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► **To cite this version:**

Léon Tremblay, Mathilde Pitoy, Lisa Gauthier, Julie Maulavé, Justine Debatisse, et al.. The SB-258585, a 5-HT₆ antagonist that blocks serotonin transmission in striatum can induce loss of food motivation and behavioral disturbances in non-human primate.. NeuroFrance, May 2023, Lyon, France. <hal-04983922>

HAL Id: hal-04983922

<https://hal.science/hal-04983922v1>

Submitted on 10 Mar 2025

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HAL Authorization

Blocking 5-HT₆ transmission in the striatum could induce a loss of food motivation and changes in macaque behavior.

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1. Introduction

The clinical interest around the new 5-HT₆ receptors (5-HT₆R) agents comes from their involvement in cognitive processes, food intake and anxiety-related behaviors. But most of the preclinical studies investigating their behavioral effects have been performed on rodent models and no public studies are available on the non-human-primate (NHP).

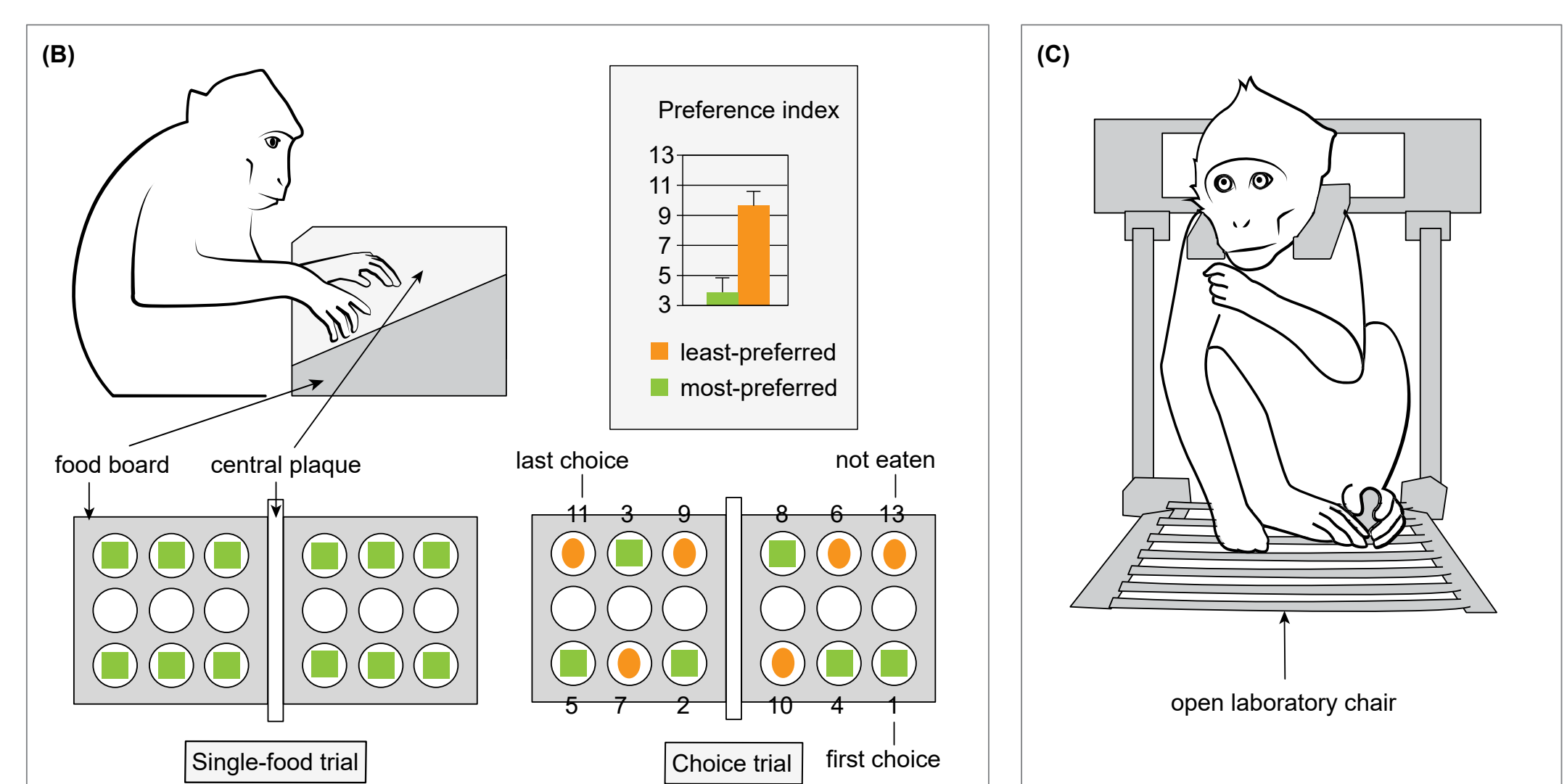
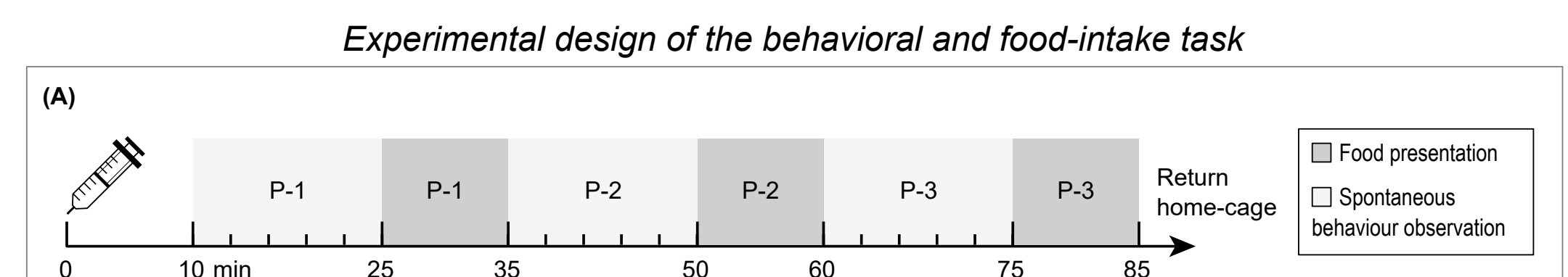
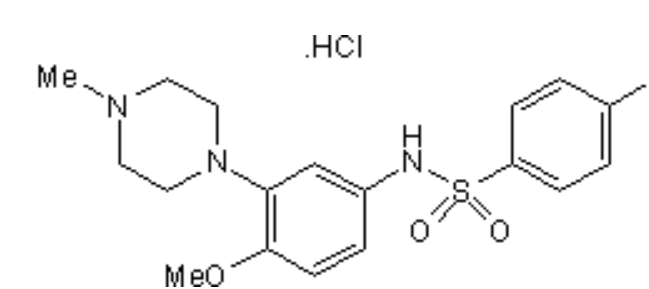
Furthermore, at this point, the site of action of these molecules has yet to be determined. Despite the striatum is a key structure in cognitive and motivational processes, notably in food intake and anxiety-related behaviors, few studies have focused on it. Moreover, PET imaging in NHP, with the recent [18F]2FNQ1P specific marker, has shown that the striatum is one of the cerebral structures expressing the highest levels of 5-HT₆R.

