

# Differential Pattern of Striatal Cerebral Blood Volume After a Haloperidol Challenge in Rats

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## Introduction

Haloperidol is a widely used antipsychotic drug with potent dopamine D<sub>2</sub> receptor antagonistic properties. It's well known to induce significant c-fos activation in the striatum [1, 2]. A T<sub>2</sub>\*-signal loss after haloperidol challenge also indicates a decrease of caudate-putamen activation [3]. Additionally, reversible alterations in the striatal gray matter volume and connectivity in humans were described recently [4]. The underlying mechanisms of these observations are currently unknown. A further step to understand the impact of haloperidol on the striatum is high-resolution regional cerebral blood volume (rCBV) mapping with magnetic resonance imaging as a functional imaging tool.

## Methods

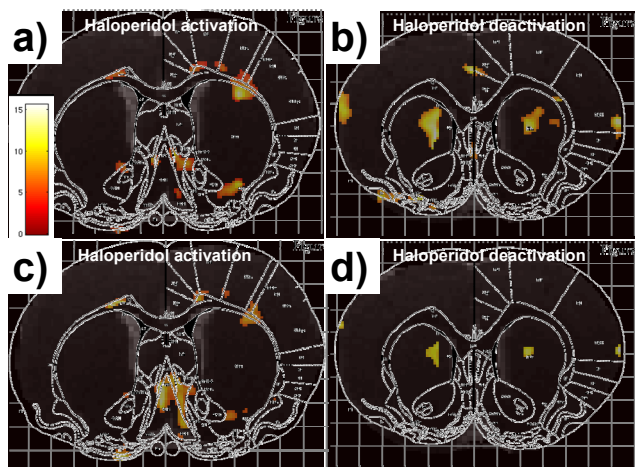
The rCBV measurements were performed in 10 rats (Sprague-Dawley rats anesthetized with dormitor) with 10mmol/kg intraperitoneally (i.p.) administered gadolinium-based contrast agent (Omniscan) [5]. Haloperidol was administered subcutaneously (s.c.) in a dose of 1mg/kg body weight 65 min before the rCBV measurements. The comparable amount of saline water was injected as a reference measurement one week before in half of the animals and one week later in the other half.

The imaging experiments were performed at a 9.4T MRI system (Bruker) equipped with a body coil for transmission and a phased array rat brain coil for signal receiving. A RARE pulse sequence (with 116x116µm<sup>2</sup> in-plane resolution) was used with 1 mm slice distance. 10 slices were measured in midbrain. For rCBV the cerebral volume was acquired two times: first - without any contrast agent (~65 min after haloperidol administration) and second - 40 min after contrast agent administration in the steady state of the contrast agent [5].

Images were motion-corrected, smoothed (0.5mm isotropic) and normalized (SPM5) to a group template in the same space as in an anatomical rat brain atlas [6]. The relative volume change rCBV was calculated voxel-based using following equation:

$$rCBV \sim \ln\left(\frac{SI(t)}{SI_{pre}}\right) / TE$$

SI(t) - the signal intensity in a voxel after injection of contrast agent at the time t, SI<sub>pre</sub> - the native signal intensity of the observed voxel. These maps were calculated for haloperidol and saline administration, respectively, and after standardization statistically pixel wise analysed (Paired T-Test, SPM8). For standardisation of the rCBV maps two methods were used. In the first method the mean of the global brain signal was used as a reference and in the second only the 4 largest rCBV values of the posterior cerebral vein (PCV) [5].



**Figure 1: Statistical analysis of the striatum. The maps show activation in the nucleus accumbens, the lateral zone of the caudate-putamen and the ventral septum for global (a) and PCV (c) standardization. Deactivation is observed in the central caudate-putamen under haloperidol for global (b) and PCV (d) standardisation of the rCBV maps.**

## Results

Our preliminary results show for both standardization methods activated areas in the lateral zone of the caudate-putamen, in the nucleus accumbens and the ventral septum (Figure 1) with higher significance for the standardization on the PCV (Figure 1,c). In contrast, the central caudate-putamen show a deactivation for both methods with higher significance for the global standardization method (Figure 1,b).

## Discussion

In our study both standardization methods of the rCBV maps show a comparable pattern of activation and deactivation of the striatum. Thereby, the areas of activation correspond well with the findings in the literature under c-fos activation [1, 2], where the lateral caudate-putamen, the nucleus accumbens and the ventral septum are described as activated. A deactivation in the central caudate-putamen could corroborate findings of a T<sub>2</sub>\* signal loss in some parts of the CPu [3]. This underlines the importance of high-resolution functional rCBV measurements covering larger parts of the brain. The next step could be the physiological interpretation of this observation of differential activation and deactivation in the striatum under haloperidol administration.

## Literature

- [1] Nguyen TV et al., Proc Natl Acad Sci U S A 1992;89(10):4270-4274.
- [2] MacGibbon GA et al., Brain Res Mol Brain Res 1994;23(1-2):21-32.
- [3] Hagino H et al., Brain Res 1998;813(2):367-373.
- [4] Tost H et al., Nat Neurosci;13(8):920-922.
- [5] Moreno H et al., NMR Biomed 2006;19(5):535-543.
- [6] Schwarz AJ et al., Neuroimage 2006;32(2):538-550.