Disruption of 5-HT$_7$ receptors accelerates age-related episodic-like memory decline

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Introduction

Increasing incidence of **cognitive impairments** related to population **ageing** is a major public health challenge. In order to identify new therapeutic targets, **modulation of serotonergic 5-HT$_7$ receptors** (5-HT$_7$R) could be an **innovative approach** since:

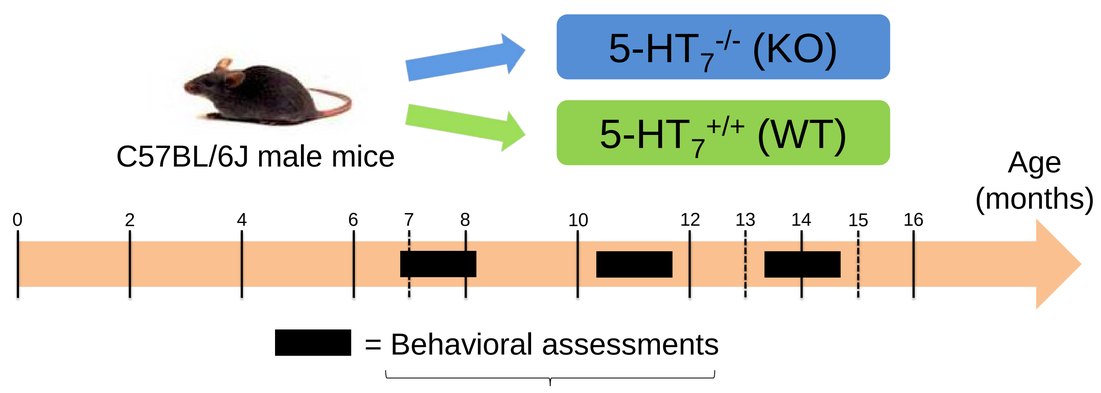
1) gene expression of 5-HT$_7$R early decreases during senescence in rats,
2) synaptic plasticity of the hippocampus is altered in 5-HT$_7$R knocked-out (KO) mice,
3) pharmacological modulation of 5-HT$_7$R improves episodic-like memory performances in mice [1].

However, considering that episodic-like memory seems not to be altered in 3 months-old 5-HT$_7$ KO mice [2], we hypothesized that a deficit could appear later.

Objectives

To identify the **implication of 5-HT$_7$R** on the onset of the **age-related memory decline**, memory performances of 7-8, 10-12 and 13-15 months-old **KO C57BL/6J mice** were compared to paired **wild type mice** (WT). **Recognition memory** performances were assessed in a two sessions Y-maze test (1-hour delay [3]). **Spatial working memory** performances were evaluated by recording spontaneous alternation behavior in the Y-maze apparatus. In addition, **locomotor activity** was recorded in an activity cage and **anxiety-related behavior** assessed in the elevated plus-maze test.

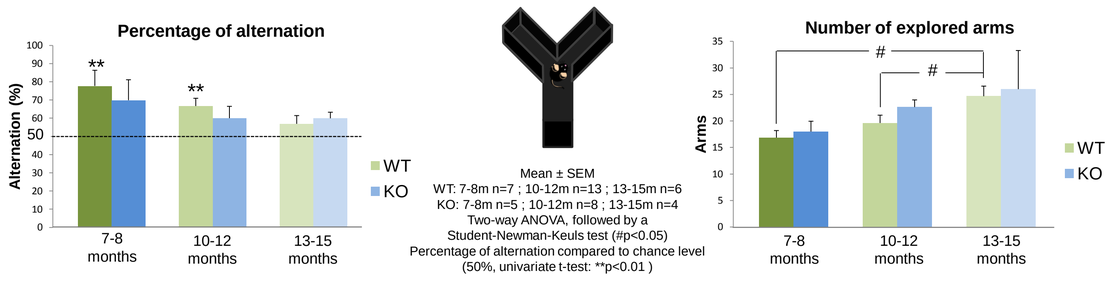
Experimental paradigm



Episodic-like memory	Spatial working memory	Anxiety-related behavior	Locomotor activity
Object recognition task (Y-maze)	Spontaneous alternation (Y-maze)	Elevated plus-maze (EPM)	Actimetry (activity cage)

Spatial working memory

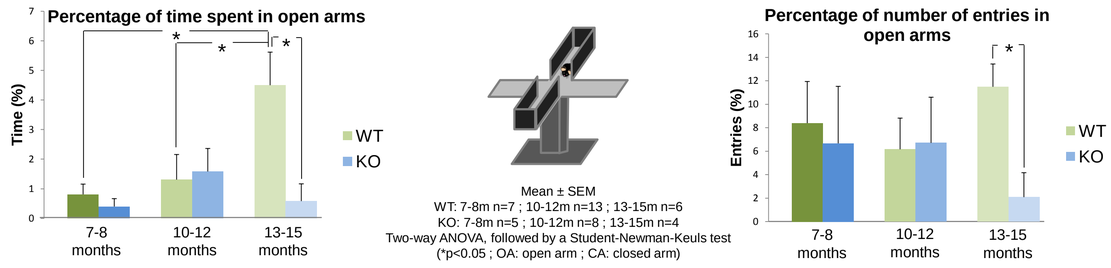
SPONTANEOUS ALTERNATION (Y-maze)



