Adding a bit of color and light to the brain

Matt Carter
Department of Biology
Williams College

August 8, 2022

eLife

RESEARCH ARTICLE

A discrete parasubthalamic nucleus subpopulation plays a critical role in appetite suppression

Jessica H Kim[1†], Grace H Kromm[1†], Olivia K Barnhill[1†], Jacob Sperber[1], Lauren B Heuer[1], Sierra Loomis[1], Matthew C Newman[1], Kenneth Han[1], Faris F Gulamali[1], Theresa B Logan[1], Katherine E Jansen[1], Samuel C Funderburk[2], Michael J Krashes[3], Matthew E Carter[1]*

[1]Department of Biology, Williams College, Williamstown, United States; [2]Department of Physics, Williams College, Williamstown, United States; [3]Diabetes, Endocrinology, and Obesity Branch, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, United States

Abstract Food intake behavior is regulated by a network of appetite-inducing and appetite-suppressing neuronal populations throughout the brain. The parasubthalamic nucleus (PSTN), a relatively unexplored population of neurons in the posterior hypothalamus, has been hypothesized to regulate appetite due to its connectivity with other anorexigenic neuronal populations and because these neurons express Fos, a marker of neuronal activation, following a meal. However, the individual cell types that make up the PSTN are not well characterized, nor are their functional roles in food intake behavior. Here, we identify and distinguish between two discrete PSTN subpopulations, those that express tachykinin-1 ($PSTN^{Tac1}$ neurons) and those that express corticotropin-releasing hormone ($PSTN^{Crh}$ neurons), and use a panel of genetically encoded tools in mice to show that $PSTN^{Tac1}$ neurons play an important role in appetite suppression. Both subpopulations increase activity following a meal and in response to administration of the anorexigenic hormones amylin, cholecystokinin (CCK), and peptide YY (PYY). Interestingly, chemogenetic inhibition of $PSTN^{Tac1}$, but not $PSTN^{Crh}$ neurons, reduces the appetite-suppressing effects of these hormones. Consistently, optogenetic and chemogenetic stimulation of $PSTN^{Tac1}$ neurons, but not $PSTN^{Crh}$ neurons, reduces food intake in hungry mice. $PSTN^{Tac1}$ and $PSTN^{Crh}$ neurons project to distinct downstream brain regions, and stimulation of $PSTN^{Tac1}$ projections to individual anorexigenic populations reduces food consumption. Taken together, these results reveal the functional properties and projection patterns of distinct PSTN cell types and demonstrate an anorexigenic role for $PSTN^{Tac1}$ neurons in the hormonal and central regulation of appetite.

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[†]These authors contributed equally to this work

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Introduction

The brain regulates food intake behavior through the coordinated activity of several distinct neuronal populations (Andermann and Lowell, 2017; Sternson and Eiselt, 2017). Activity in anorexigenic