The first aim of this study, carried out on 6 macaques, was to determine the effects of intramuscular injections of a 5-HT₆R antagonist (SB-258585) on food motivation and behavioral expression. In addition, we determined the occupancy of the receptors by the molecule regionally, and in the whole brain.

Given the location of these receptors, we hypothesized that the blockage of 5-HT₆ transmission will decrease food motivation and will modulate behavioral expression in NHP by acting on striatal 5-HT₆R.

2. Materials and Methods

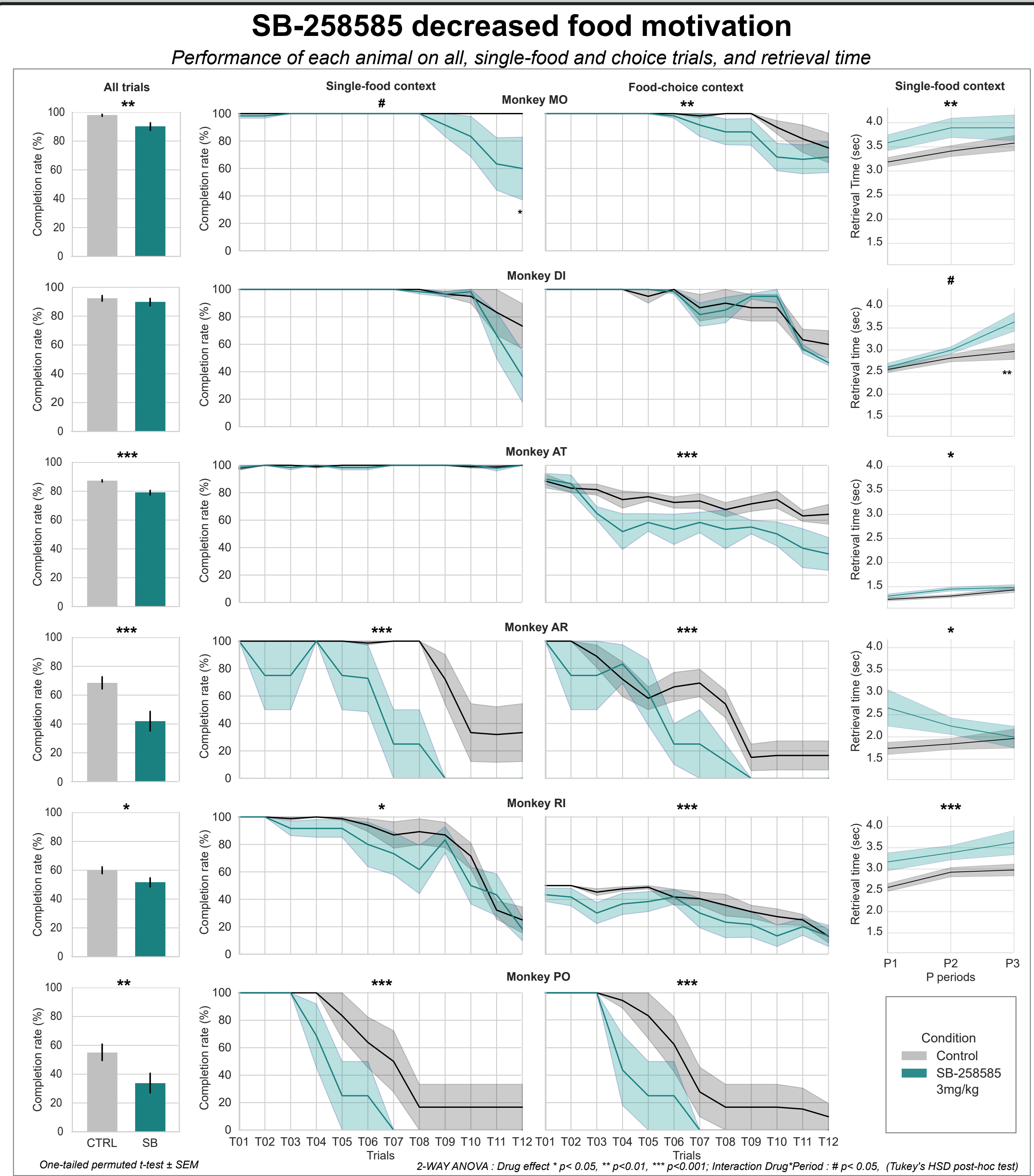
- Subjects: 6 male cynomolgus monkeys
- Molecule: SB-258585 hydrochloride: potent, selective 5-HT₆ antagonist
- Injections: 1/week acute IM injection of 3mg/kg during 4 to 5 weeks
- Behavioral task: evaluating both food motivation and spontaneous behaviors.



- Food intake parameters are measured in two types of contexts: single-food trials and choice trials.
- Completion rate (%): n food items retrieved/n food items available in any type of trial.
 - Retrieval time (RT) (sec): time taken to retrieve items from the plate /n food items retrieved in single-food trials.
 - Preference index: score calculated using item retrieval order in choice trials.
- Spontaneous behaviors duration (sec) and occurrences (n) were analyzed using BORIS® software, in 3min periods.
- PET imaging: [18F]2FNQ1P (5-HT₆R specific ligand). Region of interest (ROI) and voxel-based analysis.

Categories	Behaviors
Inactive	resting (open eyes) drowsy & yawning (closed eyes)
Object-oriented behaviors	touching equipment cleaning equipment
Non-goal movements	mouth, arm, leg movements (without goal)
Anxious-like behaviors	self-grooming self-scratching self-licking or biting
Others	object scratching licking-biting chair pull/push others behaviors (tail grabbing, body exam ...)