- **Spatial working memory deficits** appeared **earlier** in **KO** mice, compared to WT (before 7-8 versus 13-15 months-old ; regarding the percentage of alternation)
- **Locomotor activity** was **similar** between genotypes, although it seemed to increase with age in WT mice

Anxiety-related behavior

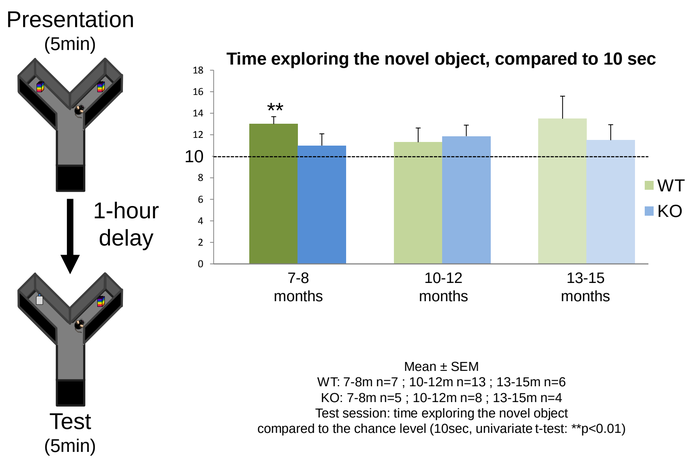
ELEVATED PLUS-MAZE (EPM)



- Increased time spent in open arms suggested a **reduction of anxiety-related behavior** (13-15 months-old **WT**)
- There was **no decrease** of **anxiety-related behavior** in **KO** mice at **13-15 months-old**, contrary to WT mice
- Both genotypes had **similar locomotor activity** (similar level of total number of entries, data not shown)

Episodic-like memory

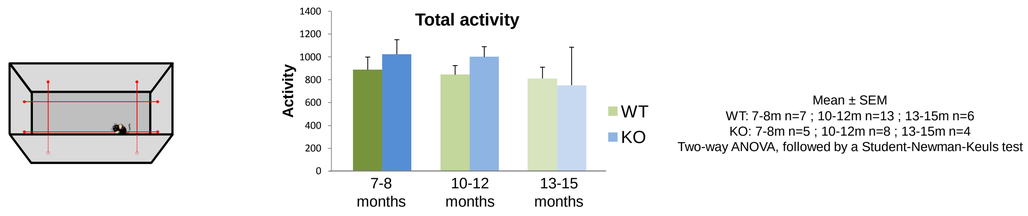
OBJECT RECOGNITION TASK (Y-maze)



- 10-12 and 13-15 months-old **WT** mice did not **discriminate** the novel object contrary to **7-8 months-old** WT mice
- Disruption of 5-HT$_7$R (**KO** mice) led to an **impaired object discrimination** in 7-8 months-old and older mice
- **Exploration** of the objects during the **presentation session** was **similar** whatever the genotype and the age (data not shown)

Locomotor activity

ACTIMETRY (activity cage)



- Both **WT** and **KO** mice exhibited an **equivalent basal level of locomotion** whatever the age

Conclusions

- Our data show that **WT** mice **older than 10 months-old** have **episodic-like memory deficits**. These ones appear **earlier in 5-HT$_7$R disrupted** mice.
- Likewise, **spatial working memory deficits** appear around **13 months-old** in **WT** mice, whereas they appear **earlier in mutant** mice.
- However, KO and WT mice exhibit an **equivalent basal level of locomotion**.
- Moreover, **WT** mice seem to present a **reduction** of **anxiety-related behavior** at **13-15 months-old**, contrary to KO mice.

This suggests that the **onset of episodic-like memory decline** comes **between 7-8 and 10-12 months-old** of age in **C57BL/6J** mice. However, **spatial working memory deficits** seem to occur later (**around 13 months-old**) in **WT** mice. **Disruption of 5-HT$_7$R** could **accelerate the onset of both memories decline**, with **no relation** to **inhibition of locomotor activity** or **increased anxiety**-like behavior.

[1] Freret, T., Paizanis, E., Beaudet, G., Gusmao-Montaigne, A., Nee, G., Dauphin, F., Bouet, V., Boulouard, M., 2012. Activation of 5-HT$_7$ receptors has pro-mnesic effects on object recognition in mice. Submitted to Psychopharmacology.
[2] Sarkisyan, G., Hedlund, P.B., 2009. The 5-HT7 receptor is involved in allocentric spatial memory information processing. Behavioural Brain Research 2002, 26-31.
[3] Leger, M., Quiedeville, A., Paizanis, E., Natkunarajah, S., Freret, T., Boulouard, M., Schumann-Bard, P., 2012. Environmental enrichment enhances episodic-like memory in association with a modified neuronal activation profile in adult mice. PLoS One 7, 10.

No potential conflict of interest