining structures (Martin and Ghez, 1999). Additionally, fluorescent conjugates, like fluorophore-conjugated muscimol (FCM), may help to evaluate the spatial extent of drug-infused tissue.

In the present study, reversible inactivation of the rats' NAc core and shell via bilateral microinfusion of the $GABA_A$ receptor agonist muscimol and FCM was used for the first time to analyse their contribution to impulse control in the 5-CSRTT and impulsive choice in a delay-based decision-making T-maze task.

2. Methods

2.1. Subjects

The study was conducted using a total of 32 adult male Lister Hooded rats (210–310 g) obtained from Harlan (Borchen, Germany) which were assigned to two testing cohorts (n = 16). Each cohort was further subdivided into a NAc core group and a NAc shell group (n = 8 each). The first cohort was trained in a delay-based decision-making task (T-maze), and the second performed the 5-CSRTT. The animals were housed in groups of four to six in standard Macrolon cages (type IV) under controlled ambient conditions (21–22 °C, 45–55% humidity, 12 h light/dark cycle, lights on at 7:00 a.m.). The rats were kept on their experimental body weight by controlled feeding of 12 g laboratory rodent chow (Nohrlin GmbH, Bad Salzuflen, Germany) per rat per day and received tap water ad libitum. Behavioural testing took place between 8:00 a.m. and 6:00 p.m. The experiments were performed in accordance with the National Institutes of Health ethical guidelines for the care and use of laboratory animals for experiments and were approved by the local animal care committee (Senatorische Behörde, Bremen, Germany).

2.2. Experiment 1: 5-CSRTT

2.2.1. Apparatus

The 5-CSRTT was conducted in two operant aluminium chambers (26 × 26 × 26 cm; Campden Instruments Ltd., Loughborough, UK),

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