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Functional brain and trigeminovascular changes in migraine using a new approach of neuroimaging: the functional ultrasound imaging (fUSi)

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► To cite this version:

Lauriane Delay, Samuel Diebolt, Nathalie Ialy-Radio, Thomas Deffieux, Mickaël Tanter, et al.. Functional brain and trigeminovascular changes in migraine using a new approach of neuroimaging: the functional ultrasound imaging (fUSi). Neuroscience 2022 - Annual Meeting, Nov 2022, San Diego (CA), United States. . hal-04849429

HAL Id: hal-04849429

<https://uca.hal.science/hal-04849429v1>

Submitted on 19 Dec 2024

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Introduction

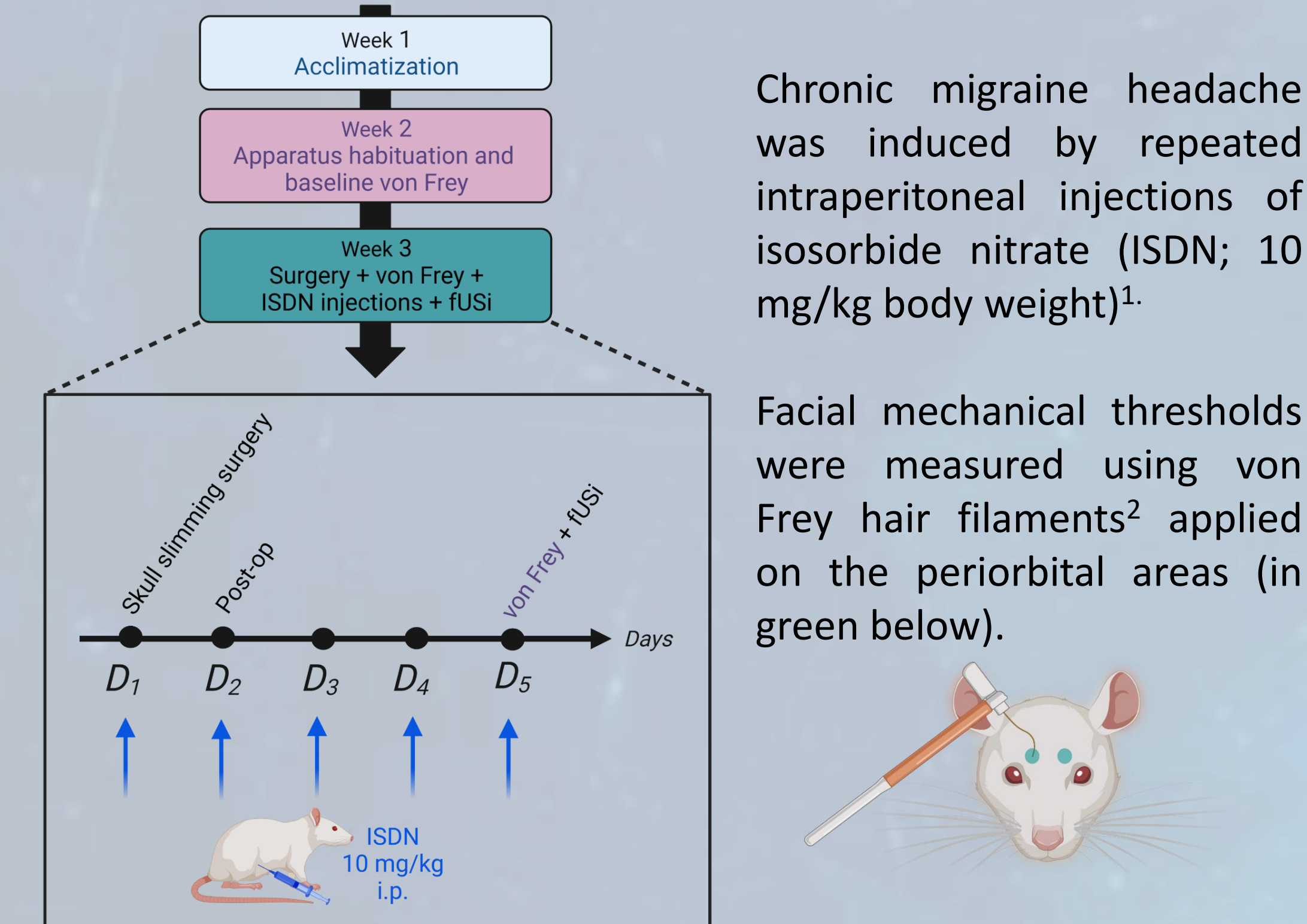
As a leading cause of disability worldwide, migraine is a neurovascular disorder characterized by headaches crisis and sensory hypersensitivities such as photophobia and allodynia. Migraine pathophysiology is complex and still partially understood. We used a novel brain neuroimaging modality that is particularly interesting for vascular diseases: the functional ultrasound imaging (fUSi). As an alternative to functional magnetic resonance imaging (fMRI), this modality of neuroimaging enables the measurement of cerebral blood volume with a high sensitivity and spatio-temporal resolution (100 μ m and 1 ms, respectively).

