Back translational study: social dysfunction association with Default Mode Network

P.0614

Elmira Khatamsaz[1,2], Franziska Stoller[1], Susanne Zach, Dennis Kätzel[2], Bastian Hengerer[1]

[1]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany
[2]Ulm University, Germany

Elmira.khatamsaz@boehringer-ingelheim.com

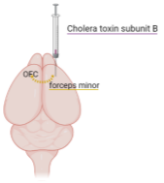
INTRODUCTION

PRISM* project focuses on understanding the biological background behind social deficits, specifically social withdrawal irrespective of diagnosis. Reduced connectional integrity in fiber tracts such as Forceps minor has been indicated in low social individuals in PRISM1. These fiber tracts are also involved in the Default Mode Network (DMN) and the Social network and they share a common region, the **Orbitofrontal Cortex (OFC)**. This study aims to back translate the clinical data to preclinical studies and associate social dysfunction in rodents with DMN and particularly OFC.

METHODS

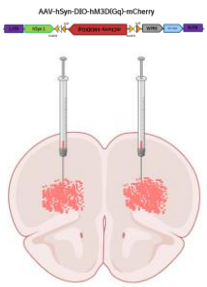
Projection neurons characterization

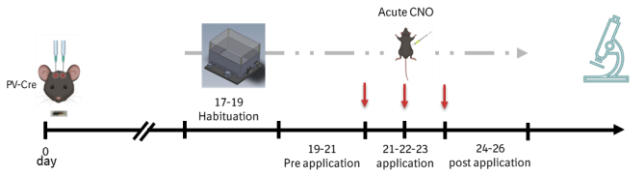
Combining retrograde tracer Cholera Toxin subunit B (CTB) and *In Situ* hybridization technique using glutamatergic (vesicular glutamate transporter [VGLUT]) and GABAergic (vesicular GABA transporter [VGAT]) markers.



Chemogenetic modulation of OFC in PV-Cre mouse line

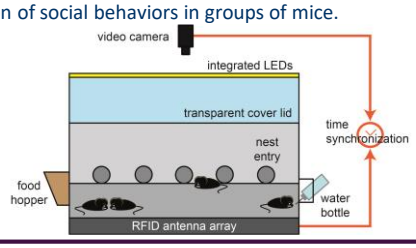
Modulation of OFC was performed by stereotaxically injecting an AAV virus which drives expression of an excitatory (hM3Dq) DREADD to PV+ interneurons in a PV-Cre mouse line. Intraperitoneal administration of the synthetic drug clozapine-N-oxide (CNO) as chemical actuator, induces Gq activation which mediates increased neuronal activity selectively in PV+ interneuron, leading to hypoactivation of OFC.





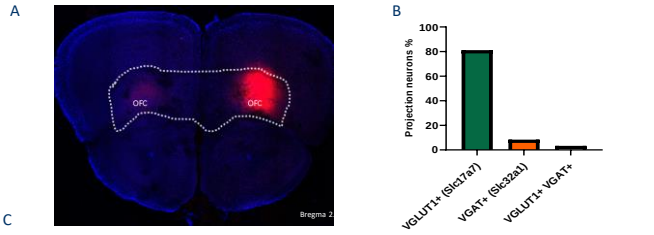
Automated behavioral analysis

For behavioral analysis, RFID-assisted SocialScan combined with video tracking has been used. This tool provides a long-term observation of social behaviors in groups of mice.

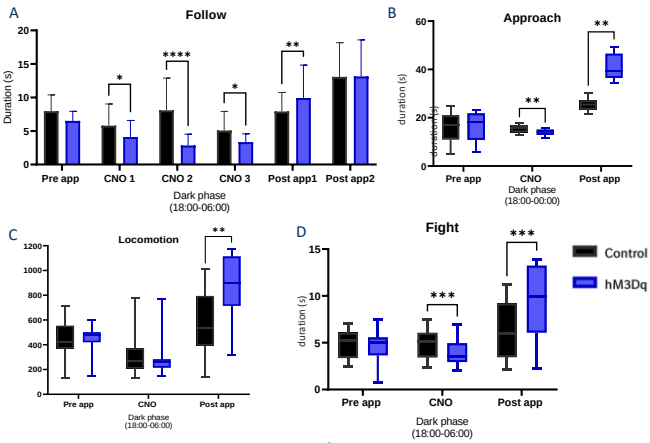


RESULTS

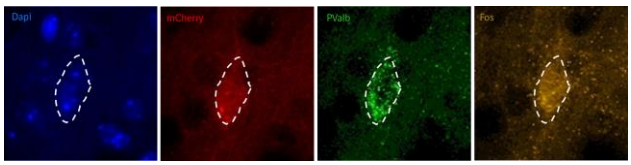
Slc17a7 abundant neuronal population



Social /non-social behaviors



PV+ interneurons transfection/activation



CNO treatment leads to activation of PV+ interneurons (shown by Fos expression)

CONCLUSION

We demonstrate less social interaction after bilateral chemogenetic activation of PV+ interneurons in the OFC and impairing the E/I balance in this brain area. Unexpectedly, our data indicate a subsequent compensatory long-term effect of OFC PV-interneuron activation after termination of CNO application. In this case social and non-social parameters are significantly higher compared to control group up to 2 days after the last CNO administration. These observations suggest that increasing the inhibitory drive in the OFC is manipulating a brain circuit involved in behavioral regulation.

PRISM: Psychiatric Ratings using Intermediate Stratified Markers
Two figures are Created with Biorender.com
Authors have no financial disclosures that would be a potential conflict of interest with this poster