St Petersburg University

Университет Сириус

AI-POWERED IN VIVO SCREENS FOR NEUROACTIVE DRUG DISCOVERY USING ZEBRAFISH (DANIO RERIO)

Уральский федеральный университет

НИИНМ

Научно-исследовательский институт нейронаук и медицины

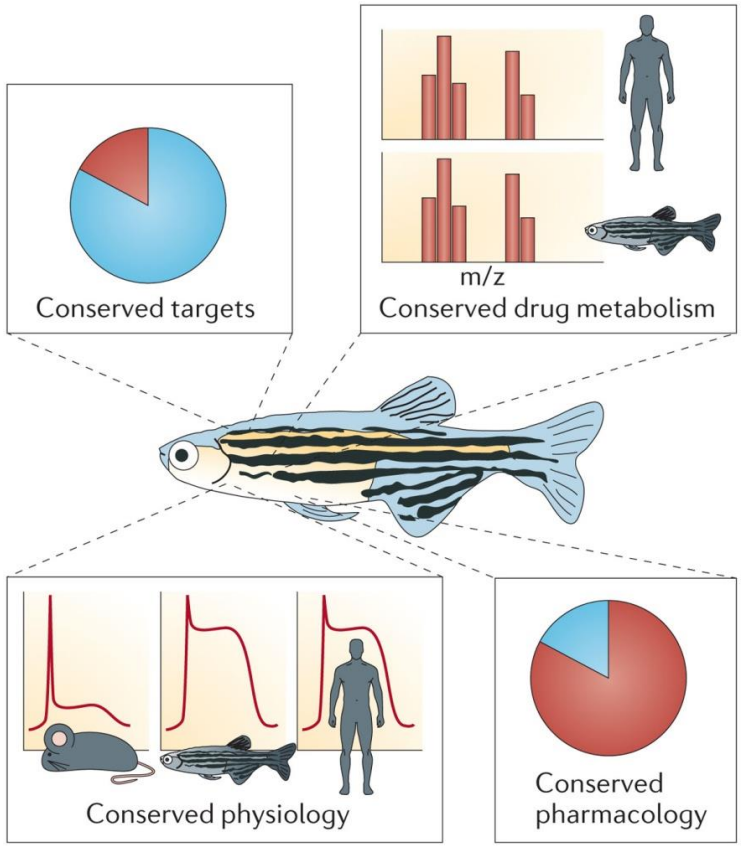
RAS Professor Allan V. Kalueff, PhD

MIPT
MOSCOW INSTITUTE OF PHYSICS AND TECHNOLOGY

September 18, 2023

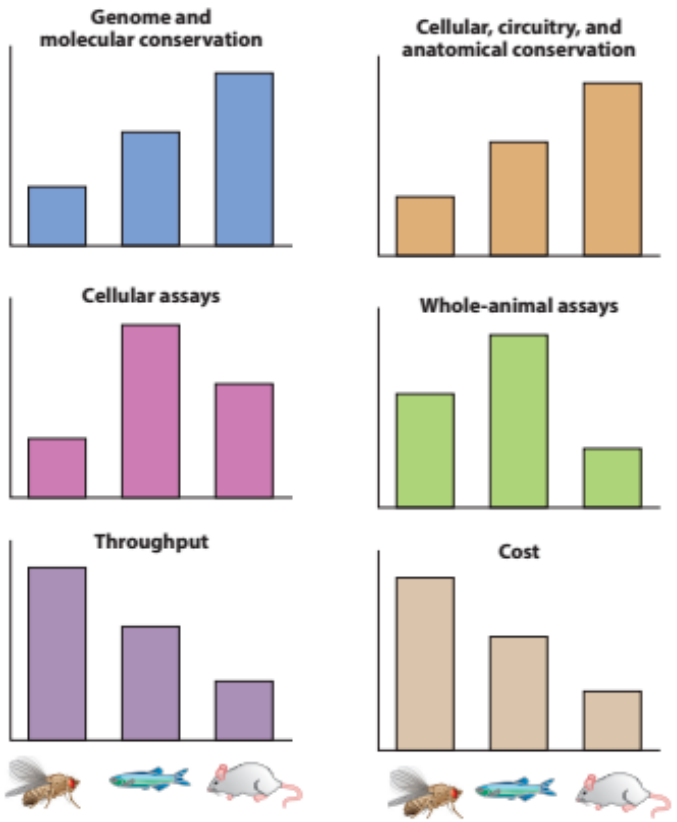
Национальный медицинский исследовательский центр имени В. А. Алмазова

Zebrafish as a model in biomedicine



Nature Reviews | Drug Discovery

MacRae & Peterson, 2015



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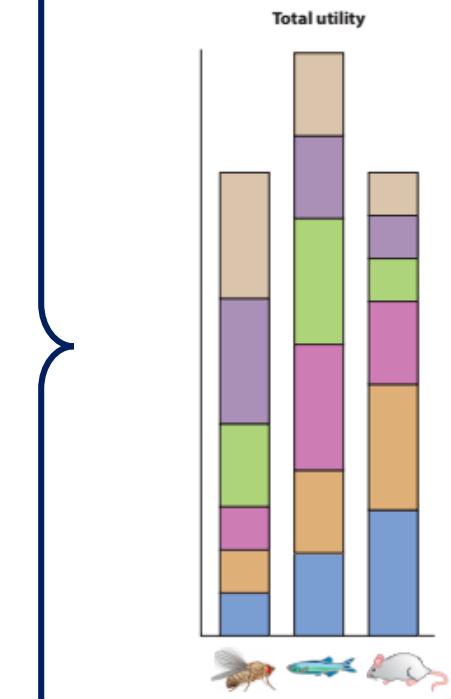

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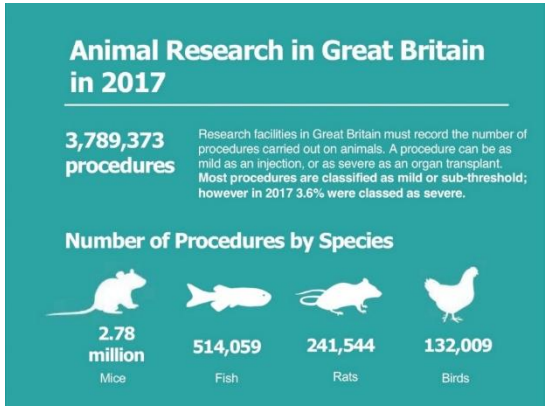
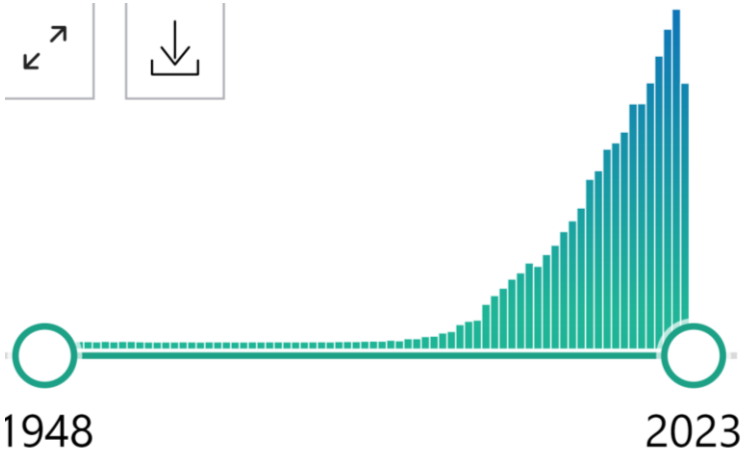
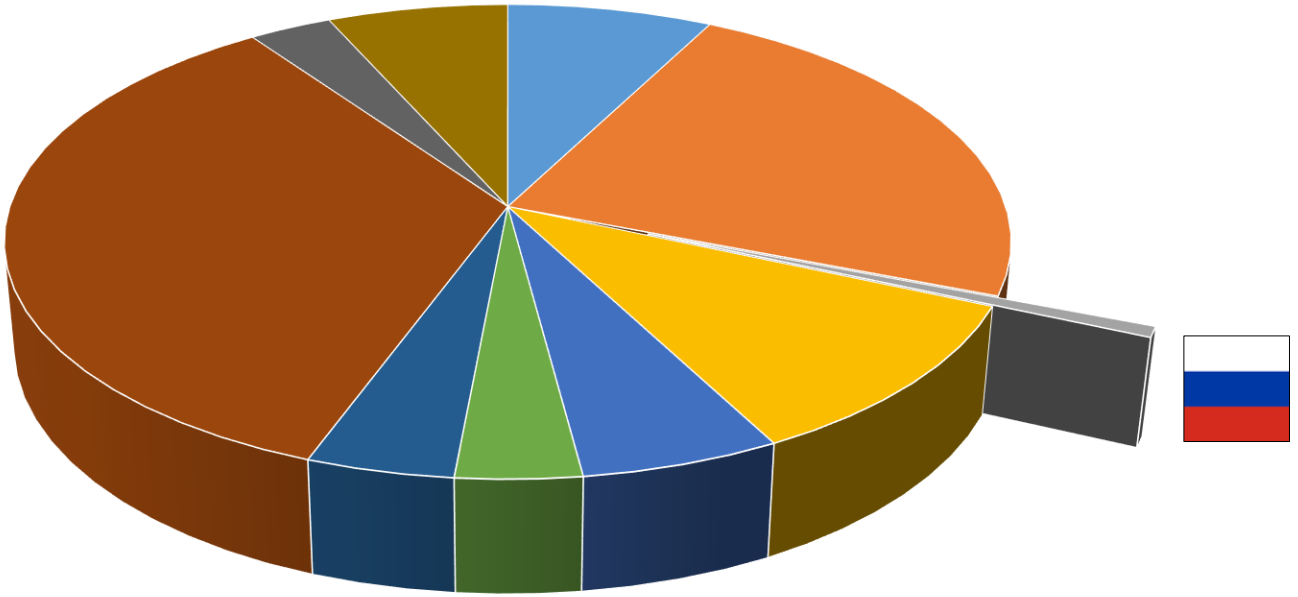




