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5-HT_{1A} biased agonists induce different hemodynamic responses, a pharmacological MRI study

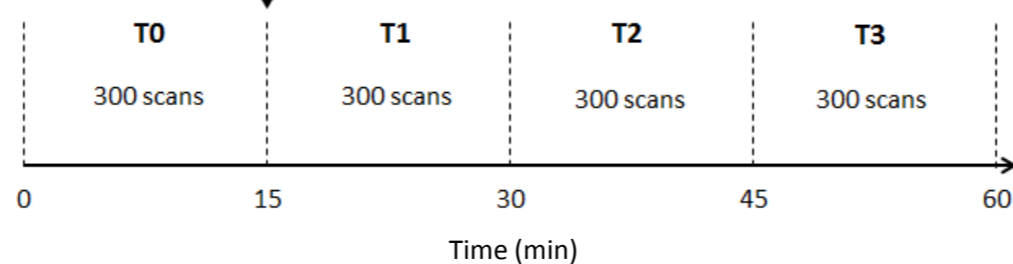
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Background

The recent concept of “biased agonism” or “functional selectivity” suggests that highly specific agonists can preferentially direct receptor signalling to specific intracellular responses, avoiding side effects and/or targeting more subtly signalling pathways associated with therapeutic effects [1]. In CNS research, biased agonists offer the potential to more precisely target receptors in specific brain regions. This is particularly interesting for exploring improved serotonin 5-HT_{1A}-receptor therapeutics with improved specificity and efficacy than those that are currently used in neurology and psychiatry [2]. **The aim of this study was to bring additional support to this concept using non-invasive functional magnetic resonance imaging in rat brain.** We mapped central hemodynamic effects of two selective 5-HT_{1A} receptor biased agonists: NLX-112 (a.k.a. befiradol, F13640), intended for the treatment of L-DOPA-induced dyskinesia [3] and NLX-101 (a.k.a. F15599), intended for the treatment of breathing deficits in Rett syndrome [4], at different doses. Contrary to NLX-112, NLX-101 is known to preferentially activate postsynaptic 5-HT_{1A} receptors compared to raphe autoreceptors [2].

Injection



PharmacMRI protocol time line. The 60-min acquisition was divided into four 15-min periods of 300 images, with T0 as the baseline period and T1, T2, T3 as the successive post-injection periods.