This study aimed at i) deciphering the sequence of **vascular dynamic changes** in a large part of the brain and ii) study **changes of functional connectivity** in different parts of the brain in a relevant animal model of migraine induced by repeated systemic administrations of isosorbide dinitrate (ISDN), a nitric oxide (NO) donor.

Material & Methods

Study design:

A first set of data was obtained on 9 male Sprague-Dawley rats.



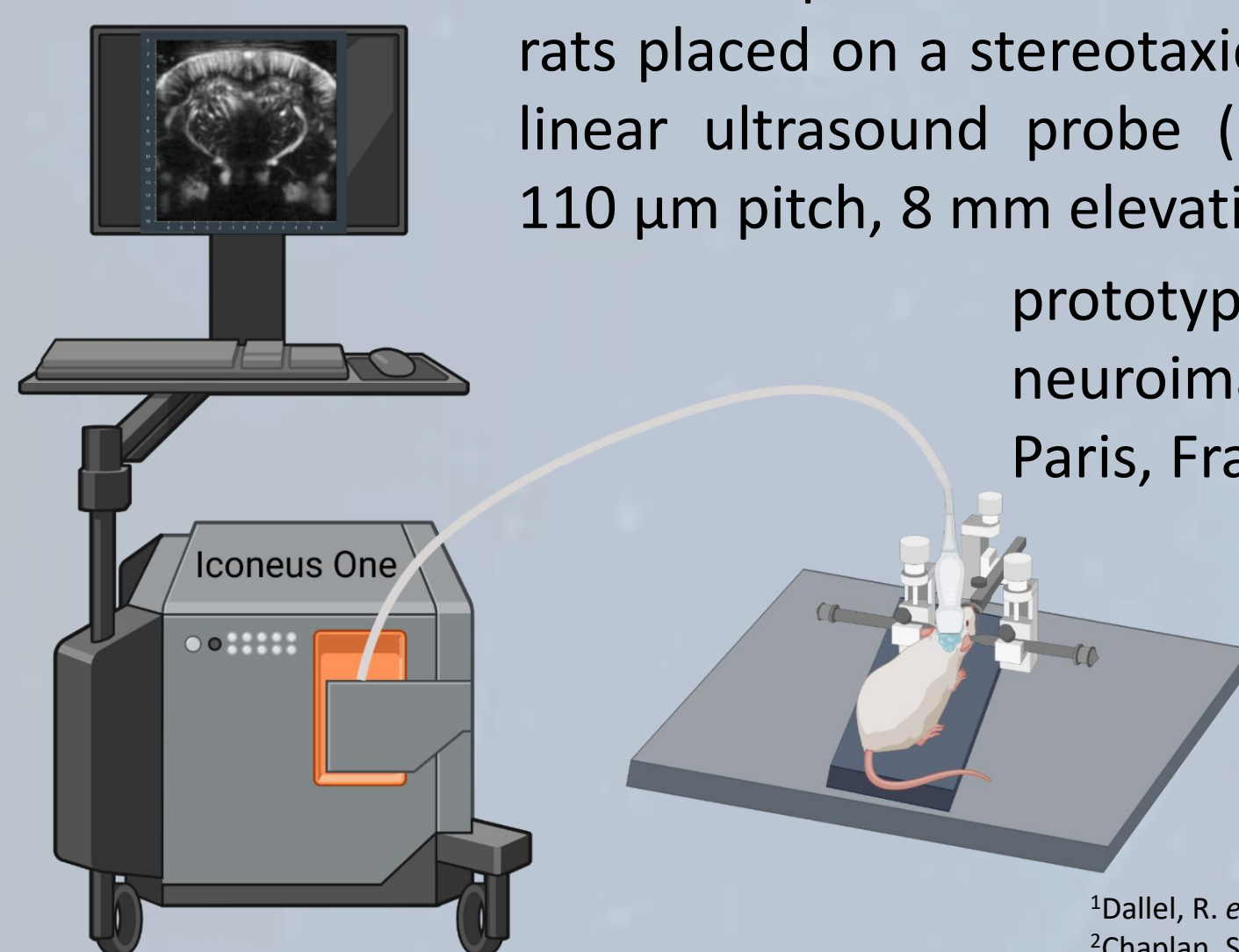
Chronic migraine headache was induced by repeated intraperitoneal injections of isosorbide nitrate (ISDN; 10 mg/kg body weight)¹.

