The Central Amygdala as a Motivational Hub: Paving the Way for Personalized Therapies in Behavioral Disorders

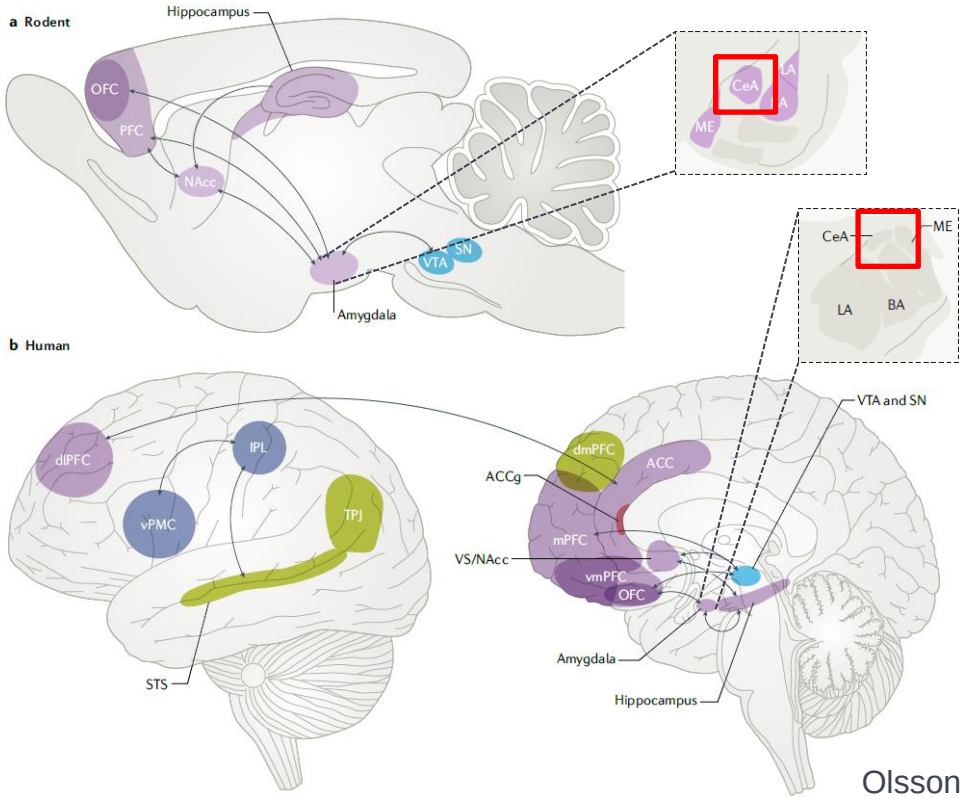
Ewelina Knapska

Impaired motivation

general motivational deficits

social interaction deficits

Reward system in the brain



CeA encodes motivational significance of stimuli

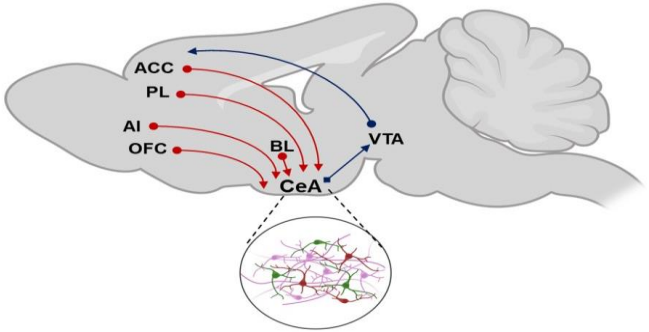
CeA stimulation amplifies motivation for food and drug rewards