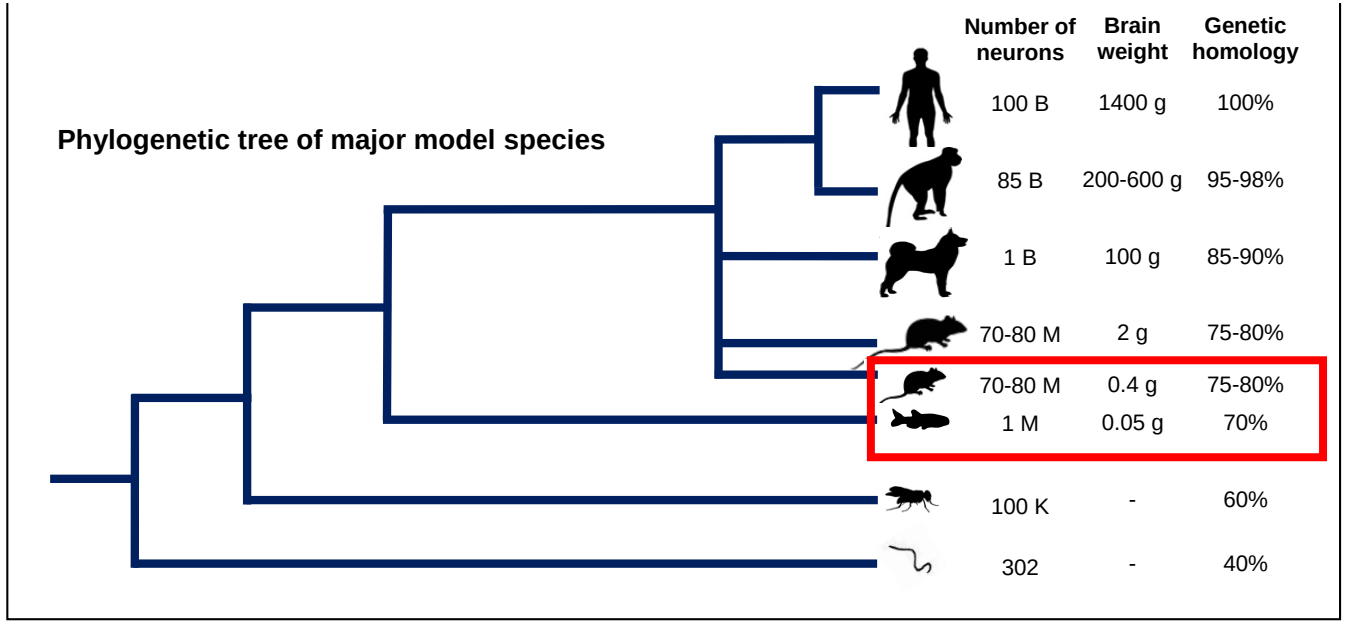
>50 000 papers

Zebrafish publications (%) by major world countries



United Kingdom
China
Russia
Germany
France
Spain
Italy
USA
Brazil
Japan

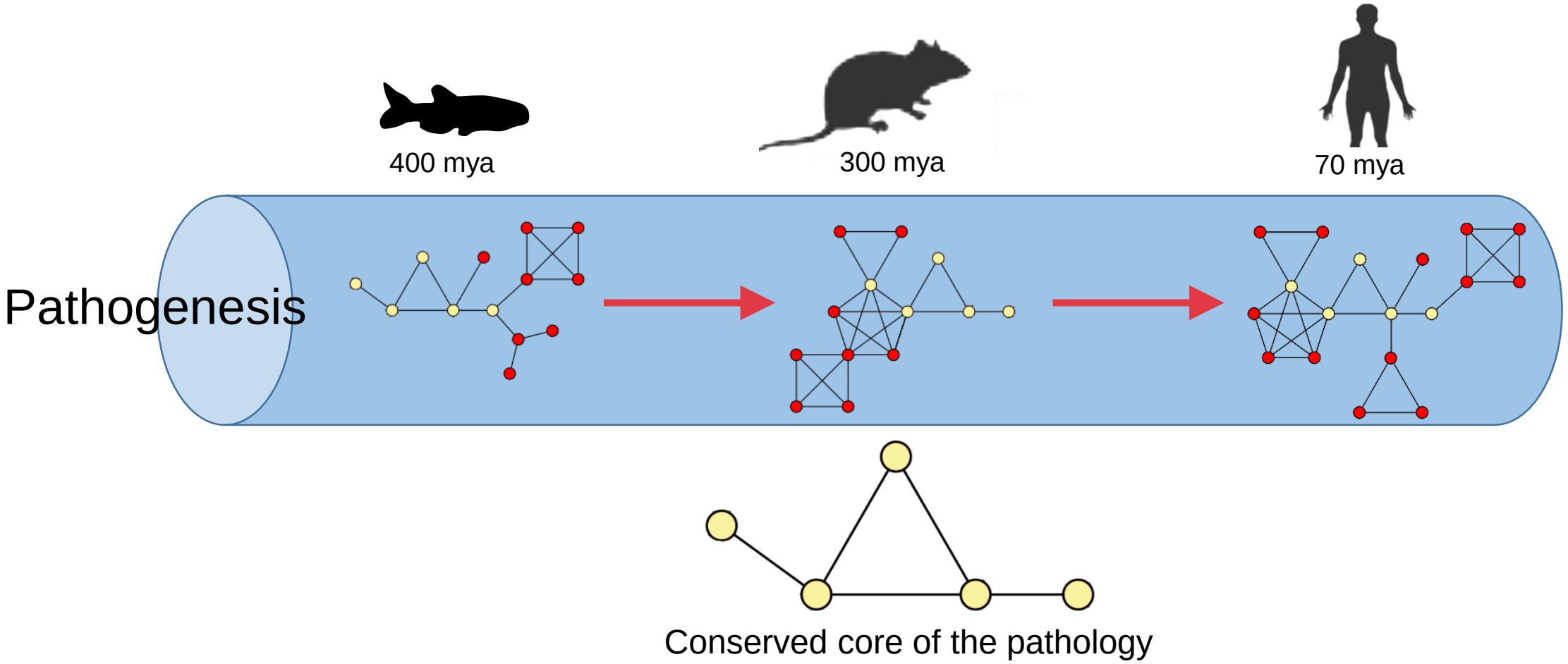
Zebrafish as a genetic machine



Stewart et al 2014

Genetic homology

Zebrafish as a translational machine



Chronic stress and brain genomics

A – arrestins and GPCRs

B – genes related to ubiquitins

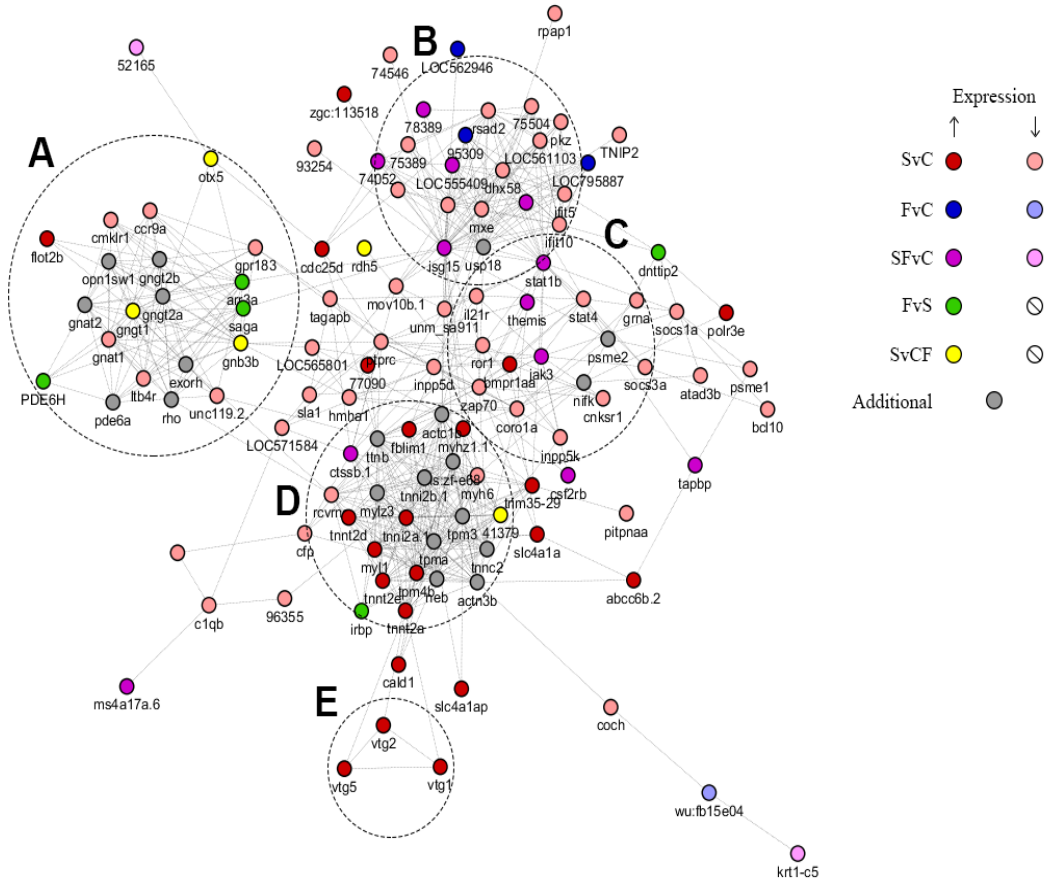
C – inflammation-related genes

D – cytoskeletal genes

› Prog Neuropsychopharmacol Biol Psychiatry. 2018 Feb 2;81:384-394.