Facial mechanical thresholds were measured using von Frey hair filaments² applied on the periorbital areas (in green below).

Set-up for functional ultrasound imaging (fUSi)

fUSi was performed on anesthetized (isoflurane) rats placed on a stereotaxic apparatus at D₅ using a linear ultrasound probe (128 elements, 15 MHz, 110 μ m pitch, 8 mm elevation focus) driven by a

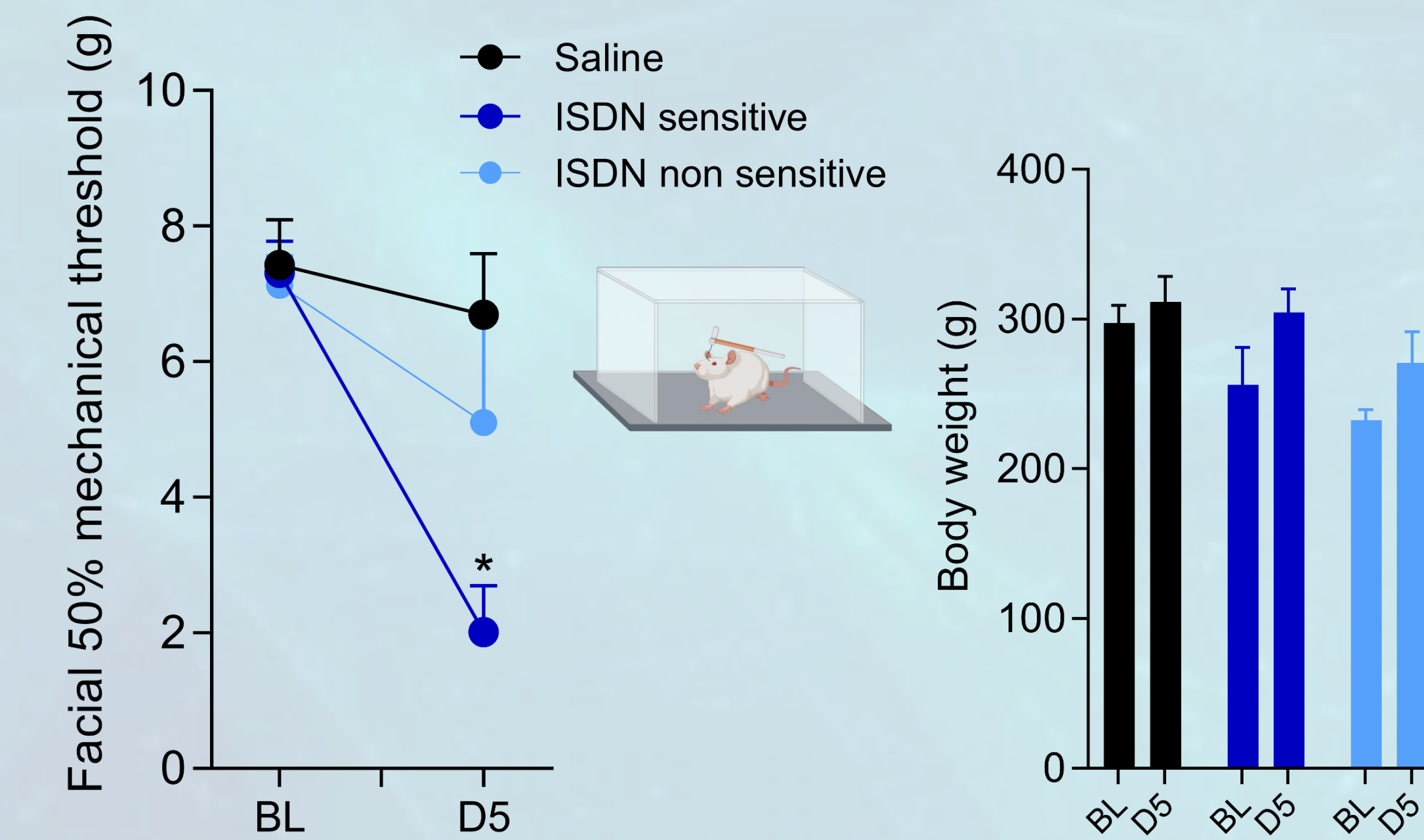
prototype ultrasonic ultrafast neuroimager (Iconeus One³, Paris, France).