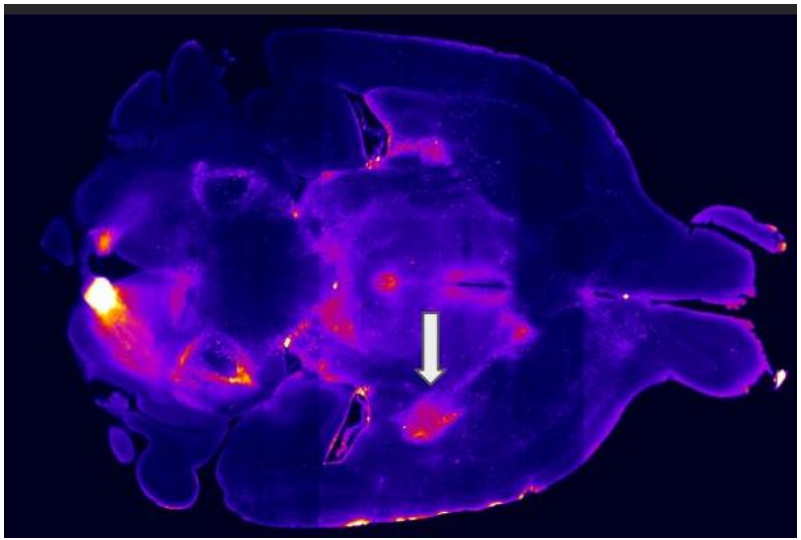
Balleine and Killcross, Trends Neurosci, 2006
Robinson et al., J Neurosci, 2014;
Warlow et al., J Neurosci, 2017;
Warlow et al., Nat Commun, 2020

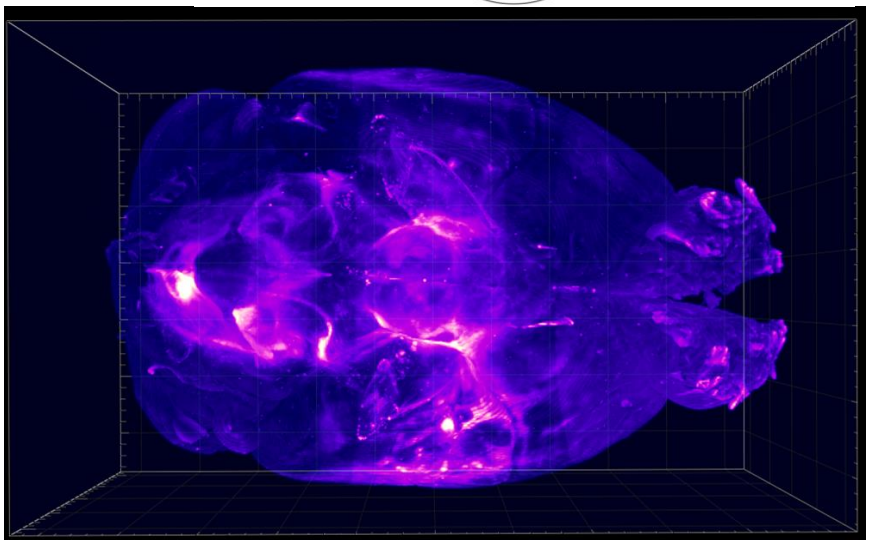
Olsson, Knapska, Lindstrom., Nat. Rev. Neurosci., 2020