doi: 10.1016/j.pnpbp.2017.08.021. Epub 2017 Aug 26.

Modeling consequences of prolonged strong unpredictable stress in zebrafish: Complex effects on behavior and physiology

Cai Song [1], Bai-Ping Liu [2], Yong-Ping Zhang [2], Zhilan Peng [2], JiaJia Wang [2], Adam D Collier [3], David J Echevarria [4], Katerina V Savelieva [3], Robert F Lawrence [5], Christopher S Rex [5], Darya A Meshalkina [6], Allan V Kalueff [7]



Laser-induced brain trauma

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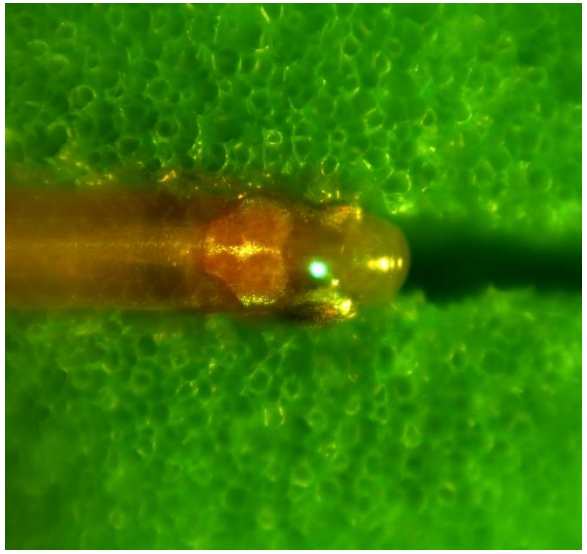
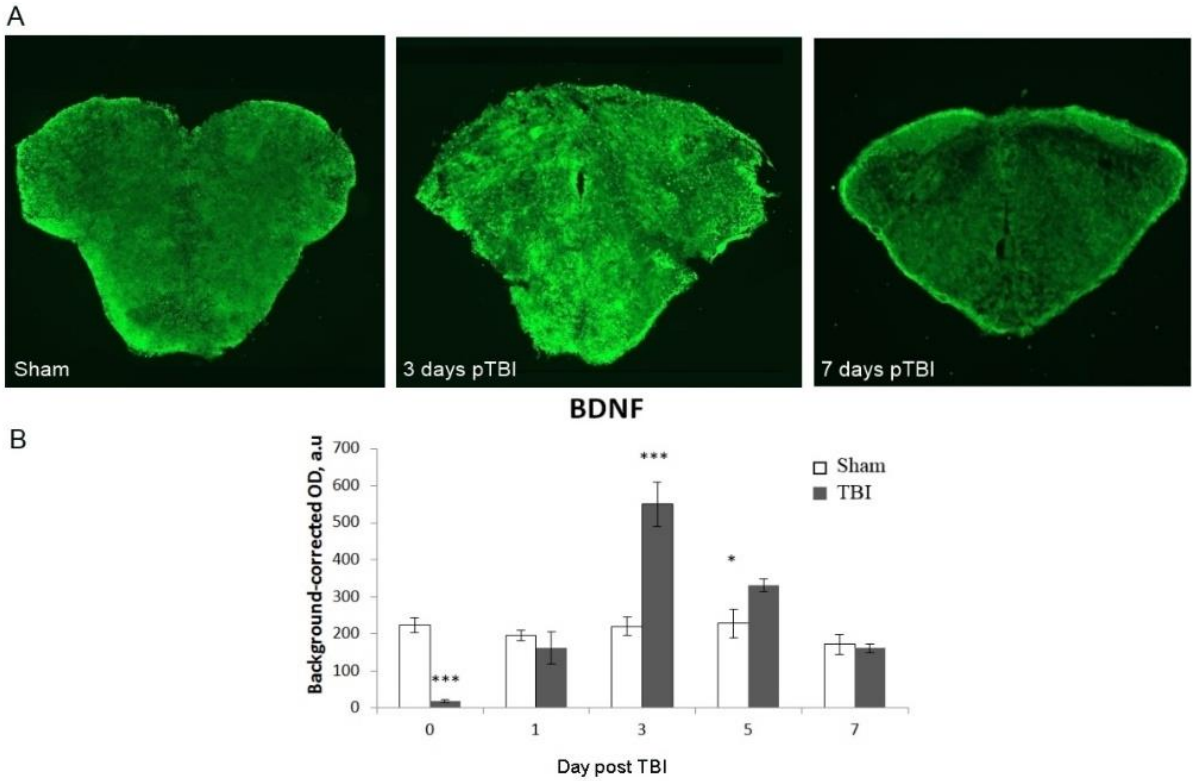
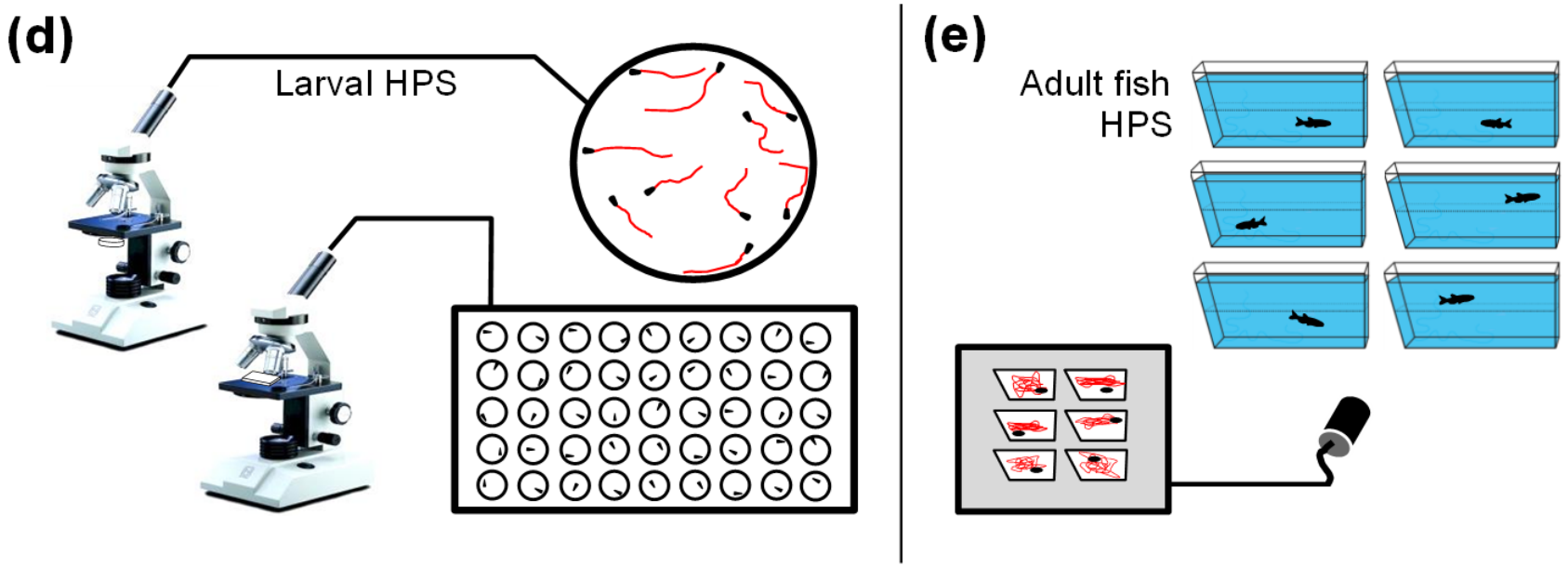


