



## Research report

# Deep brain stimulation of the rostromedial tegmental nucleus: An unanticipated, selective effect on food intake



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## ABSTRACT

The rostromedial tegmental nucleus (RMTg) is a relatively newly described brainstem structure. The RMTg is extensively connected to both dopaminergic (DA) and serotonergic key areas and it fulfills a pivotal role in the regulation of mesolimbic and nigrostriatal DA release. The RMTg may directly influence DA- and 5-HT associated motor and possibly also mood related behavior, the latter of which has not yet been well described. The current study explored the consequences of RMTg manipulation on DA- and 5-HT related behavior through the application of RMTg deep brain stimulation (DBS) with both high and low frequency stimulation (LFS and HFS). We used a wide array of motor and mood tests to assess changes in behavior. RMTg DBS did not change behavioral outcomes in the Skinner box task, nor in the Catwalk, the sucrose intake test, the open field test, the elevated zero maze, or the place preference test, but LFS did induce a significant decrease in food intake. This seems to be a selective effect as no motor or anxiety changes were observed that could lead to attenuated food intake. This finding not only underlines the RMTg's braking effect on the VTA, but possibly also on the forebrain, where GABA-ergic RMTg efferent may cause suppression of feeding in the lateral hypothalamus.

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## 1. Introduction

The rostromedial tegmental nucleus (RMTg) is a recently identified midbrain structure thought to be of profound interest with regards to the control of midbrain dopamine (DA) pathways (Bourdy and Barrot, 2012). Ever since various experiments showed the RMTg's influence of both mesolimbic and nigrostriatal DA release (Barrot et al., 2012), the RMTg receives increasing attention and evidence provides insight into the functional role of the RMTg in DA-linked behavior.

Tracing studies have identified a number of structures that are targeted by the RMTg and that are known to be heavily involved in the regulation of midbrain DA. These targets, both mesolimbic and nigrostriatal in DA-ergic nature, are the ventral tegmental area (VTA), substantia nigra pars compacta (SNc) and lateral hypothalamus (LH) (Jhou et al., 2009a; Kaufling et al., 2009). Located just posterior to the VTA, the RMTg seems to exert an inhibitory influence on its main target structures and therefore can be considered

a control center for both mesolimbic (VTA) and nigrostriatal (SNc) DA (Barrot et al., 2012). The influence of the RMTg on the VTA, the key source of mesolimbic DA and an integral part of the reward circuitry has mainly revolved around experiments concerning aversive stimuli and the accompanying avoidance behavior. Studies in both rodents and primates (Jhou et al., 2009b; Stamatakis and Stuber, 2012) showed that the RMTg is activated in response to aversive cues: unconditioned footshock increased cFos expression in VTA-projecting RMTg fibers (Jhou et al., 2009b), acting as a brake on its downstream DA-ergic target neurons in the VTA (Barrot et al., 2012; Balcita-Pedicino et al., 2011). With regard to the RMTg's nigrostriatal DA regulation in the SNc, Bourdy et al. (2014) showed that neurochemical lesioning of the RMTg resulted in increased contralateral rotational behavior in the rotometer test, suggesting a loss of inhibitory control on the SNc. This finding was supported by a decrease in electrophysiological activity of SNc neurons upon RMTg stimulation (Bourdy and Barrot, 2012). Again, the RMTg is staged as a functional brake on the midbrain DA release.

The RMTg is thought to effectuate its inhibitory role through activation of its GABA-ergic efferent fibers. Electrophysiologically, the RMTg's direct and monosynaptic inhibitory output has been demonstrated by a complete suppression of neuronal activity of approximately half of VTA DA-ergic neurons examined upon RMTg

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stimulation (Lecca et al., 2011) and neurochemical hybridization experiments with GAD67 characterized the majority of RMTg neurons as GABA-ergic (Jhou et al., 2009a).

In addition to its connections with the key midbrain DA structures, a number of tracing studies have shown that the RMTg is also linked to the dorsal raphe nucleus (DRN), the primary serotonin (5-hydroxytryptamine; 5-HT) production area (Lavezzi et al., 2012; Sego et al., 2014). Not much is known yet about the functional role of the RMTg on 5-HT related behavior.

In view of its intricate connectivity and its pivotal role in mid-brain DA and possibly also 5-HT regulation, it is conceivable that the RMTg acts as a hub where DA-ergic and serotonergic systems converge and diverge and that it may also exert control over not only DA-related behavior, but also 5-HT related behavior such as mood and motivation.

In this light, it is interesting to explore the consequences of RMTg modulation on the DA as well as the 5-HT domain, i.e. to explore the changes in motor and mood related behavior, respectively. Therefore, our research question is: What is the behavioral consequence of RMTg modulation with regards to DA and 5-HT related behavior? In the present explorative study, we perturbed the RMTg through deep brain stimulation (DBS) and assessed the behavioral consequences of both low and high frequency stimulation (LFS and HFS) through a well-established set of behavioral tasks covering both the motor and mood domains. To our knowledge, this is the first study that neuromodulated the RMTg and relating it to concurrent behavior.