Central amygdala (CeA) as a hub structure

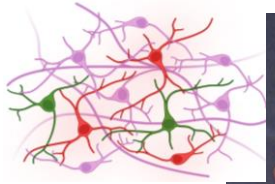
BRAIN CLEARING

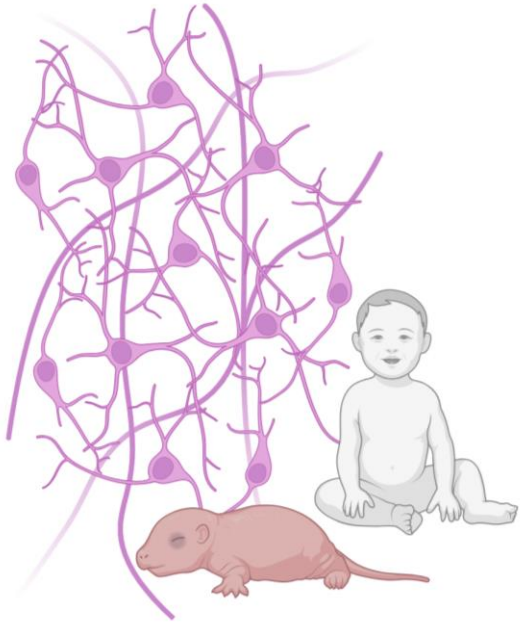


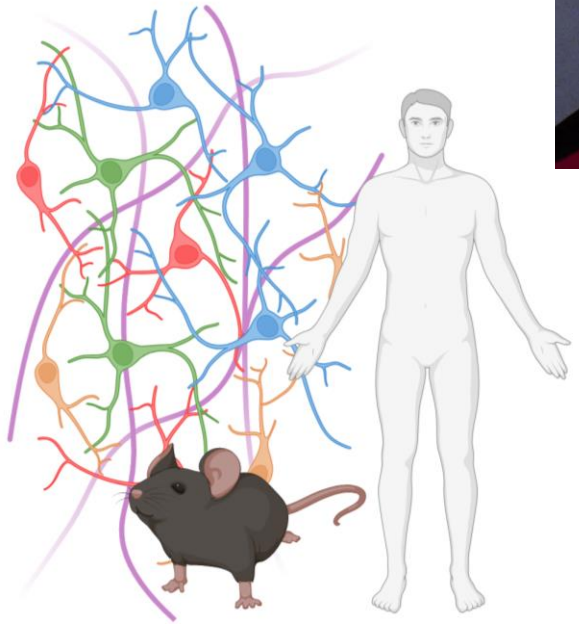


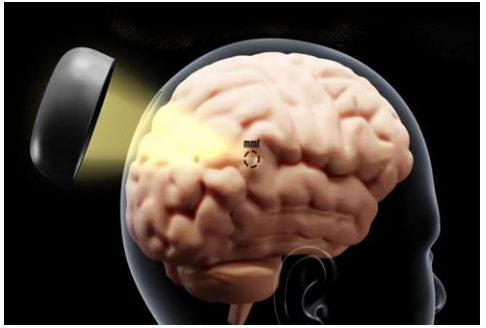


Neuronal circuits in the adult brain are highly specialized









Transcranial Ultrasound Stimulation

Central Amygdala (CeA) is activated by food-motivated behavior and social interaction

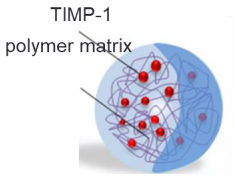
Knapska et al., Learning&Memory, 2006
Knapska et al., PNAS, 2006;
Rojek-Sito et al. PLOS Biology, accepted

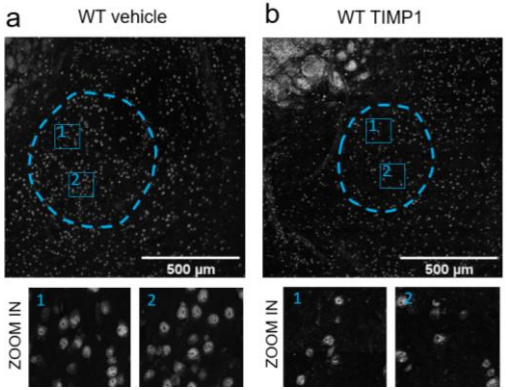
…but it hosts specialized neuronal circuits

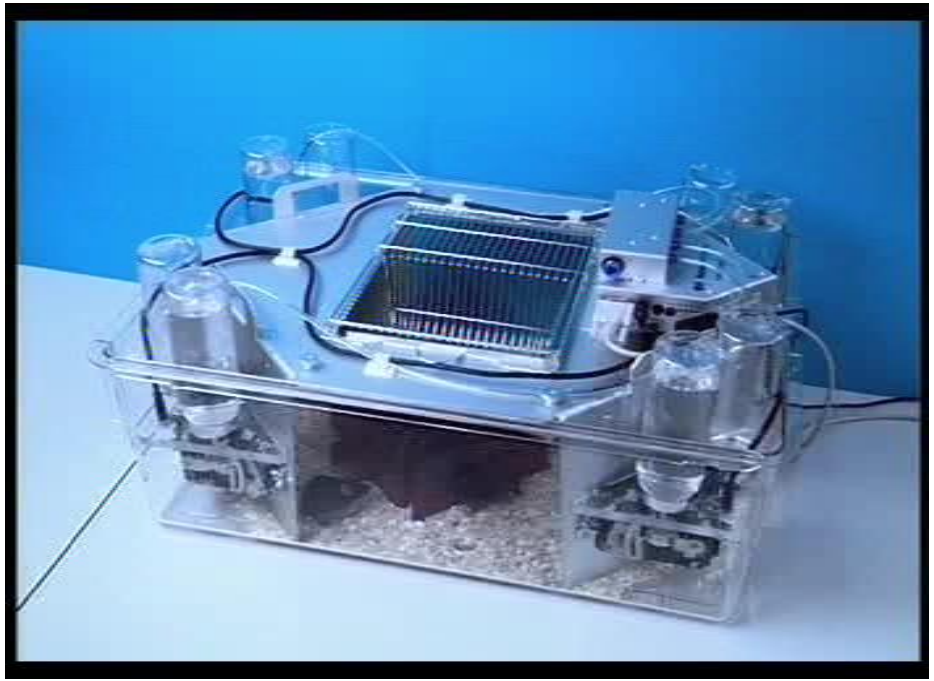
MMP-9-dependent neuronal circuit mediates food seeking behavior but not social interaction