BDNF expression in telencephalon



High-throughput drug screening in zebrafish

Can test 10 000 drugs a day!

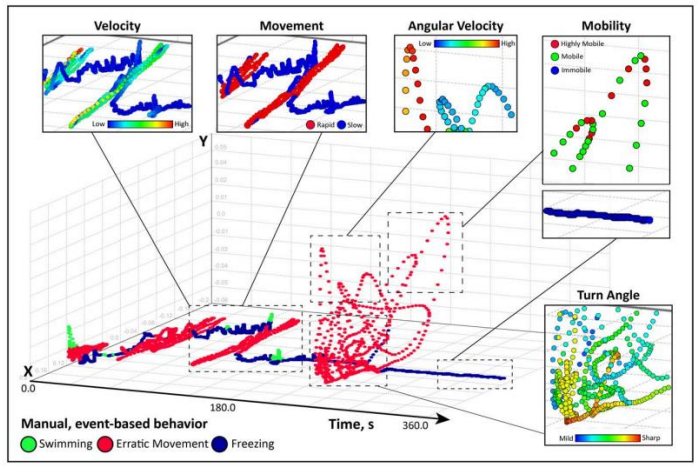


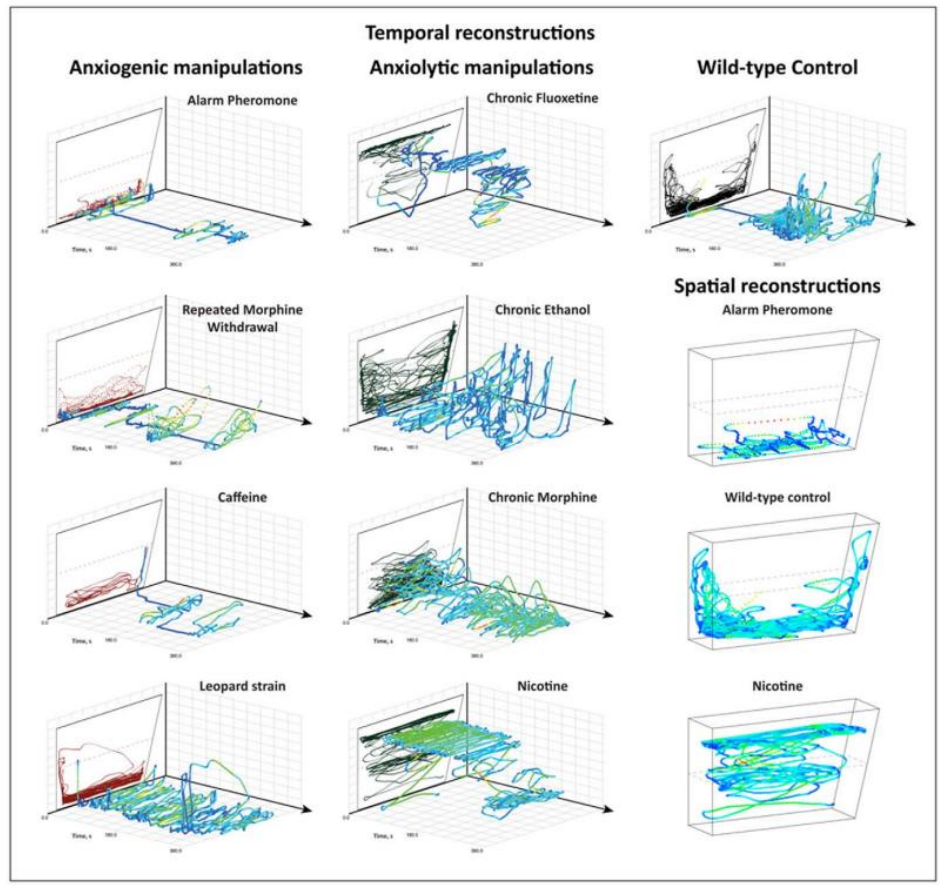
OPEN ACCESS Freely available online

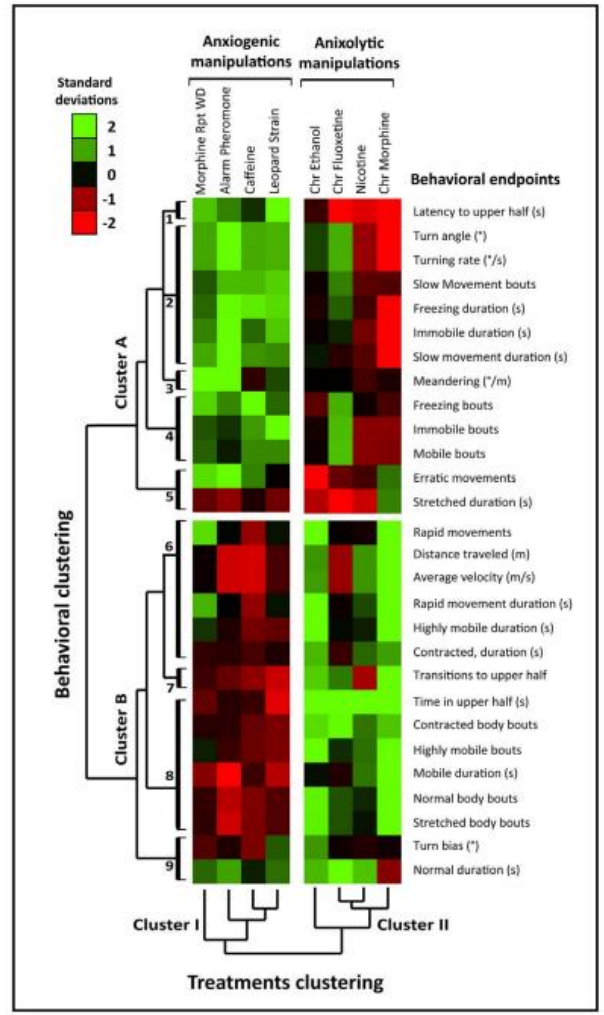
PLoS one

Three-Dimensional Neurophenotyping of Adult Zebrafish Behavior

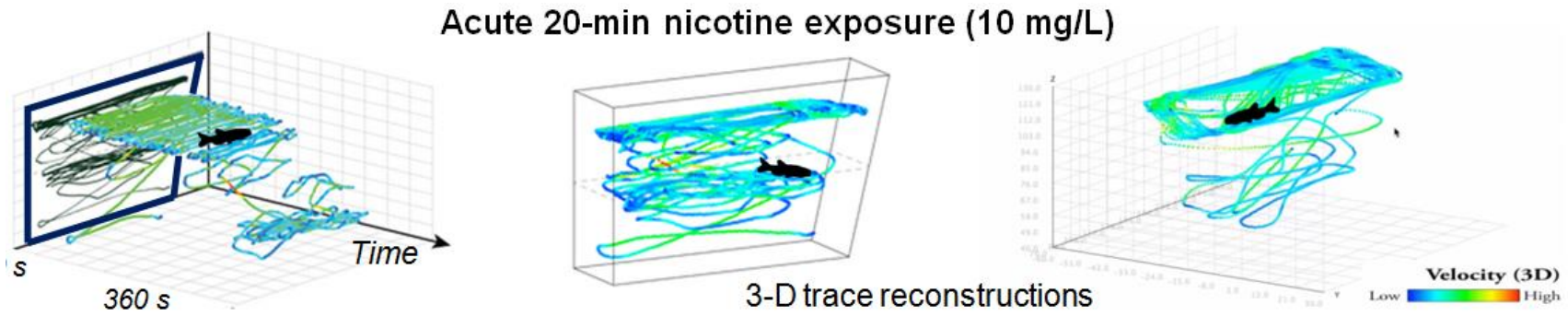
Jonathan Cachat, Adam Stewart, Eli Utterback, Peter Hart, Siddharth Gaikwad, Keith Wong, Evan Kyzar, Nadine Wu, Allan V. Kalueff*