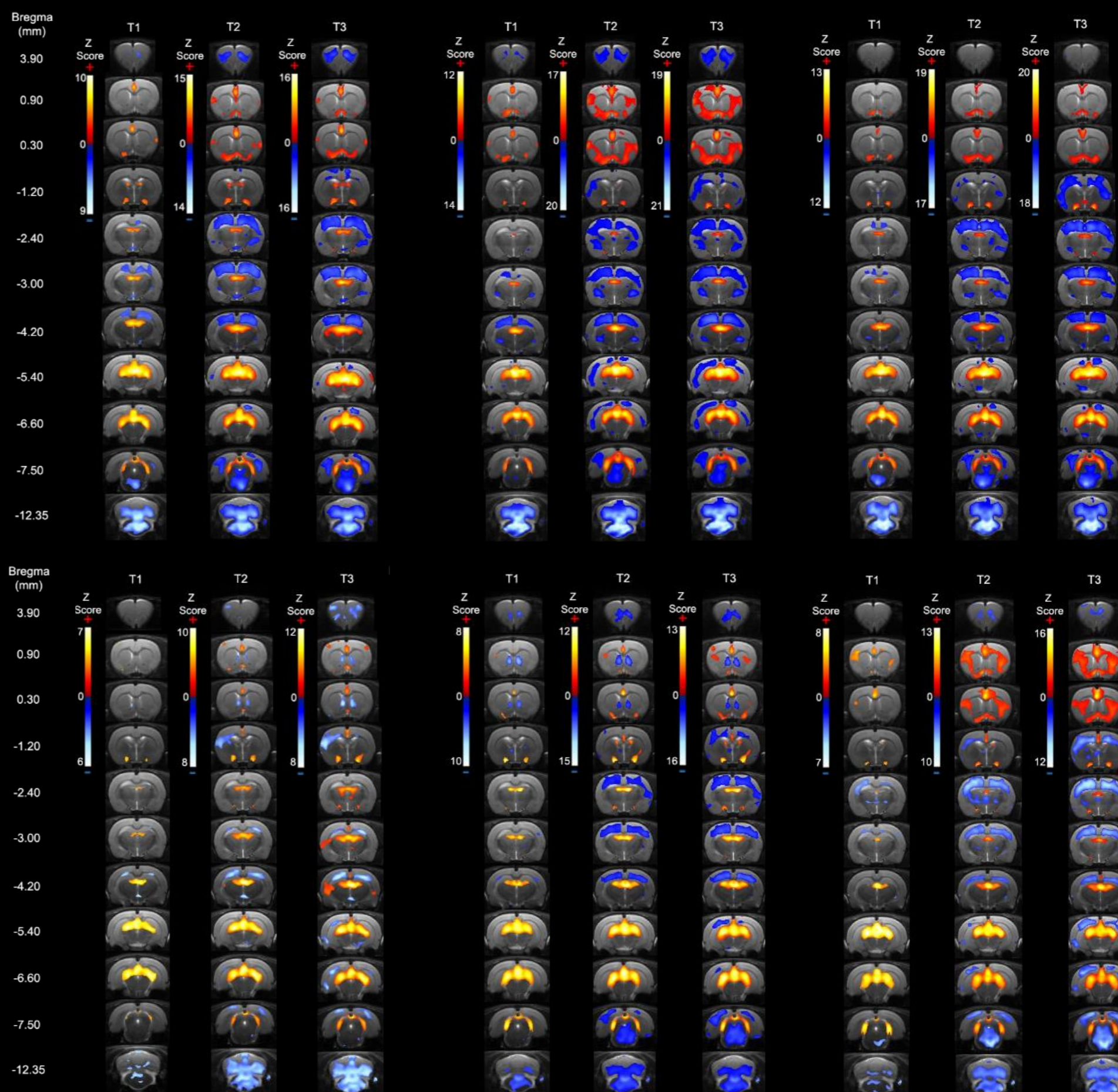
Methods

The pharmacological MRI (phMRI) data were acquired on a 7-Tesla Bruker Biospec MR system camera (CERMEP-Imaging Platform). The modifications of blood oxygen level dependant (BOLD) signal induced by the drugs, indirectly related to changes in neuronal activity, were measured in isoflurane-anesthetized rats. A continuous T2* echo planar imaging (EPI) sequence was used during 1 hour and a repetition time (TR) of 3 seconds. All rats were scanned under four conditions in a randomized order: a saline injection and three increasing doses of 5-HT_{1A} agonist (0.16 – 0.32 – 0.63 mg/kg). The animals were divided in two groups, one for each molecule (n=9 for NLX-112; n=9 for NLX-101). The intraperitoneal injection of agonist or saline was performed 15 minutes after the beginning of the phMRI session, resulting in 300 baseline scans and 900 post-injection scans. A voxel-based analysis of the data was performed at an individual level (for each scan, comparison between different time periods post-injection versus baseline), with the non-specific changes of BOLD signal in ventricles and white matter as regressors of non-interest, followed by a second-level analysis in a block design using a General Linear Model (GLM) approach (comparison between agonists conditions and saline condition) with the software Statistical Parametric Mapping (SPM12, The Wellcome Trust Center for Neuroimaging, London, UK). The statistical significance was set at p<0.001 uncorrected.