¹Dallel, R. et al., (2018), doi: 10.1177/0333102417714032
²Chaplan, S. R. et al. (1994) doi: 10.1016/0165-0270(94)90144-9
³https://iconeus.com/iconeus-one/

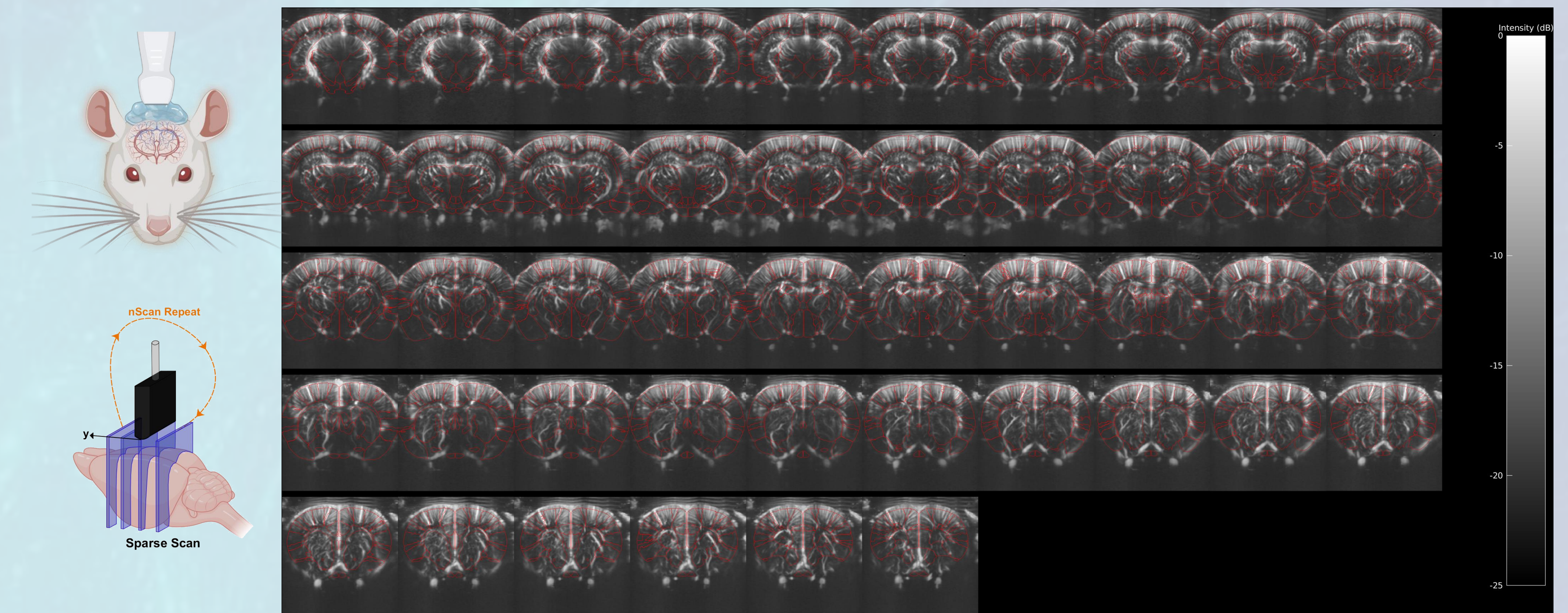
Results

Repetitive injections of ISDN induced facial mechanical allodynia in sensitive rats without affecting body weight gain.