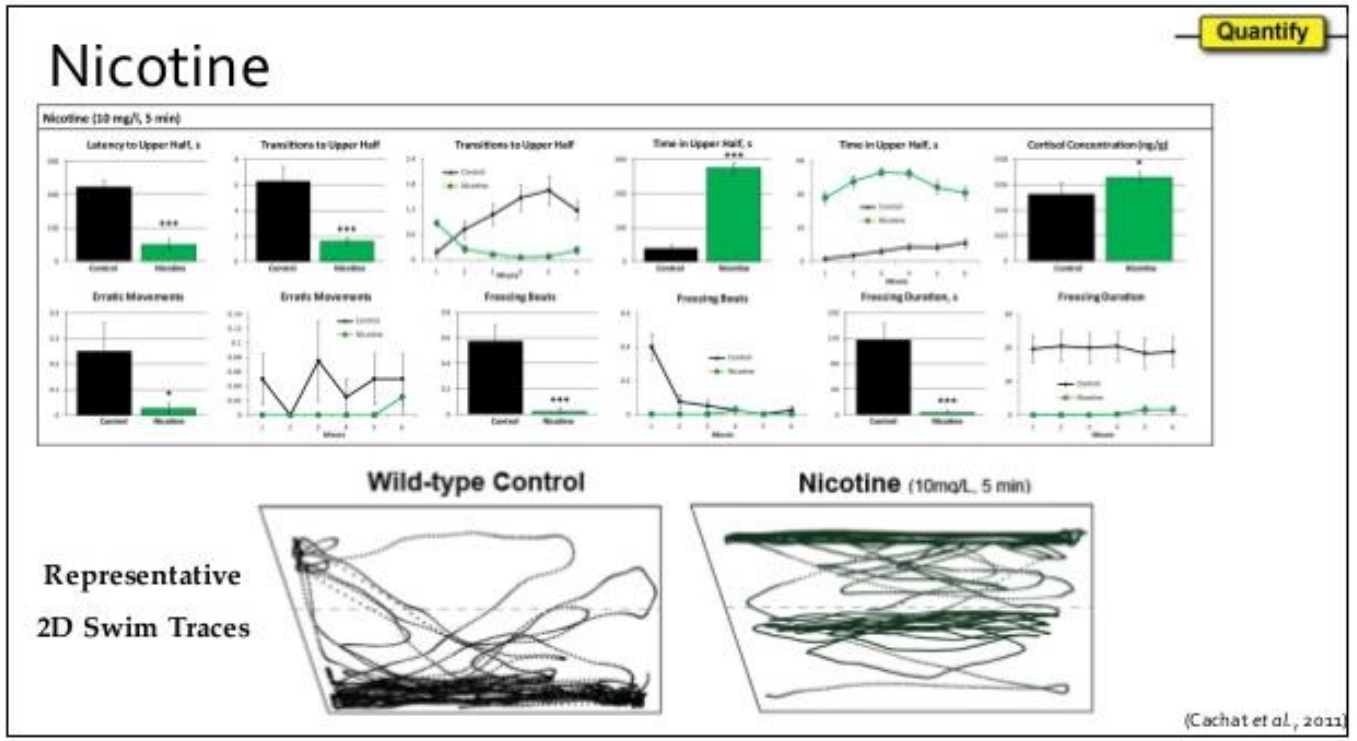




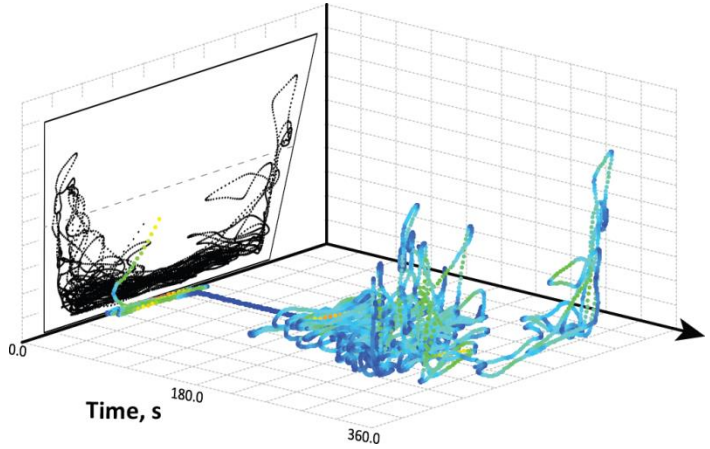


Острые эффекты никотина (10 мг/л)