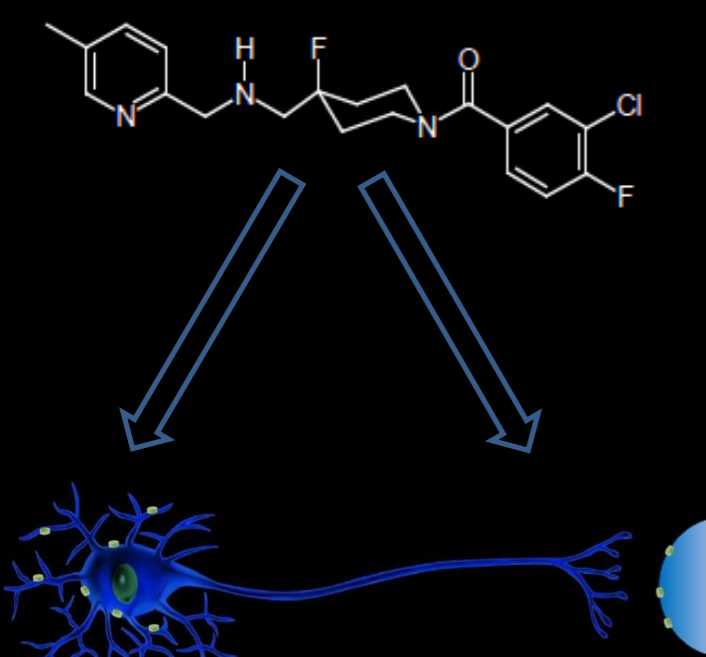
0.16 mg/kg

0.32 mg/kg

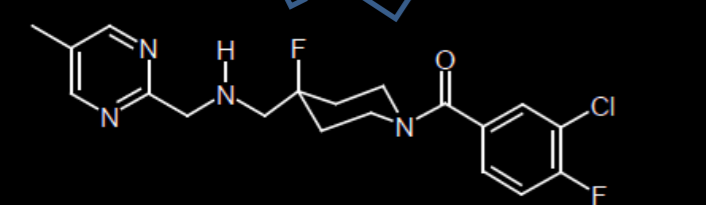
0.63 mg/kg



NLX-112



NLX-101



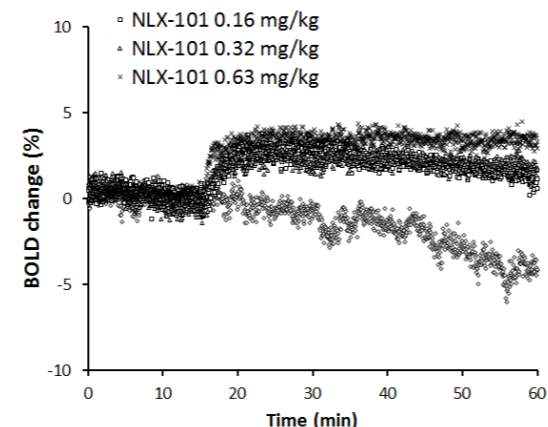
Results

At equal doses, NLX-112 and NLX-101 induced distinct patterns of hemodynamic changes.

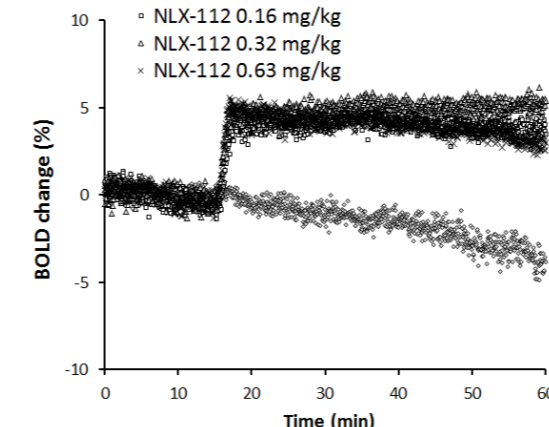
NLX-112 elicits increased BOLD signal in cingulate cortex, thalamus and colliculi, and decreased BOLD signal in somatosensory cortex, hippocampus, amygdala, raphe nuclei, brainstem, and cerebellum at every doses.

NLX-101 elicited weaker increases in thalamus and stronger increases in cingulate cortex, and weaker decreases in brainstem and cerebellum. NLX-101 also inhibits lateral septum contrary to NLX-112, and produces no effect in dorsal raphe nucleus at 0.16 mg/kg, consistently with its preference for postsynaptic receptors, as previously reported at this dose [2].

A



B



Mean change (%) in overall BOLD signal intensity in cingulate cortex. The time courses obtained from each rat, i.e. the average of all voxels in the region in individual datasets, were normalized compared to the baseline period. A – Effect of NLX-101 at different doses compared to saline (n=9); B – Effect of NLX-112 at different doses compared to saline (n=9). The same rats received the four scans in each group. These changes in BOLD signal were statistically compared for each voxel of the brain between postinjection and baseline, then between agonists and saline, to generate the maps above.

Conclusions

In continuity with previous findings [5], this study suggests that 5-HT_{1A} biased agonists, preferentially targeting different intracellular pathways, can display different hemodynamic signatures, due to the stimulation of receptors located in different regions of the brain. Our results are consistent with previous studies of NLX-112 and NLX-101 using microdialysis and electrophysiology [2].

PharmacMRI is therefore a useful approach to non-invasively map the central effects of biased agonists in vivo, and is even able to distinct between two structural analogs like NLX-112 and NLX-101.

Disclosure statement

Adrian Newman-Tancredi is employed by Neurolix Inc. The authors declare no competing financial interests.

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