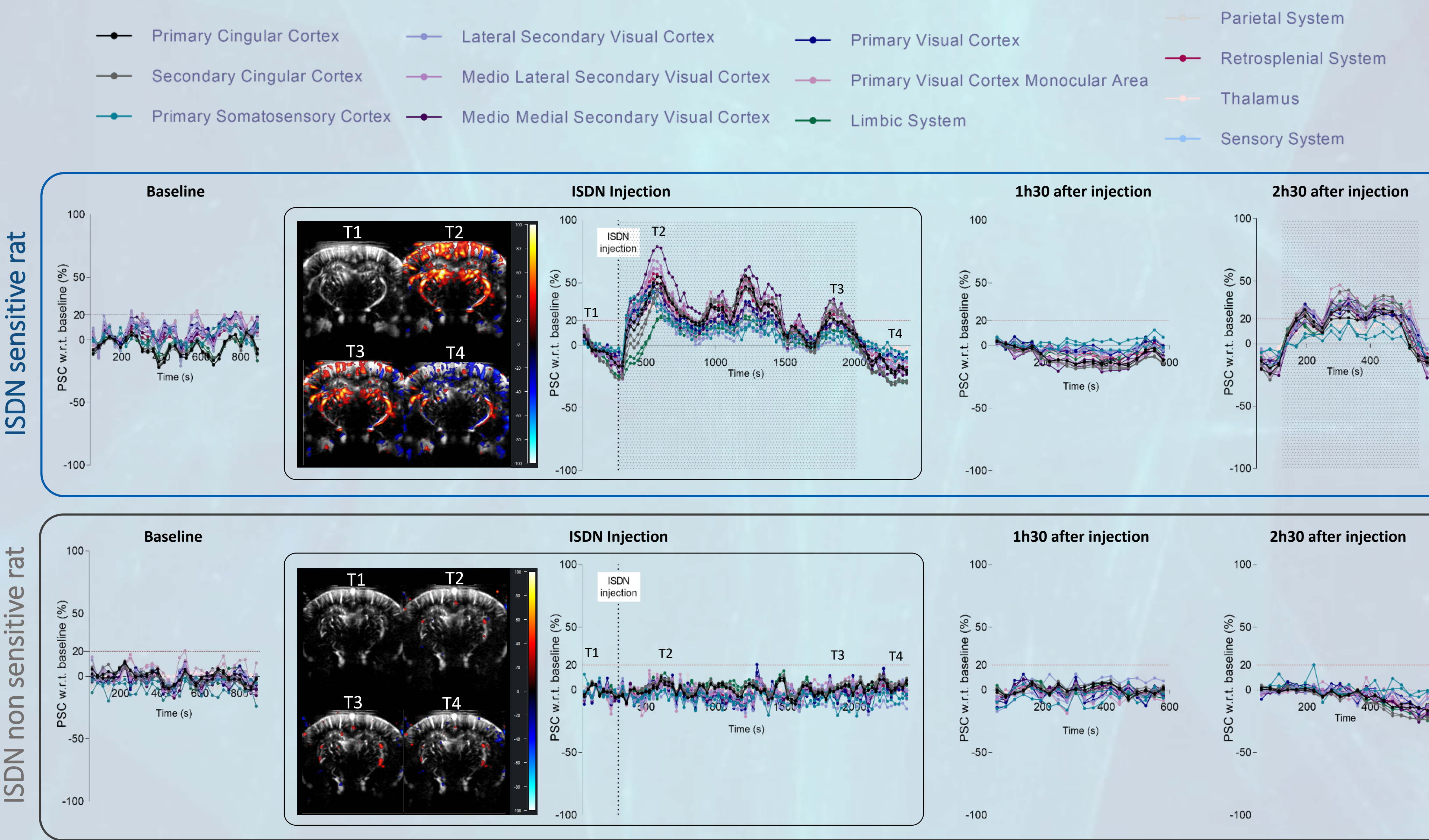


n=3 Saline, n=4 ISDN sensitive, n=2 ISDN non sensitive; Two way ANOVA/Tukey post-hoc test, * p < 0.05 compared to Saline