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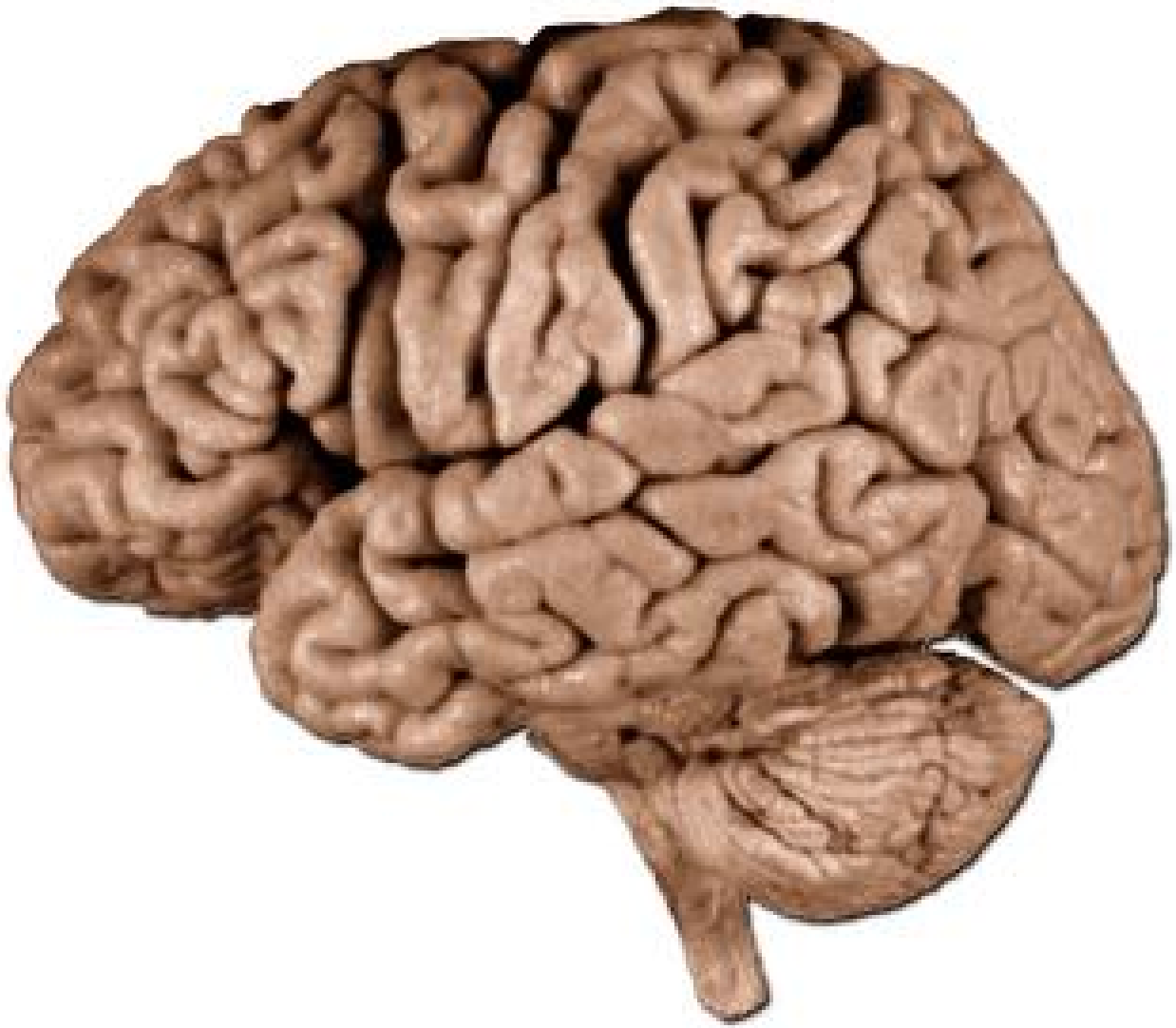