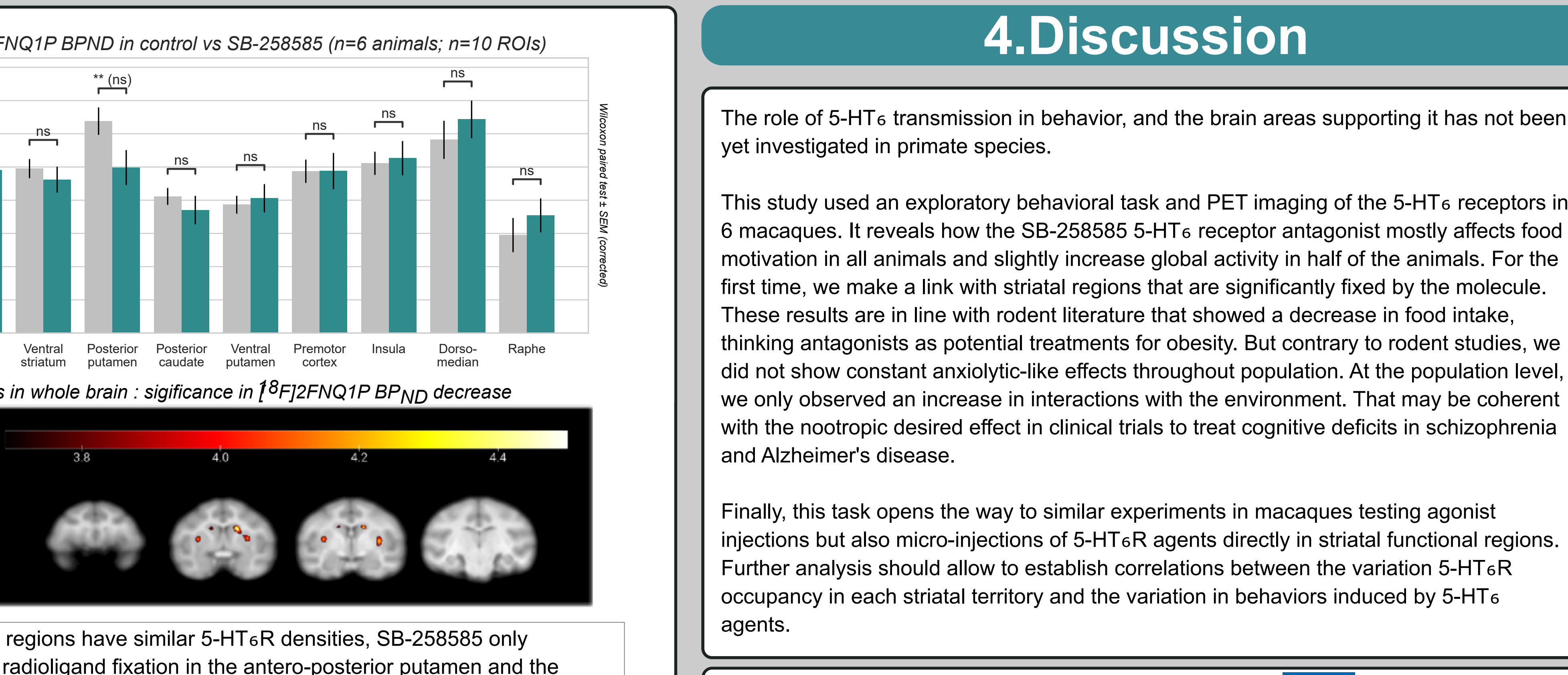
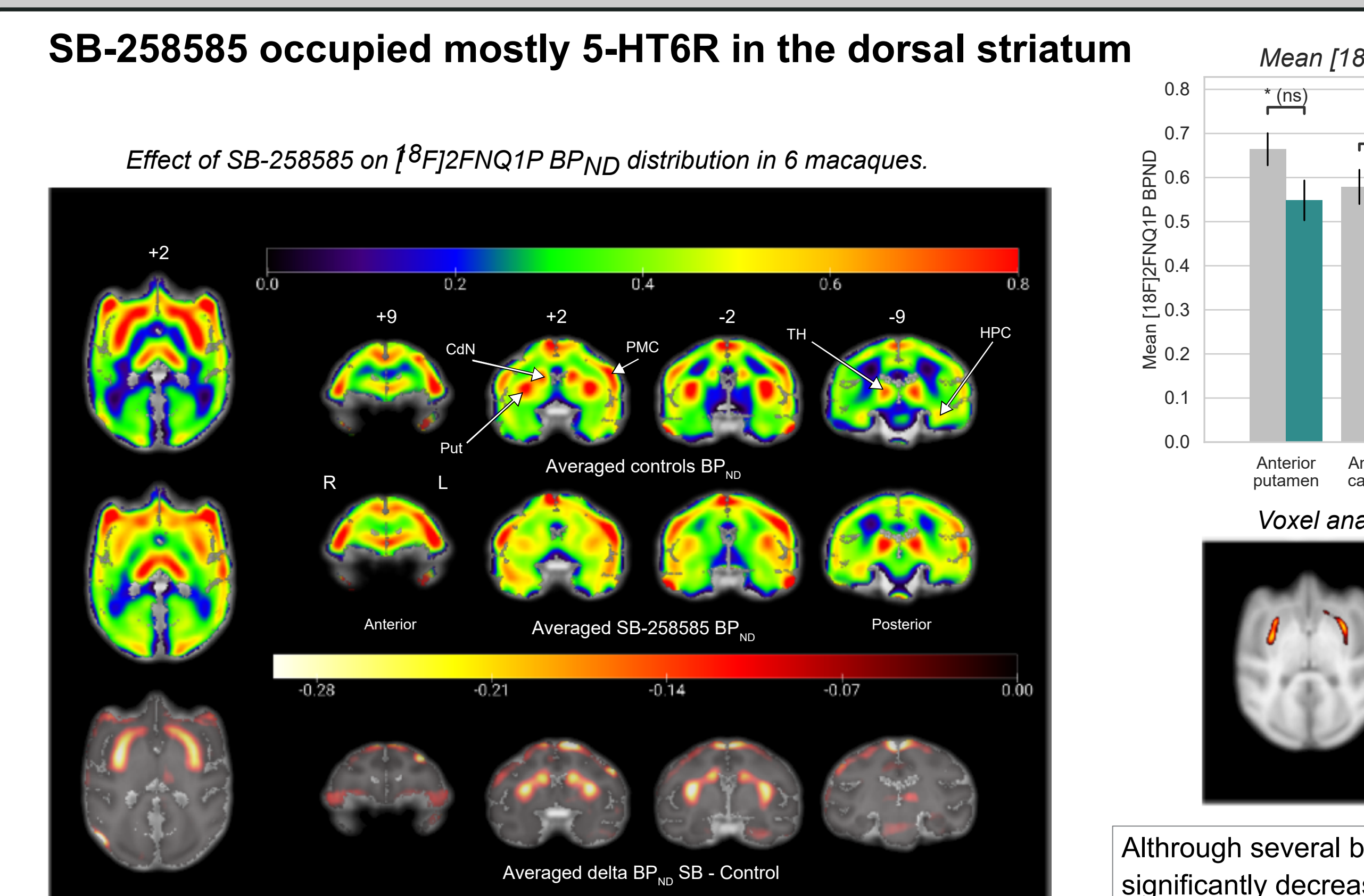