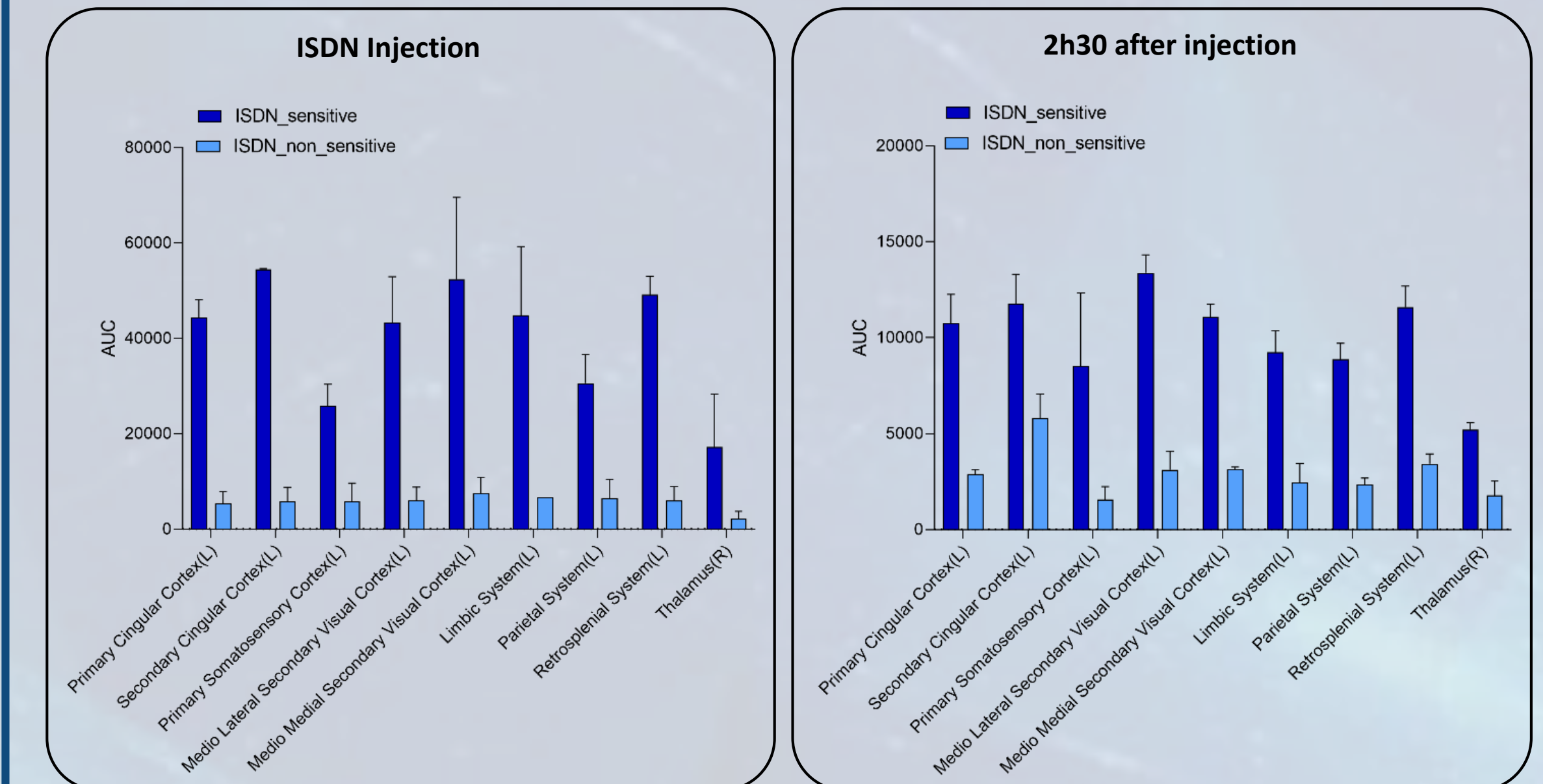
Example of average power Doppler for a sparse scan of 46 scans, 0,2 mm step, and brain atlas ROI mapping.