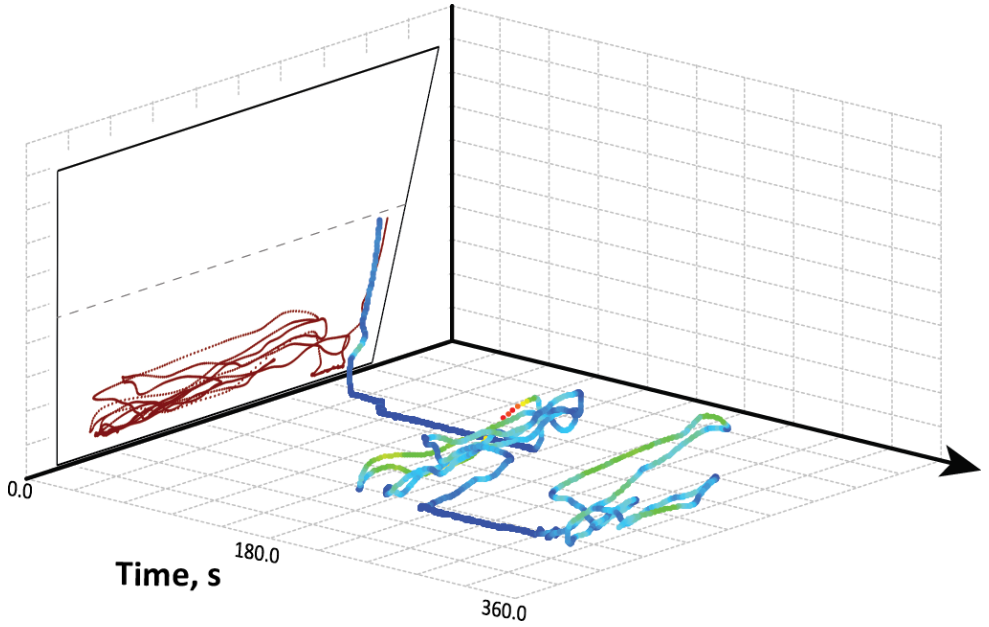




Anxiogenic Treatments

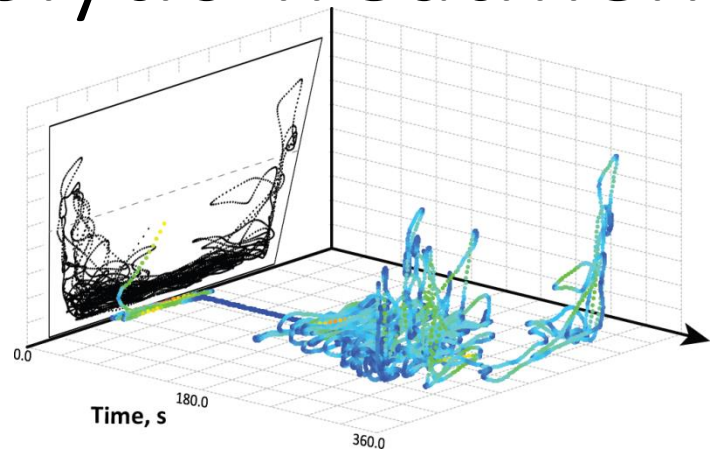


Wild-type Control

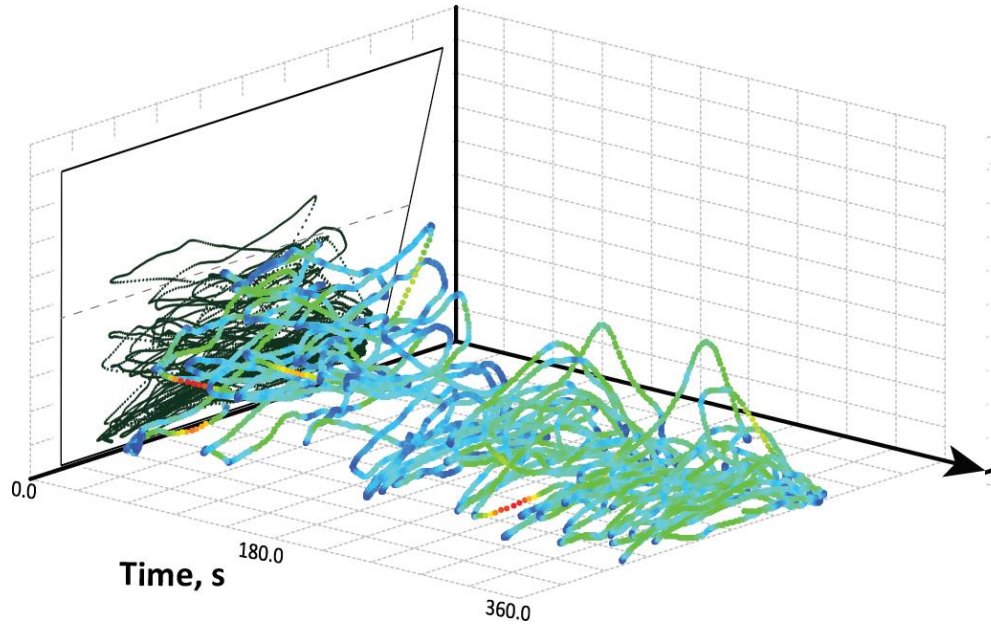


Caffeine (250mg/L , 20mins)

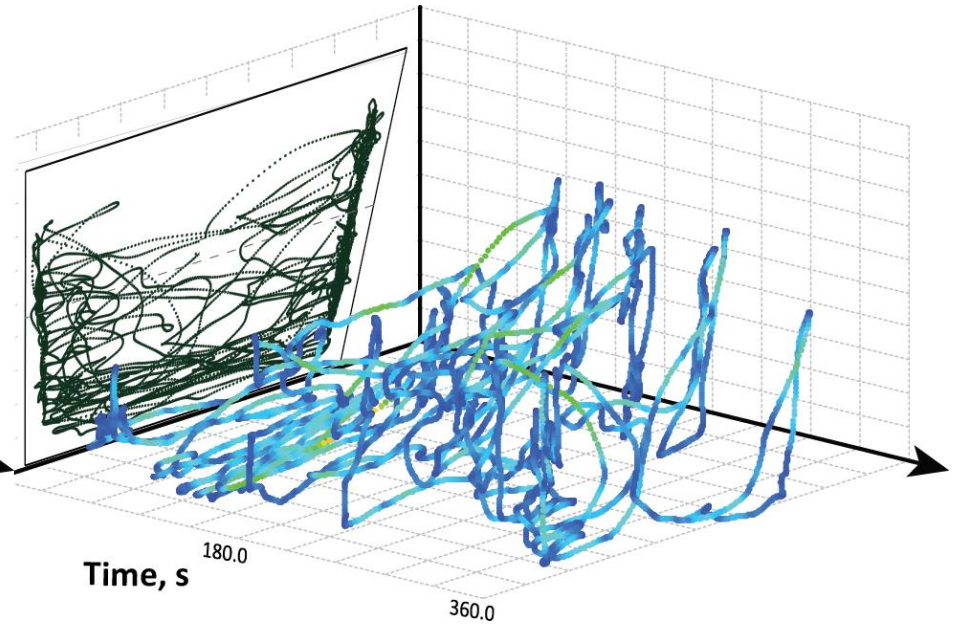
Anxiolytic Treatments



Wild-type Control



Chronic Morphine (1.5mg/L, 2 wks)



Chronic Ethanol (0.3%, 2 wks)

First application of Artificial Intelligence (AI) to zebrafish CNS models

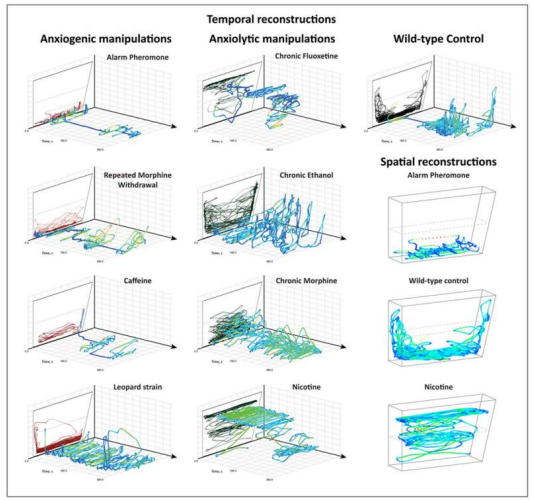
› Prog Neuropsychopharmacol Biol Psychiatry. 2022 Jan 10;112:110405.
doi: 10.1016/j.pnpbp.2021.110405. Epub 2021 Jul 25.

Artificial intelligence-driven phenotyping of zebrafish psychoactive drug responses

Dmitrii V Bozhko [1], Vladislav O Myrov [1], Sofia M Kolchanova [1], Aleksandr I Polovian [1], Georgii K Galumov [1], Konstantin A Demin [2], Konstantin N Zabegalov [3], Tatiana Strekalova Murilo S de Abreu [5], Elena V Petersen [6], Allan V Kalueff [7]

Affiliations + expand

PMID: 34320403 DOI: 10.1016/j.pnpbp.2021.110405

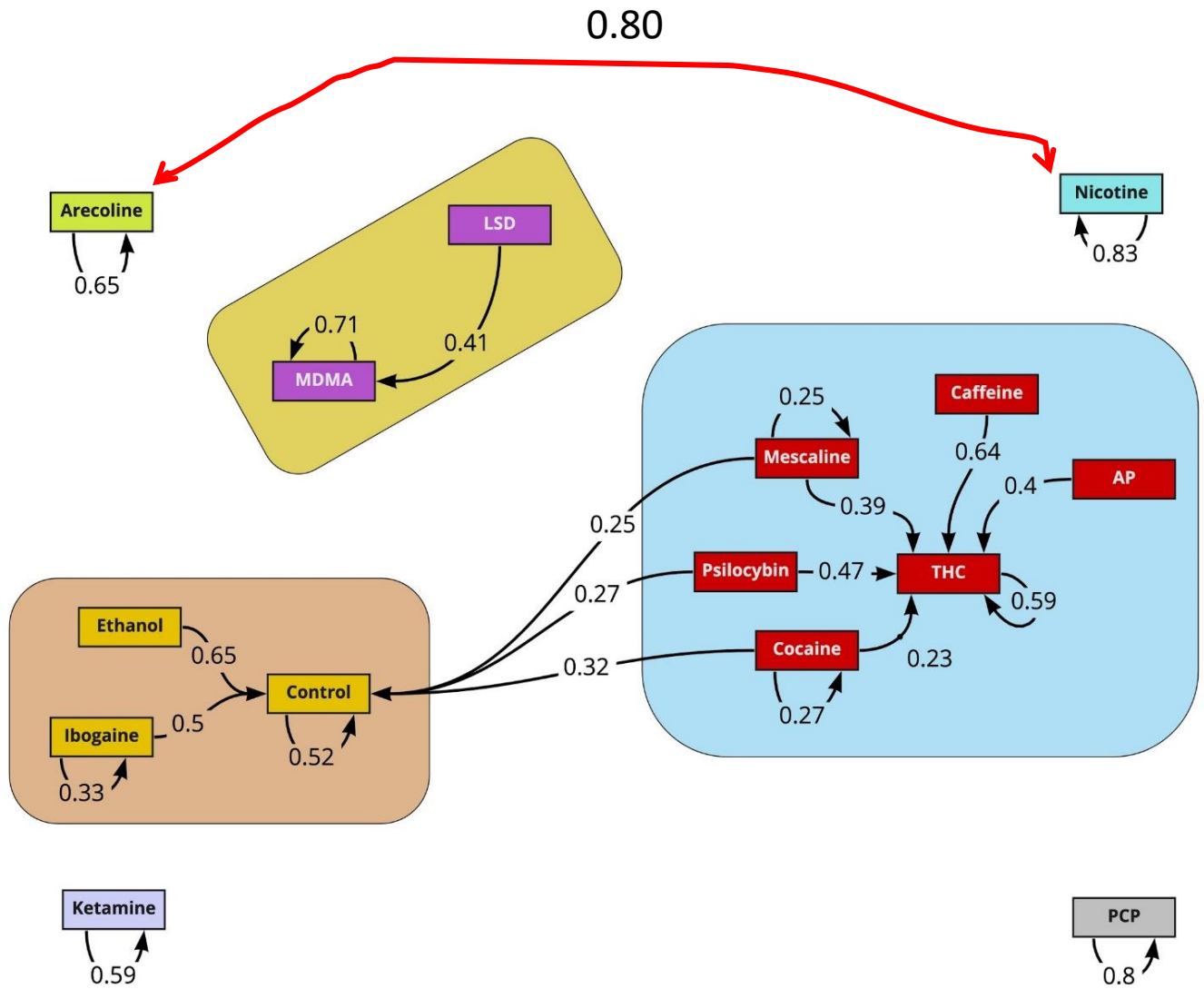


We applied the artificial intelligence (AI) neural network-based algorithms to a large dataset of adult zebrafish locomotor tracks collected previously in a series of in vivo experiments with multiple established psychotropic drugs.