Knapska et al., J. Neurosci., 2013
Puscian et al., Mol. Psychiatry, 2022
Lebitko et al., in prep.

MMP-9-dependent neuronal circuit mediates food seeking behavior

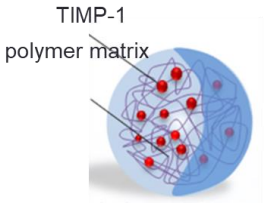




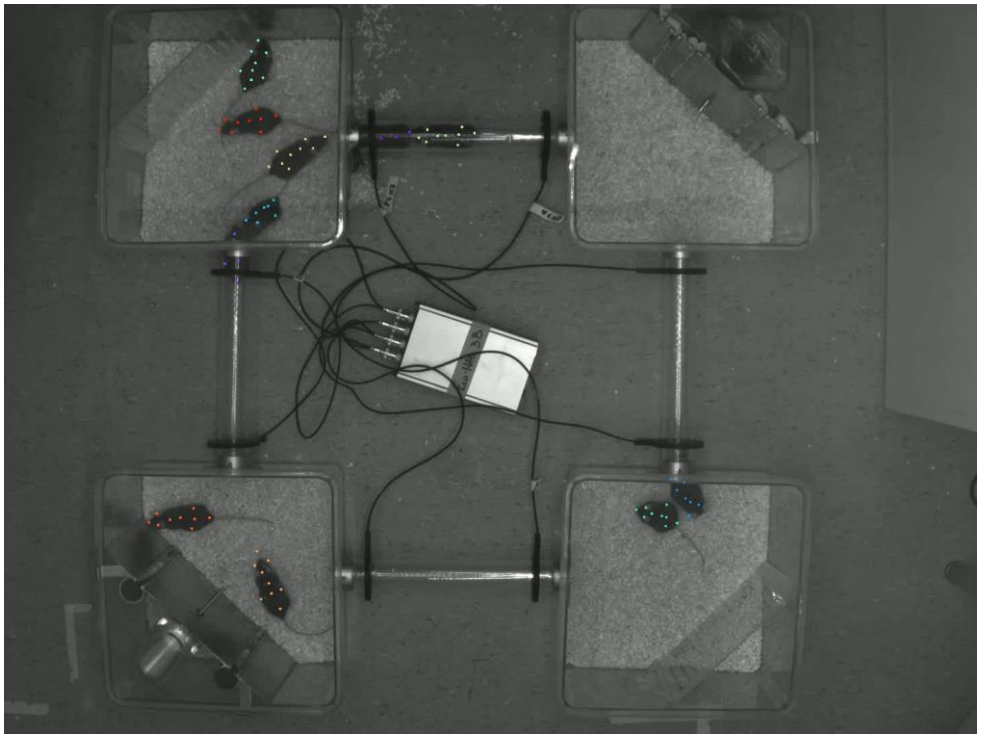


>> Studying voluntary behavior under more naturalistic settings consistently engaging well-defined, evolutionarily conserved neural circuits

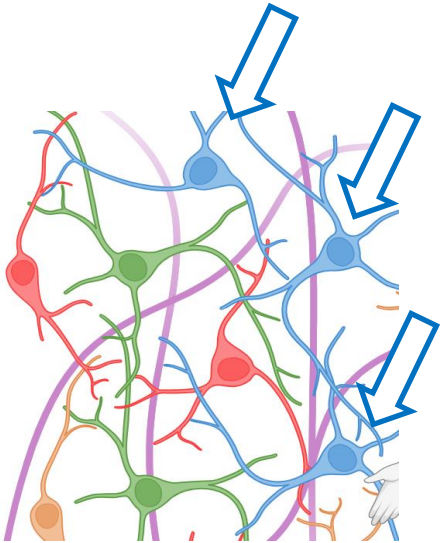
MMP-9-dependent neuronal circuit mediates food seeking behavior