ISDN injection induced an increase of cerebral blood flow in several parts of the pain matrix and photophobia-associated cortical areas, immediately and 2h30 after the fifth injection of ISDN in sensitive rats but not in control non sensitive rats : focus on one representative ISDN sensitive and one representative ISDN non sensitive rats.

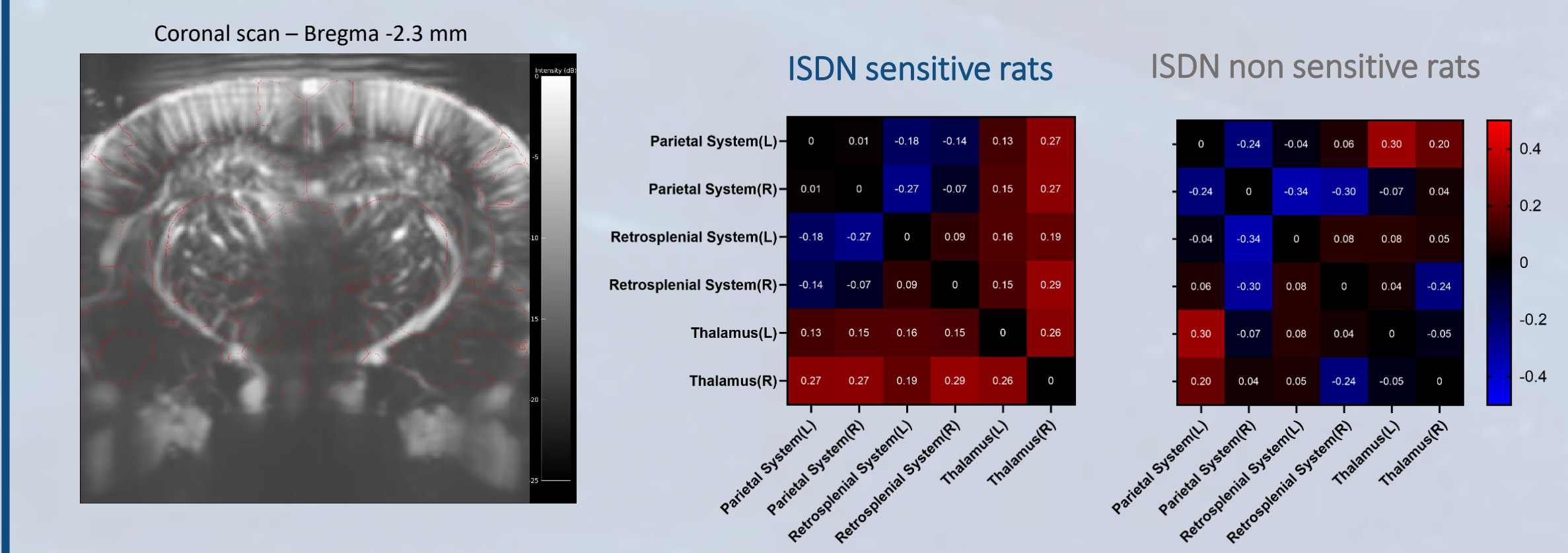


ISDN sensitive rats exhibit a significant increase of the CBV mean variations within selected ROI compared to ISDN non sensitive rats.



Mean for n=3 ISDN sensitive, n=2 non sensitive

Change in difference of functional connectivity between before and after the fifth ISDN injection for parietal and retrosplenial systems, and thalamus in ISDN sensitive rats versus ISDN non sensitive rats.



Mean for n=3 ISDN sensitive, n=2 ISDN non sensitive

Conclusions

Our first set of data validates the use of functional ultrasound imaging to explore cerebral blood flow variations and functional connectivity during migraine crisis induced by repeated systemic injection of nitric oxide donor. ISDN sensitive rats (4/7 rats) exhibit facial mechanical allodynia, and cerebral blood flow changes in several parts of the pain matrix (e.g. cingulate cortex, retrosplenial system, thalamus, somatosensory cortex), in the limbic system known to regulate the motivational or behavioral responses to pain, and in photophobia-associated cortical areas, immediately after the fifth injection of ISDN and 2h30 later. These results are not seen in ISDN non sensitive control rats (2/7 rats).