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# Enhancing excitability of dopamine neurons promotes motivational behaviour through increased action initiation

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**Abstract**
Motivational deficits are a key symptom in multiple psychiatric disorders, including major depressive disorder, schizophrenia and addiction. A likely neural substrate for these motivational deficits is the brain dopamine (DA) system. In particular, DA signalling in the nucleus accumbens, which originates from DA neurons in the ventral tegmental area (VTA), has been identified as a crucial substrate for effort-related and activational aspects of motivation. Unravelling how VTA DA neuronal activity relates to motivational behaviours is required to understand how motivational deficits in psychiatry can be specifically targeted. In this study, we therefore used designer receptors exclusively activated by designer drugs (DREADD) in TH:Cre rats, in order to determine the effects of chemogenetic DA neuron activation on different aspects of motivational behaviour. We found that chemogenetic activation of DA neurons in the VTA, but not substantia nigra, significantly increased responding for sucrose under a progressive ratio schedule of reinforcement. More specifically, high effort exertion was characterized by increased initiations of reward-seeking actions. This effect was dependent on effort

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requirements and instrumental contingencies, but was not affected by sucrose pre-feeding. Together, these findings indicate that VTA DA neuronal activation drives motivational behaviour by facilitating action initiation. With this study, we show that enhancing excitability of VTA DA neurons is a viable strategy to improve motivational behaviour.


## 1. Introduction

Motivational processes regulate the drive to overcome costs and exert effort in order to obtain a desired goal. Conversely, deficits in motivation are a key symptom of multiple psychiatric disorders, including major depressive disorder, schizophrenia and addiction, which strongly interfere with functional outcome and quality of life (Fervaha et al., 2016, 2015; Robinson and Berridge, 1993; Wise, 2004). In order to successfully treat motivational deficits in psychiatric disorders, it is essential to better understand the neurobiological substrates underlying distinct aspects of motivational behaviour. It has been hypothesized that motivational deficits observed in psychiatric disorders may arise from alterations in dopamine (DA) neuronal activity (Maia and Frank, 2016; Whitton et al., 2015). Although the brain DA system has been widely implicated in regulating motivation (Berridge, 2007; Salamone and Correa, 2012; Wise, 2004), the exact relationship between midbrain DA neuronal activity and motivational behaviour remains incompletely understood.

DA signalling in the nucleus accumbens (NAc), originating from VTA DA neurons, has been identified as a crucial substrate for motivational behaviour (Nunes et al., 2013; Salamone and Correa, 2012). Thus, blockade of NAc DA neurotransmission strongly diminished responding for rewards under a progressive ratio (PR) schedule of reinforcement in rodents (Aberman et al., 1998; Aberman and Salamone, 1999; Bari and Pierce, 2005), whilst enhancing NAc DA signalling increased motivational behaviour (Peciña et al., 2003; Trifilieff et al., 2013). We have previously shown that enhanced activity of VTA mesolimbic neurons increased the motivation for sucrose in rats (Boender et al., 2014; de Jong et al., 2015). However, it has been suggested that also the nigrostriatal DA pathway, from SNc towards dorsal striatum, may play an important role in motivational processes (Ikemoto et al., 2015; Palmiter, 2008; Wise, 2009). For example, both VTA and SNc DA neurons display reward prediction errors (Barter et al., 2015; Schultz et al., 1997), and mice have been shown to self-administer optogenetic stimulation of DA neurons in VTA as well as SNc, suggesting that activation of either of these neuronal populations is sufficient to reinforce behaviour (Ilango et al., 2014; Rossi et al., 2013). However, direct evidence for a role of SNc DA neuron activity in driving motivational behaviour is lacking. In this study, we directly compared the effects of chemogenetic activation of DA neurons in the VTA or SNc on motivational behaviour, using designer receptors exclusively activated by designer drugs (DREADD) technology in TH:Cre transgenic rats.

In addition, it remains unknown which aspects of motivation are affected by VTA DA neuronal activity that drive the increase in responding. Mesolimbic DA is thought to be particularly involved in effort-related and activational aspects of motivational behaviour (Salamone et al., 2016a; Salamone and Correa, 2012). For example, DA depletion selectively impairs instrumental behaviour under high effort requirements (Aberman and Salamone, 1999). Recently, it was observed that phasic DA transients in the NAc were associated with the initiation of actions as well as the level of effort performed within these actions (Ko and Wanat, 2016). In the present study, we therefore investigated which aspects of motivational behaviour were affected by chemogenetic activation of DA neurons. Chemogenetic activation of DA neurons enhances the excitability of VTA DA neurons (Boekhoudt et al., 2016). We hypothesized that this stimulates the initiation of reward-seeking actions, promoting the animal to engage in motivational behaviour. We tested this by examining whether the DA-induced increase in responding was dependent on prior access to the reinforcer, presence of the reinforcer, effort requirement, and action-outcome contingencies.

## 2. Experimental procedures

### 2.1. Subjects

In total, 49 male rats were used for the experiments. TH:Cre transgenic rats (Witten et al., 2011) were bred in-house, by crossing heterozygous TH:Cre$^{+/-}$ (Cre$^{+}$) rats with wild type Long Evans mates. TH:Cre$^{-/-}$ (Cre$^{-}$) littermates were used for control groups. Animals were socially housed with ad libitum access to regular chow and water in their home cage, and were kept on a reversed 12-hour light-dark schedule (lights off 7:00). All experiments were performed in accordance with Dutch laws (Wet op Dierproeven, 1996) and European regulations (Guideline 86/609/EEC), and were approved by the Animal Experiments Committee of Utrecht University.

### 2.2. Surgical procedures

Experiments were conducted as described previously (Boender et al., 2014). In brief, rats were injected bilaterally with AAV2.5-hSyn-DIO-hM3D(Gq)-mCherry (1.0-7.6*E12 molecules/ml) purchased from UNC Vector Core. Rats were allocated to one of three experimental groups: 1) VTA:D(Gq)+: Cre$^{+}$ rats injected with the DREADD virus into the VTA; 2) SN:D(Gq)+: Cre$^{+}$ rats injected with the DREADD virus into the SNc; and 3) Cre-: Cre$^{-}$ rats injected with the DREADD virus into either the VTA or SNc (control group). Perioperative care and anaesthesia were performed as described previously (Boender et al., 2014). There was a minimum of seven weeks in between surgery and behavioural testing. All behavioural experiments were carried out in adult rats.

Experiments were performed in four cohorts. Injection coordinates were adjusted to the rats' body weight (BW) during surgery. The first group (n=6 Cre$^{+}$ + 6 Cre$^{-}$, mean BW 482 g) received viral injections into the VTA: AP −5.8, ML +1.3 (5° angle), DV −8.4;

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