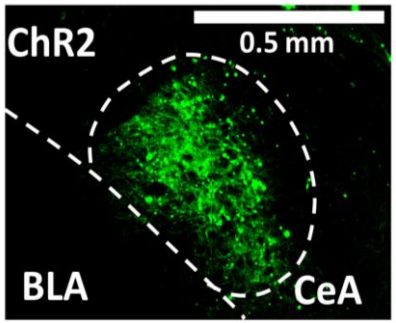
Puscian et al., eLife., 2016
Winiarski et al., in revision

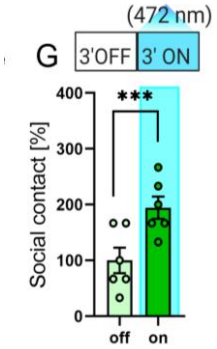


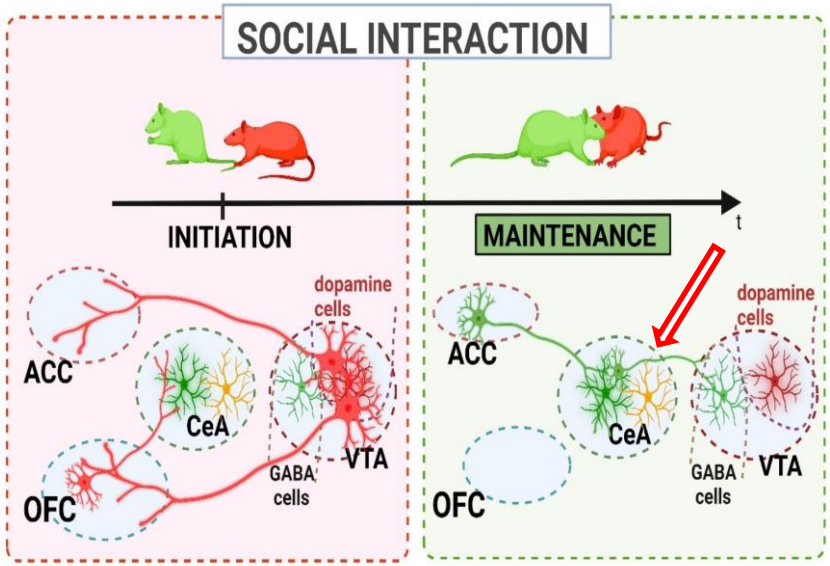
MMP-9-dependent neuronal circuit mediates food seeking behavior



There are CeA circuits involved in social interaction but not food-motivated behavior