## 2. Materials and methods

### 2.1. Subjects

A total of 29 male Sprague-Dawley rats (Charles River, L'Arbresle, France) were housed pairwise in standard laboratory condition. During this test, the animals were subjected to a food deprivation regime from Monday until Friday in order to reduce body weight to 85% of their free feeding weight. All experimental procedures were reviewed and approved by the Maastricht University ethics committee.

Animals were randomly allocated one of three groups: LFS (N=9), HFS (N=9), or sham (N=8). Sham rats underwent electrode implantation and were connected to the cable but were not stimulated. All animals were tested in the following behavioral tests: Skinner test, Sucrose intake test, Food intake test, Place preference test, Open field test, Elevated zero maze test, and CatWalk. The Skinner test involved a progressive ratio schedule of reinforcement, in which the rats had to progressively increase the response requirement (number of lever presses) to obtain a food reward. The performance outcome measure was breakpoint, the maximal number of lever presses during a session. The sucrose intake test detected the amount of sucrose intake over a certain time period, as a measure of motivation and anhedonia. The level of motivation for food was tested by measuring the amount of food intake over a fixed period of time. To determine whether RMTg stimulation induced aversive avoidance behavior, we used the place preference test. The open field test was used to measure the amount of spontaneous locomotion. Lastly, we assessed generalized anxiety-related behavior in the elevated zero maze. For more elaborate description of all behavioral tests see the Supplementary material. All the tests were performed by all rats consecutively over a period of 7 weeks. We started with the Skinner task, after which the rats successively performed the CatWalk, the open field test, the elevated zero maze, the real time place preference test, the food intake test, and lastly the sucrose intake test. In between the various tests, the rats always had at least a number of days of rest.

### 2.2. Electrode implantation and deep brain stimulation

After induction of general anesthesia with isoflurane, animals were fixed in a stereotactic frame (Stoelting, Wood Dale, USA). Bipolar electrodes were implanted bilaterally into the RMTg (AP: -6.8; ML: +/-0.6; DV: -8.2) according to the rat brain atlas by Paxinos and Watson (2007) and fixed in place with dental cement. A detailed description of this method appears in our previous work (Tan et al., 2011). After a recovery period of 2 weeks, rats were tested in various behavioral tasks. Stimulation was performed using a digital stimulator and stimulus isolators (DS8000, World Precision Instruments, Berlin, Germany). Stimulation was performed during the behavioral testing, with 3 min of pre-stimulation in the animals' home cage prior to the start of every test. Stimulation settings used were 10 Hz frequency, 60  $\mu$ s pulse width and 20  $\mu$ A amplitude for the LFS group, and 130 Hz, 60  $\mu$ s, 20  $\mu$ A for the HFS group. We chose to use a 20  $\mu$ A stimulus amplitude because amplitudes of 30  $\mu$ A or higher evoked a clear motor response, with the regularly used 100  $\mu$ A amplitude causing motor disturbances similar to motor seizures.

At the end of behavioral testing, rats were sacrificed and the brain tissue was extracted and fixated. Coronal sections (30  $\mu$ m) were cut and stained with a standard hematoxylin-eosin histological procedure (Merck, Darmstadt, Germany). Only animals with correct placement of the stimulation electrode were included for further analysis.

### 2.3. Statistical analysis

All statistical tests were performed in SPSS (IBM, version 20). The skinner data were analyzed with a repeated measures general linear model, using the Huynh-Feldt correction to correct for significant sphericity as determined by Mauchly's test. The sucrose or food intake tests, the open field test, the elevated zero maze and CatWalk data were analyzed using one-way ANOVA. In addition, to assess whether differences existed in the amount of time the animals spent in the two compartments of the place preference test we performed paired *t*-tests within the three experimental groups.

## 3. Results

Electrodes were positioned correctly in the RMTg of 25 rats. In four animals the electrodes were found to be placed outside the RMTg in different regions around target. The behavioral consequences of stimulating those regions were not clear due to the fact it is hard to draw any conclusions based on just one or two subjects.

We did not observe detectable tissue damage due to the applied electrical stimulation current (Fig. 1).

### 3.1. Elevated zero maze test

Stimulation of the RMTg did not cause any significant differences in the time spent in the open or closed arms of the maze ( $p > 0.05$ ;  $F 0.417$ ). Changes in distance moved or velocity were not apparent (Fig. 2A).

### 3.2. Sucrose intake test

Pre-stimulation weights did not significantly differ between the groups preceding the sucrose intake test. Stimulation of the RMTg did not change the intake of sucrose in the sucrose intake test ( $p > 0.05$ ;  $F 0.331$ ). Correction of the sucrose intake for body weight did not make a difference (Fig. 2B).

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