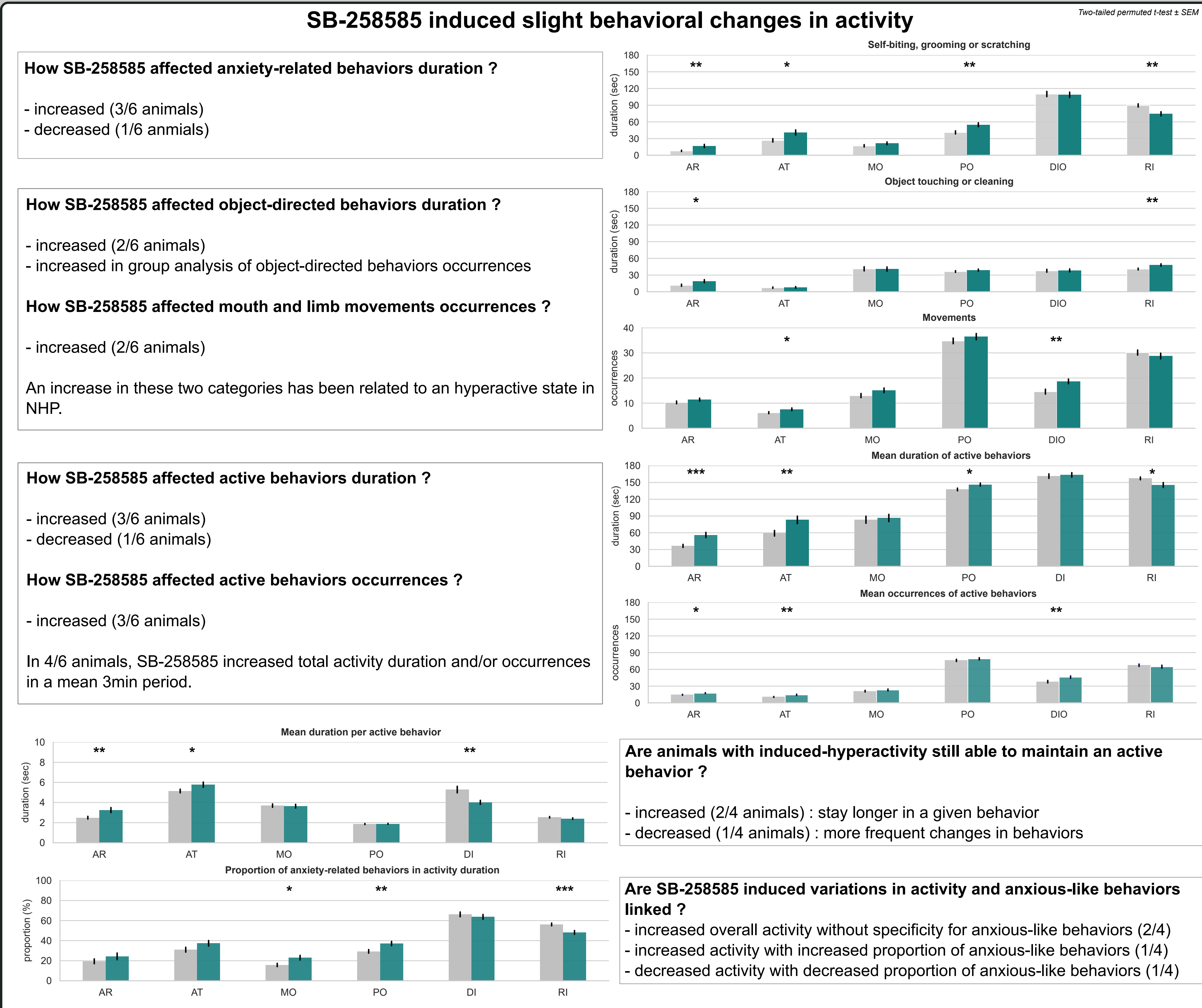
3. Results