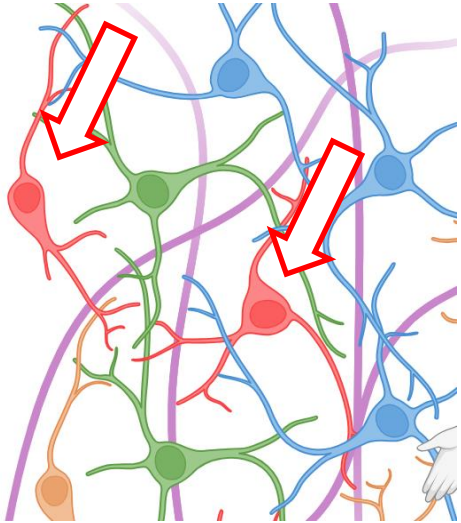




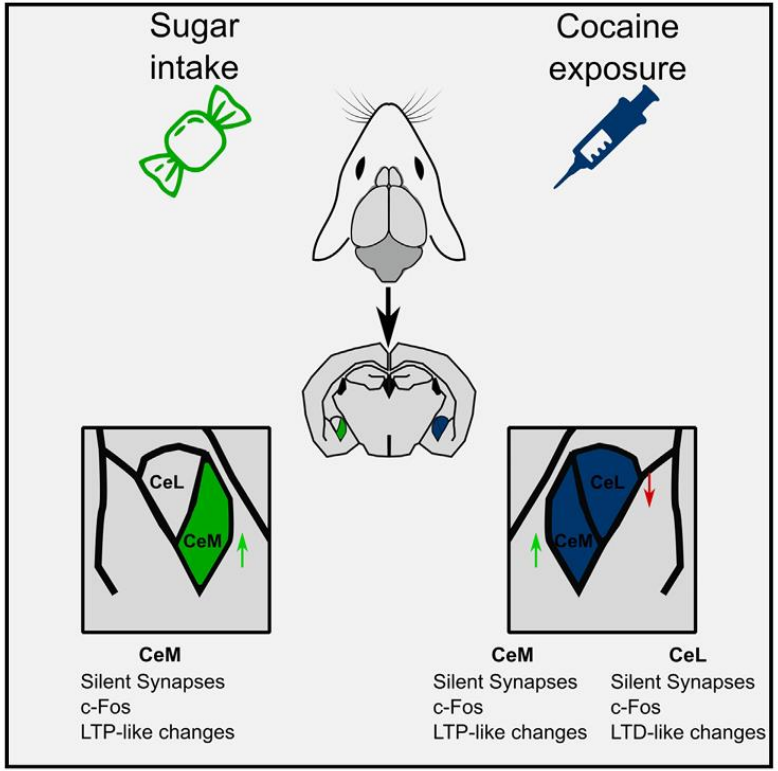


Knapska et al., PNAS, 2012;
Andraka, Kondrakiewicz et al. Current Biol. 2021;
Rojek-Sito et al., PLOS Biology, accepted

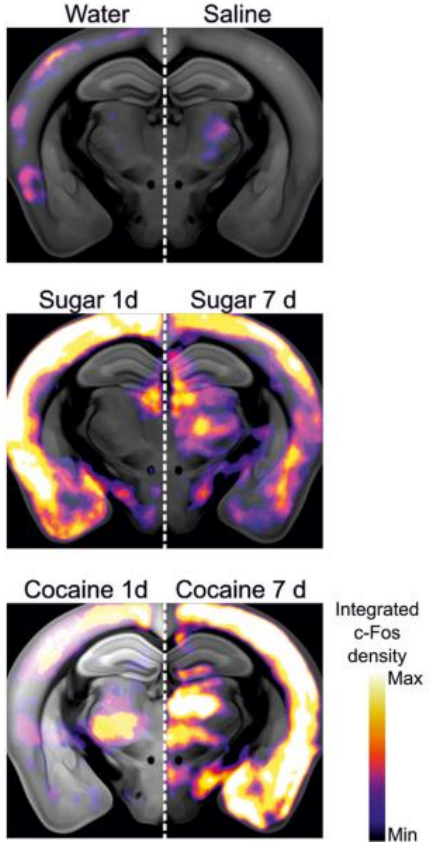
There are CeA circuits involved in social interaction but not food-motivated behavior



Different neuronal circuits of the CeA are activated by food and drugs



Bijoch et al., Cell Reports, 2023



Bijoch et al., Translational Psychiatry, 2023

Manipulating plasticity of MMP-9-dependent neuronal circuits in the CeA to rescue impaired behavior

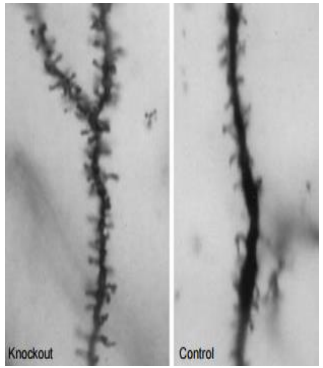
Fragile X Syndrome (FXS)

FXS patients and FMR1 KO mice have increased level of MMP-9
(Li et al. 2001)

- a neurodevelopmental disorder

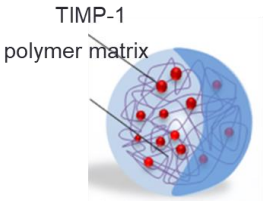
- lack of the FMR1 protein, a translational repressor, leads to up-regulation of locally translated proteins involved in synaptic transmission and plasticity, including MMP-9

