OXYTOCIN BRAIN-WIDE FUNCTIONAL ARCHITECTURE WITH OPTO-fMRI

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Background: Oxytocin (OT) is crucial in the regulation of social cognition. OT is synthetized in discrete hypothalamic areas, mainly paraventricular (PVN) and supraoptic nucleus of the hypothalamus. Although the effects of OT on behavior have been studied for years, the mechanisms by which OT acts are unclear, in part because its effects on the activity of its many downstream targets are largely unknown.

Aims: Here, we sought to identify the functional networks where OT exert its effects, using a combination of optogenetics, electrophysiology and functional magnetic resonance imaging (fMRI).

Method: We expressed channelrhodopsin-2 (Chr2) in OT neurons of the PVN in adult male Sprague-Dawley rats using an adeno-associated virus. After AAV expression, rats were implanted with unilateral fiber optic cannulas targeting the PVN and placed in a 7-Tesla fMRI scanner under anesthesia. We then optically stimulated OT neurons in a dose-dependent manner by varying the light intensity of the laser while recording changes in the blood-oxygen level dependent (BOLD) signal.

Preliminary results: After anatomical and electrophysiological validation of our optogenetic stimulation protocols, control and opsin-expressing rats were tested in opto-fMRI experiments. Optogenetic activation of these cells induced a light-dependent increase of activated voxels, that was not observed in control (without opsin) animals. In order to identify brain-wide functional networks related to PVN OT activation, we first studied evoked changes in BOLD signal temporally locked to light stimulation. BOLD activity only survived statistical significance in very discrete brain areas, namely a subregion of the retrosprenial cortex and the vertex of the dorsal hippocampus. Probability of activation of these brain areas across animals was however low, suggesting that these effects were small. Due to the neuromodulator action of OT, we hypothesized that the effects of this neuropeptide might be more robust when analyzing changes on resting state. Identification of significant dimensions (networks) and clustering analysis revealed no significant differences between control and activated animals. Our results are thus inconclusive, most probably due to the slow dynamics of action that recent studies have proposed for OT (Wahis et al, Nat Neurosci, 2021) which fall in the minutes' range. Our fMRI acquisition protocol, in the seconds range, might have been thus blind to these very slow effects of OT.

Keywords: Oxytocin, optogenetics, fMRI, social behavior, rats

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