Different responses to acute administration of a new 5-HT7 receptor agonist as a function of adolescent pre-treatment: a phMRI study

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Introduction: LP211 is a selective agonist of serotonin (5-hydroxytryptamine, 5-HT) receptor 7 (5-HT7). The latter is proposed for a role in neuroplasticity and in patho-physiological processes like anxiety / depression, cognitive / sleep disturbances, and impaired coping with stress [1]. Evidence demonstrates that LP211 has consistent psychoactive effects onto exploratory motivation, anxiety-related profiles, and spontaneous circadian rhythm [2]. Here, using pharmacological MRI, we investigated different responses to acute LP211 in adult rats previously exposed to the same drug during adolescence. This work can be of great interest since developmental LP211 exposure may produce permanent rearrangements within forebrain circuits [3].

Methods: Wistar adolescent rats (43 to 47-day-old) were administered with LP211 (0.250 mg/kg/day) or vehicle (VEH: 1% DMSO in saline) for 5 days, and tested at adulthood (PND 73-75) for potential carry-over effects. Experiments were performed on a VARIAN/Agilent Inova MRI/MRS system operating at 4.7 T, by using a volume coil as transmitter and a surface coil constructed for rat head as receiver (RAPID Biomedical). During the scan, animals were intubated and mechanically ventilated with isoflurane at 0.6% in O_2. A continuous s.c. infusion of medetomidine (Domitor, 0.1mg/kg/h in 1ml/h) was also used in order to keep anaesthesia and constant physiological parameters [4]. The latter were monitored during the scan using a MRI-compatible pulse oximeter (MouseOx, Starr Life Sciences Corp). Echo planar (breath triggered) images were acquired (TR≈4000 ms, TE=23 ms, matrix 64x64, FOV 25x25mm^2, slice 6, thickness 1 mm). After consecutive image collection for about 12 min (20 baseline images), rats received LP211 (10 mg/kg) or VEH (i.p. 1 ml/200 g body weight). Images were then collected for further 24 min (40 post-challenge images). Initial experimental groups had a two design combining subchronic pre-treatment (LP211 or VEH) and challenge (LP211 or VEH). Finally, we merged all animals receiving acute VEH, since no difference was detected between these two pre-treatment groups, as expected. Data were analysed by a home-made program (developed in Matlab, Mathworks Inc.) [5-6]. After preprocessing (spatial smoothing, motion correction, segmentation and detrend when necessary), we obtained an activation map generated from brain templates, one for each experimental group. Significant alterations in the BOLD signal temporal profile were assessed on each template pixel-by-pixel, comparing a post challenge time window to the mean baseline signal with a two tailored Student t-test ($p<0.065$ Bonferroni corrected). Temporal profiles were then extracted from selected regions (derived from the activation map) of each animal, normalised and detrended. Repeated-measures ANOVA was then performed with three-level treatment (subchronic LP211-acute LP211 vs subchronic VEH-acute LP211 vs VEH) as between subject factor and time as repeated-measure factor. Analyses were performed for drug-induced effects (40 points after injection, 24 min).

Results: No considerable changes in physiological parameters were detected. Activation maps showed BOLD signal hyperintensity within Hippocampus (Hip, see Fig. 1), Dorsal Striatum, Septum as well as Orbital Frontal Cortex, for all animals challenged with LP211, with different extension and intensity depending on the subchronic pre-treatment. Preliminary analyses of the individual timecourses, extracted at the level of Hip (-3.3 mm. from bregma, [7], see Fig. 1), showed that the characteristics of the BOLD effect were different among the experimental groups. This was reflected by a significant interaction term (time x treatment: $F(80,840)=2.02$, $p<0.001$). As for the septum (0.7 mm. from bregma [7]), the ANOVA yielded both a significant effect of treatment ($F(2,9)=5.95$, $p=0.023$) and a significant interaction term (time x treatment: $F(80,360)=1.43$, $p=0.015$).

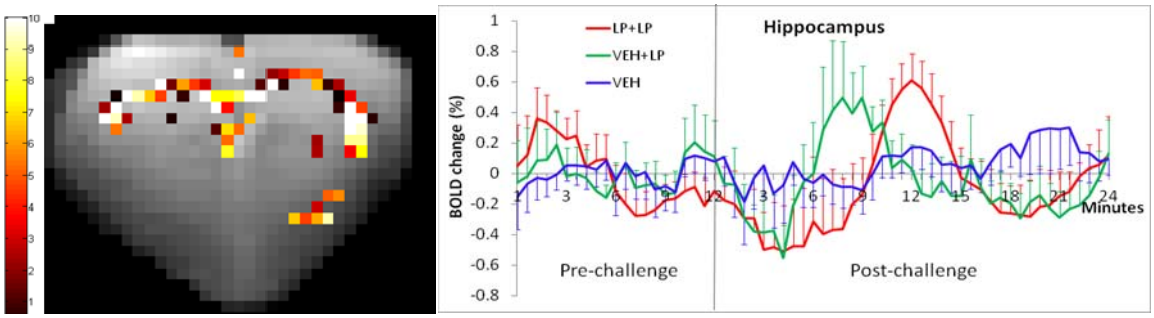

Figure 1:On the left, an example of activation map (with Student t-values in colormap) for subchronic LP211-acute LP211 group. Only pixels with significant t-values ($p<0.065$ Bonferroni corrected) are shown. On the right, mean±SEM change (%) in BOLD signal intensity in the Hip (average from n=8 per group) LP+LP: subchronic LP211-acute LP211; VEH+LP: subchronic VEH-acute LP211; VEH: acute vehicle.

Discussion and Conclusion: Thanks to our experimental setting, we were able to detect brain activations (BOLD signal changes) lower than 1%. These preliminary results show that subchronic administration of LP211 during adolescence changes permanently the response to acute administration with the same drug in adulthood. This may be possibly due to persistent modification of 5-HT7 receptor distribution and/or level of expression as well as potential rearrangement of forebrain networks [3].

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References

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