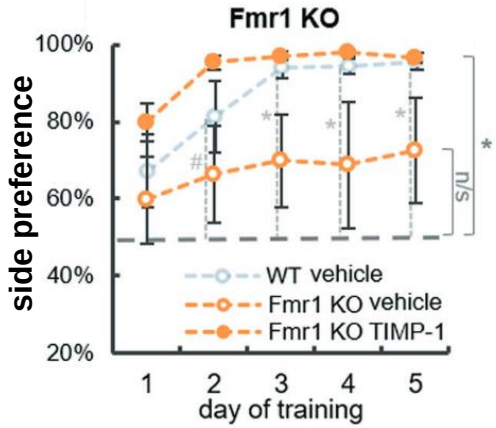
- it is the most common cause of familial (monogenic) **intellectual disabilities and autism**

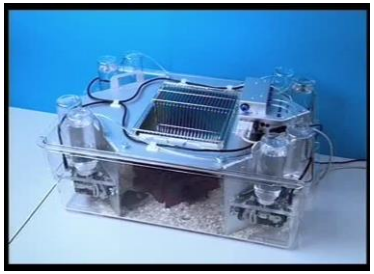


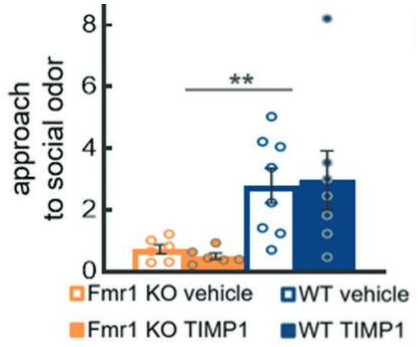
https://en.wikipedia.org/wiki/Fragile_X_syndrome

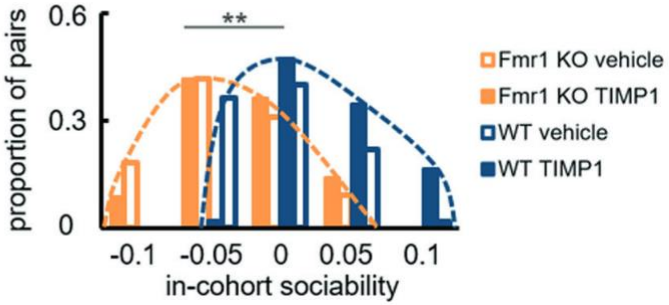
Inhibition of the CeA MMP-9 rescues food motivated learning but not social impairments







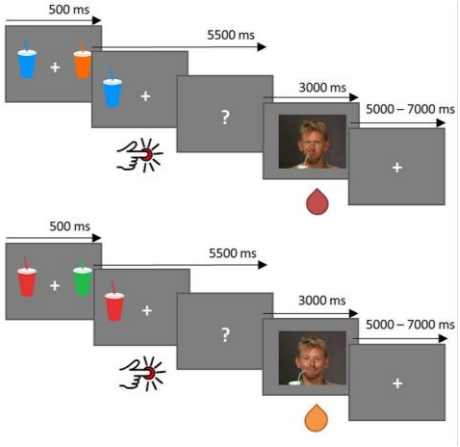


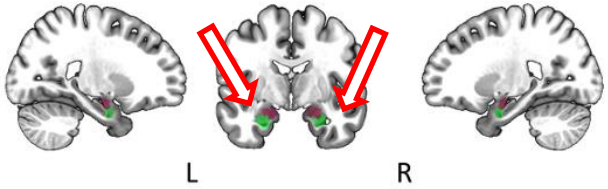


Puscian et al., Mol. Psychiatry, 2022

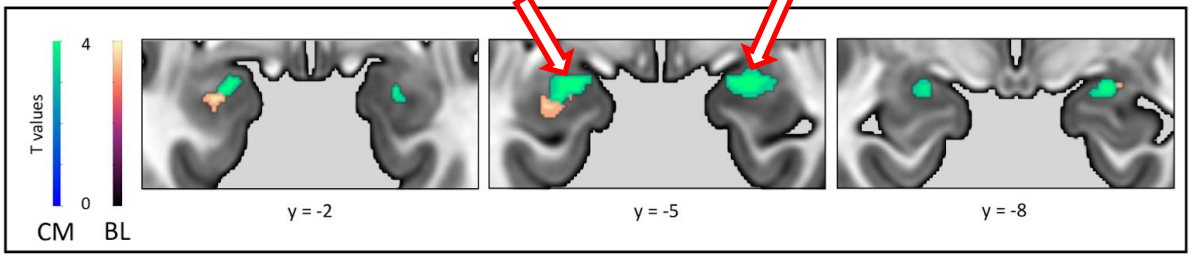
We can manipulate the CeA neuronal circuits in the symptom-specific manner to rescue impaired behavior. Restoring MMP-9 activity and subjecting mice to behavioral training rescues food motivation.