We first trained AI to recognize various drugs from a wide range of psychotropic agents tested, and then confirmed prediction accuracy of trained AI by comparing several agents with known similar behavioral and pharmacological profiles.

First AI-driven application in zebrafish

Method is based on deep learning by convolution neuronetworks (CN) of a library of 3D drug-induced phenotypes for nearly 30 major CNS drugs



ACS Chemical Neuroscience

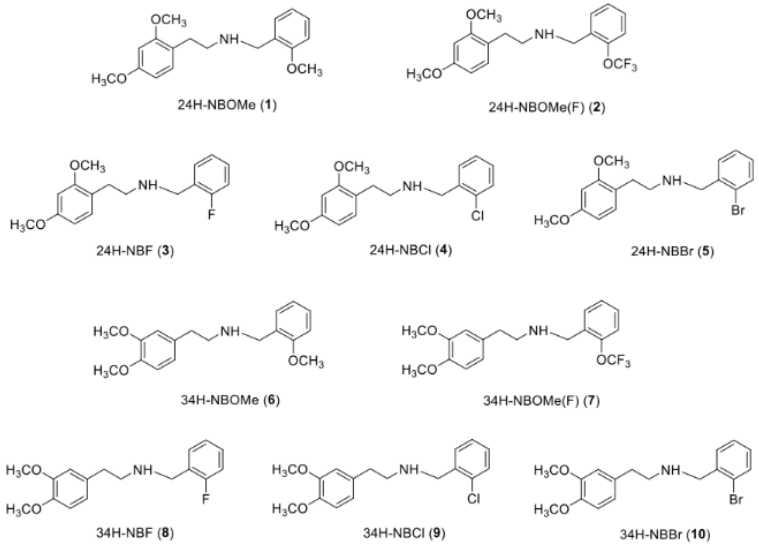
pubs.acs.org/chemneuro Research Article

Acute behavioral and Neurochemical Effects of Novel *N*-Benzyl-2-Phenylethylamine Derivatives in Adult Zebrafish

Konstantin A. Demin,* Olga V. Kupriyanova, Vadim A. Shevyrin,* Ksenia A. Derzhavina, Nataliya A. Krotova, Nikita P. Ilyin, Tatiana O. Kolesnikova, David S. Galstyan, Yurii M. Kositsyn, Abubakar-Askhab S. Khaybaev, Maria V. Seredinskaya, Yaroslav Dubrovskii, Raziya G. Sadykova, Maria O. Nerush, Mikael S. Mor, Elena V. Petersen, Tatyana Strekalova, Evgeniya V. Efimova, Savelii R. Kuvarzin, Konstantin B. Yenkoyan, Dmitrii V. Bozhko, Vladislav O. Myrov, Sofia M. Kolchanova, Aleksander I. Polovian, Georgii K. Galumov, and Allan V. Kalueff*

Cite This: https://doi.org/10.1021/acschemneuro.2c00123 Read Online

Here, we test a battery of ten novel N-benzyl-2-phenylethylamine (NBPEA) derivatives with the 2,4- and 3,4-dimethoxy substitutions in the phenethylamine moiety and the −OCH3, −OCF3, −F, −Cl, and −Br substitutions in the ortho position of the phenyl ring of the N-benzyl moiety, assessing their acute behavioral and neurochemical effects in 18 the adult zebrafish



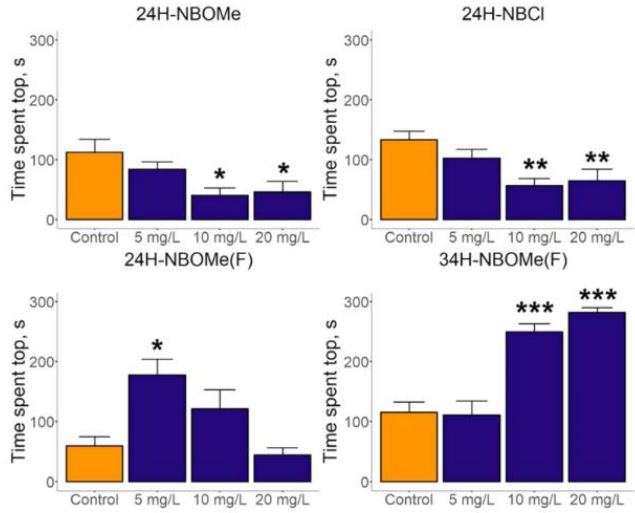


Figure 2. Behavioral effects of selected NBPEAs on the anxiety-related top time behavior assessed in the zebrafish NTT. The increased top time typically reflects an anxiolytic-like effect. Data are presented as mean ± S.E.M. (n = 15−17 per group). *p < 0.05, **p < 0.01, ***p < 0.001 versus control, posthoc Dunn's test for significant Kruskal−Wallis data. Graphs were constructed using ggplot2 R package[139] (also see Table S1 for statistical details).

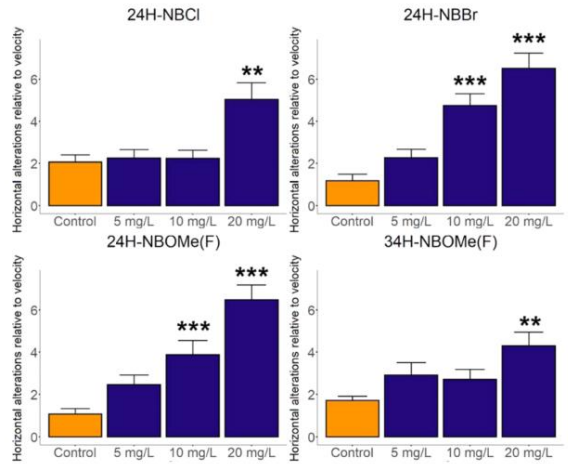


Figure 3. Behavioral effects of selected NBPEAs on the horizontal "shuttling" behavior in the zebrafish NTT. The endpoint was calculated as the total number of left-to-right or right-to-left horizontal transitions and normalized by dividing it by the distance traveled. The increased "shuttling" behavior likely reflects potential hallucinogenic-like properties. Data are presented as mean ± S.E.M. (n = 15−17 per group). *p < 0.05, **p < 0.01, ***p < 0.001 versus control, posthoc Dunn's test for significant Kruskal−Wallis data. Graphs were constructed using ggplot2 R package[139] (also see Table S1 for statistical details).