How do SB-258585 modified food task parameters in each animal ?

- decrease of completion rate in all trials types (5/6 animals)
- decrease of completion rate particularly in the choice vs single-food context (5/6 animals)
- global increase of mean retrieval time across all task P periods (4/5) or in the last period (1/5)

All 3 parameters also significantly affected at the group level : strong motivational decrease for food.



Although several brain regions have similar 5-HT₆R densities, SB-258585 only significantly decreased radioligand fixation in the antero-posterior putamen and the anterior caudate nucleus. These 2 regions are involved in hyperactivity (dorsal putamen), impulsive choices (caudate nucleus), and food motivation (ventral putamen) in NHP.

4. Discussion

The role of 5-HT₆ transmission in behavior, and the brain areas supporting it has not been yet investigated in primate species.

This study used an exploratory behavioral task and PET imaging of the 5-HT₆ receptors in 6 macaques. It reveals how the SB-258585 5-HT₆ receptor antagonist mostly affects food motivation in all animals and slightly increase global activity in half of the animals. For the first time, we make a link with striatal regions that are significantly fixed by the molecule. These results are in line with rodent literature that showed a decrease in food intake, thinking antagonists as potential treatments for obesity. But contrary to rodent studies, we did not show constant anxiolytic-like effects throughout population. At the population level, we only observed an increase in interactions with the environment. That may be coherent with the nootropic desired effect in clinical trials to treat cognitive deficits in schizophrenia and Alzheimer's disease.

Finally, this task opens the way to similar experiments in macaques testing agonist injections but also micro-injections of 5-HT₆R agents directly in striatal functional regions. Further analysis should allow to establish correlations between the variation 5-HT₆R occupancy in each striatal territory and the variation in behaviors induced by 5-HT₆ agents.