The human CeA contributes to food motivated learning and processing social emotional cues



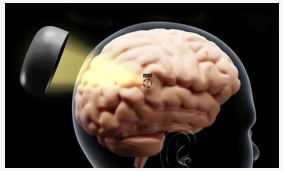


Kolada et al., J. Neurosci., 2023



Kazmierowska et al., in revision

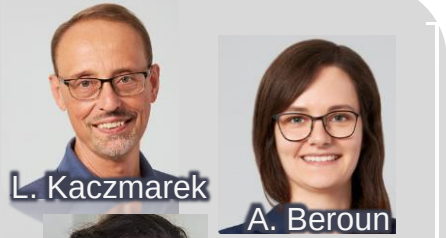
Conclusions



- The rodent and human Central Amygdala is involed in processing food- and social- related stimuli.
- The food- and social- related circuits only partially overlap.
- We can combat specific deficits in motivation or social interactions without affecting other properly working circuits.

The Central Amygdala neuronal circuits are a promising target for developing precise therapeutic interventions.

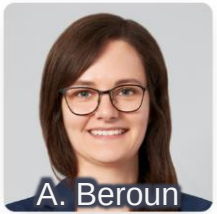
TWO-STEP BRAINCITY SYNERGY

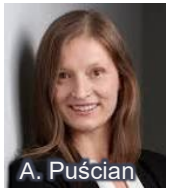


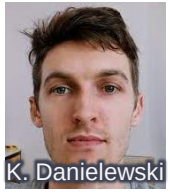
RODENT MODELS

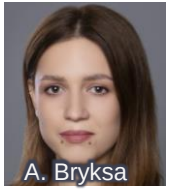
APPLICATION TO HUMANS

Acknowledgements









Knapska lab

Ksenia Meyza
Tomasz Górkiewicz
Iwona Szatkowska
Adam Gorlewicz
Anita Cybulska-Kłosowicz
Ewa Kublik
Karolina Rojek-Sito
Mateusz Kostecki
Tomasz Nikolaev
Anjaly Yadav
Adam Brosnan
Mohhamed Abdelfattah
Farzad Khanipoura
Asia Macaione

Marta Mikosz
Kacper Kondrakiewicz
Karolina Andraka
Maciej Winiarski
Aleksandra Nowak
Karolina Ziegart-Sadowska
Joanna Borowska
Maria Wołyniak
Krzysztof Bielski
Maja Wójcik
Kinga Nazaruk
Marta Wiatrowska
Łukasz Charzewski
Fahmida Haque
Anju Cyriac

E. Kolada

Nencki Institute
Wójcik lab
Gabriela Mochol
Szymon Łęski
LOBI (Imaging Unit)
Anna Kaźmierowska
Michał Szczepanik
Marek Wypych
Bartosz Kossowski
Dawid Droździel
Artur Marchewka
International Institute of Molecular and Cell Biology
Jacek Jaworski
Matylda Macias
Dorota Owczarek
Marcin Wawrzyniak
Marcelina Pieprzyk
Iwa Cymerman
University of Warsaw
Magdalena Dziembowska
Joanna Chmielewska
Miron Kursa
Krzysztof Turzyński
Jagiellonian University
Wojciech Solecki
Michał Kiełbiński
Lukasiewicz Research Network-PORT
Witold Konopka
SWPS University
Jarosław Michałowski
Technical Warsaw University
Grzegorz Kasprowicz

University of Michigan/ Texas A&M University
Stephen Maren
University of Zurich
Hans-Peter Lipp
Frieder Neuhäusser-Wespy
Karolinska Institutet
Andreas Olsson
Institut d'Investigacions Biomèdiques August Pi i Sunyer
Jaime de la Rocha
Daniel Duque
NERF/University of Leuven
Sebastian Haesler
Netherlands Institute for Neuroscience
Christian Keysers
Valeria Gazzola

European Funds Smart Growth
Republic of Poland
FNP Foundation for Polish Science
European Union European Regional Development Fund
erc European Research Council
NCN Narodowe Centrum Nauki
FENS KAVLI NETWORK OF EXCELLENCE