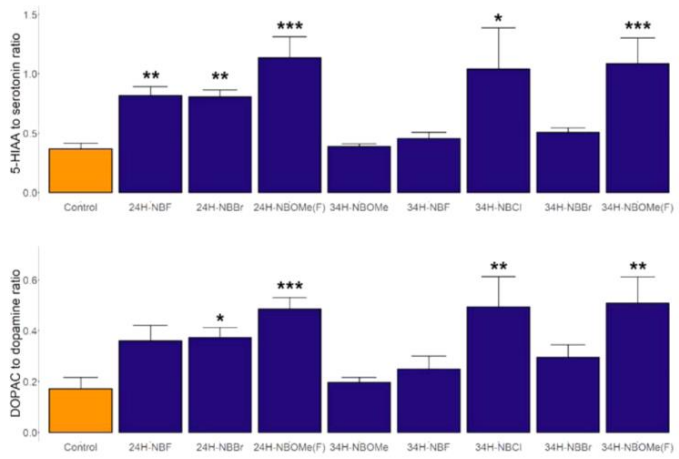


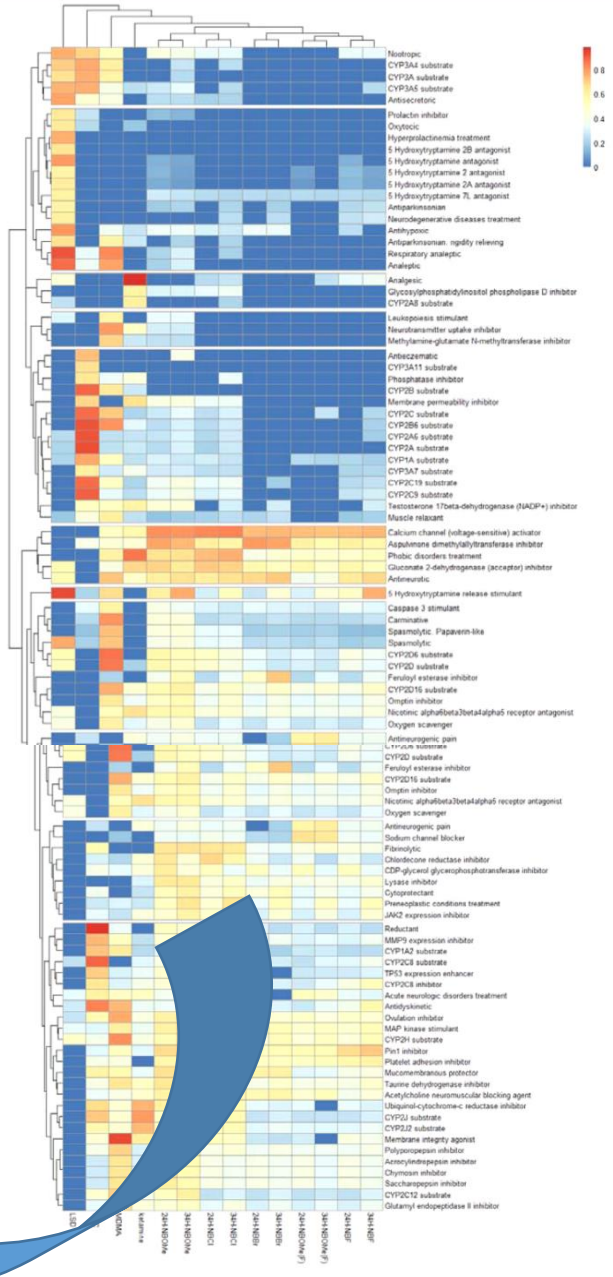
Figure 4. Altered brain SERT and DAT turnover (assessed as the corresponding metabolite/neurotransmitter ratios) by selected NBPEAs in the adult zebrafish. Data are presented as mean ± S.E.M. (n = 8−10 per group). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ versus control, posthoc Dunn's test for significant Kruskal−Wallis data. Graphs were constructed using ggplot2 R package[139] (also see Table S3 for statistical details).

- Overall, substitutions in the N-benzyl moiety modulate locomotion, and substitutions in the phenethylamine moiety alter zebrafish anxiety-like behavior, also affecting the brain serotonin and/or dopamine turnover.

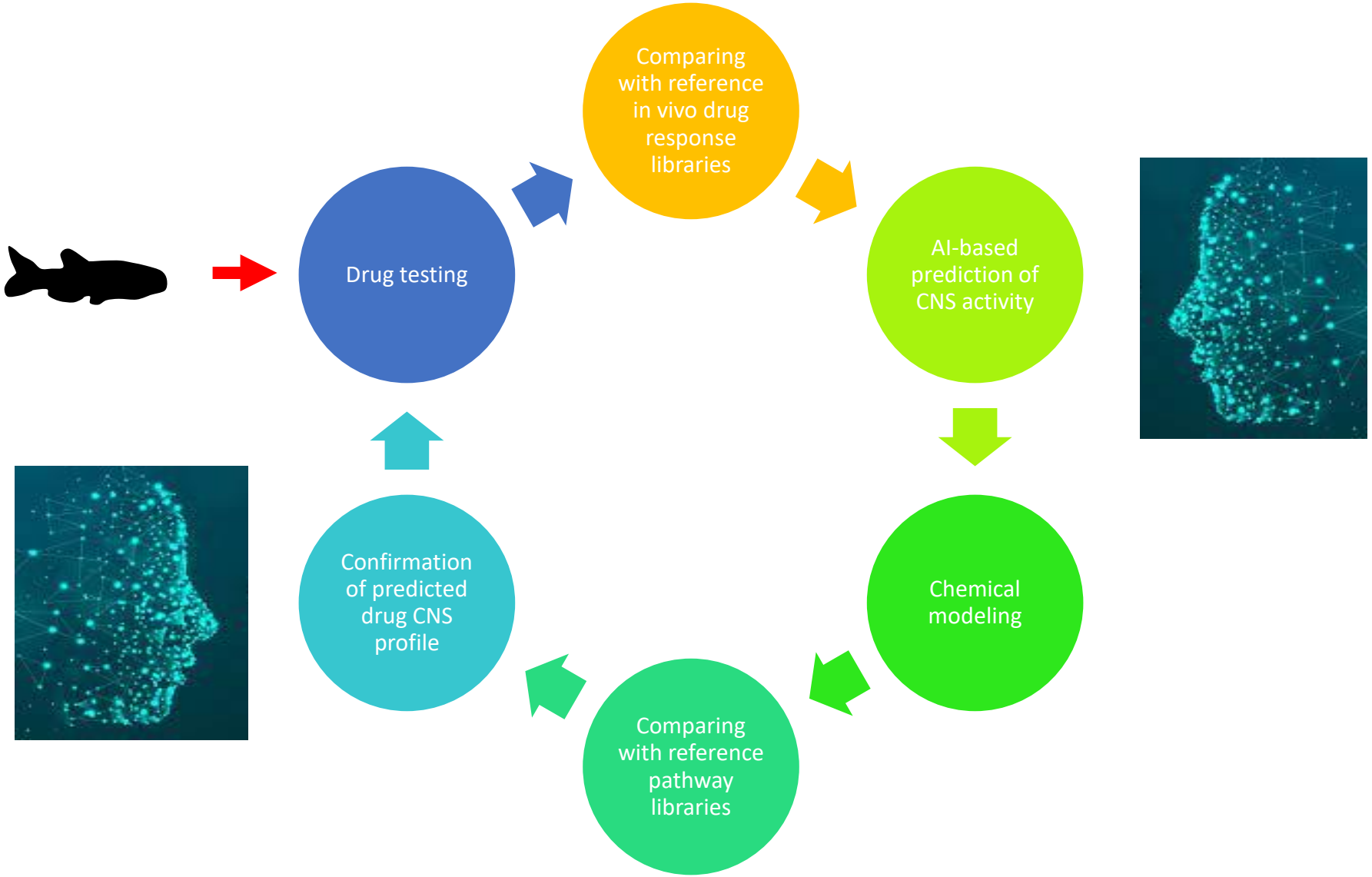
- Computational analyses of zebrafish behavioral data by artificial intelligence identified several distinct clusters for these agents, including anxiogenic/hypolocomotor (24H−NBF, 24H−NBOMe, and 34H− NBF), behaviorally inert (34H−NBBr, 34H−NBCl, and 34H−NBOMe), anxiogenic/hallucinogenic-like (24H−NBBr, 24H−NBCl, 24 and 24H−NBOMe(F)), and anxiolytic/hallucinogenic-like (34H−NBOMe(F)) drugs.

- Our computational analyses also revealed phenotypic similarity of the behavioral activity of some NBPEAs to that of selected conventional serotonergic and antiglutamatergic hallucinogens.

- In silico functional molecular activity modeling further supported the overlap of the drug targets for NBPEAs tested here and the conventional serotonergic and antiglutamatergic hallucinogens.



Heatmap diagram showing the probability of functional activities (Pa, %) of the drugs assessed using PASSonline software[129] with hierarchical clustering. Note the tight clustering of novel NBPEAs with MDMA and ketamine (see main functional activity clusters summarized in Table 4).


Drug testing
Comparing with reference in vivo drug response libraries
AI-based prediction of CNS activity
Chemical modeling
Comparing with reference pathway libraries
Confirmation of predicted drug CNS profile

Conclusions

Zebrafish provide an excellent platform for in-vivo CNS drug screening

Zebrafish-based platforms enable high-throughput, automated analyses of drug-induced responses in vivo

AI-based systems empower zebrafish-based drug screening platforms, as they:

- Help create comprehensive libraries of drug-induced responses
- Provide unbiased extraction of drug-induced phenotypical data
- Compare experimental data with those in reference libraries of known activity
- Analyze drug responses to predict their pharmacological activity

Thank you for your attention!

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