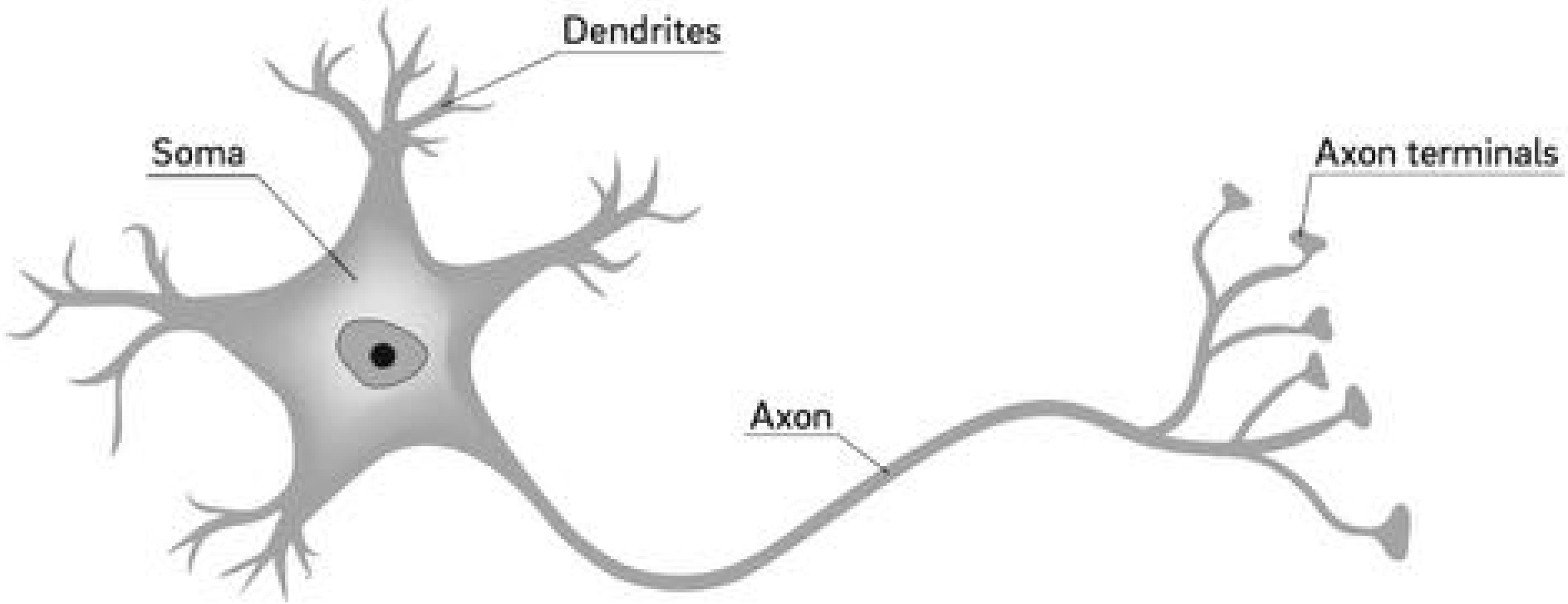
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Soma
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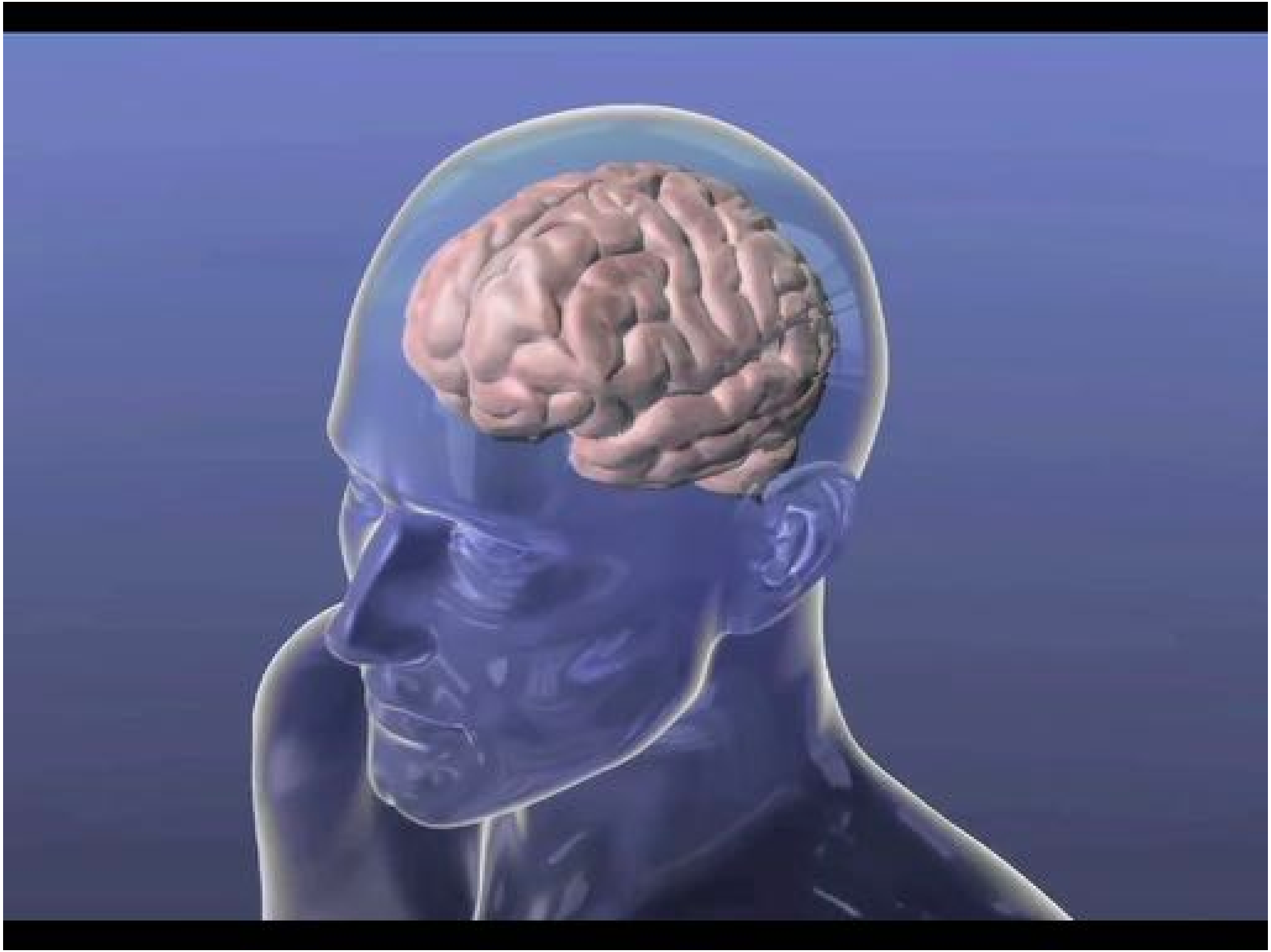
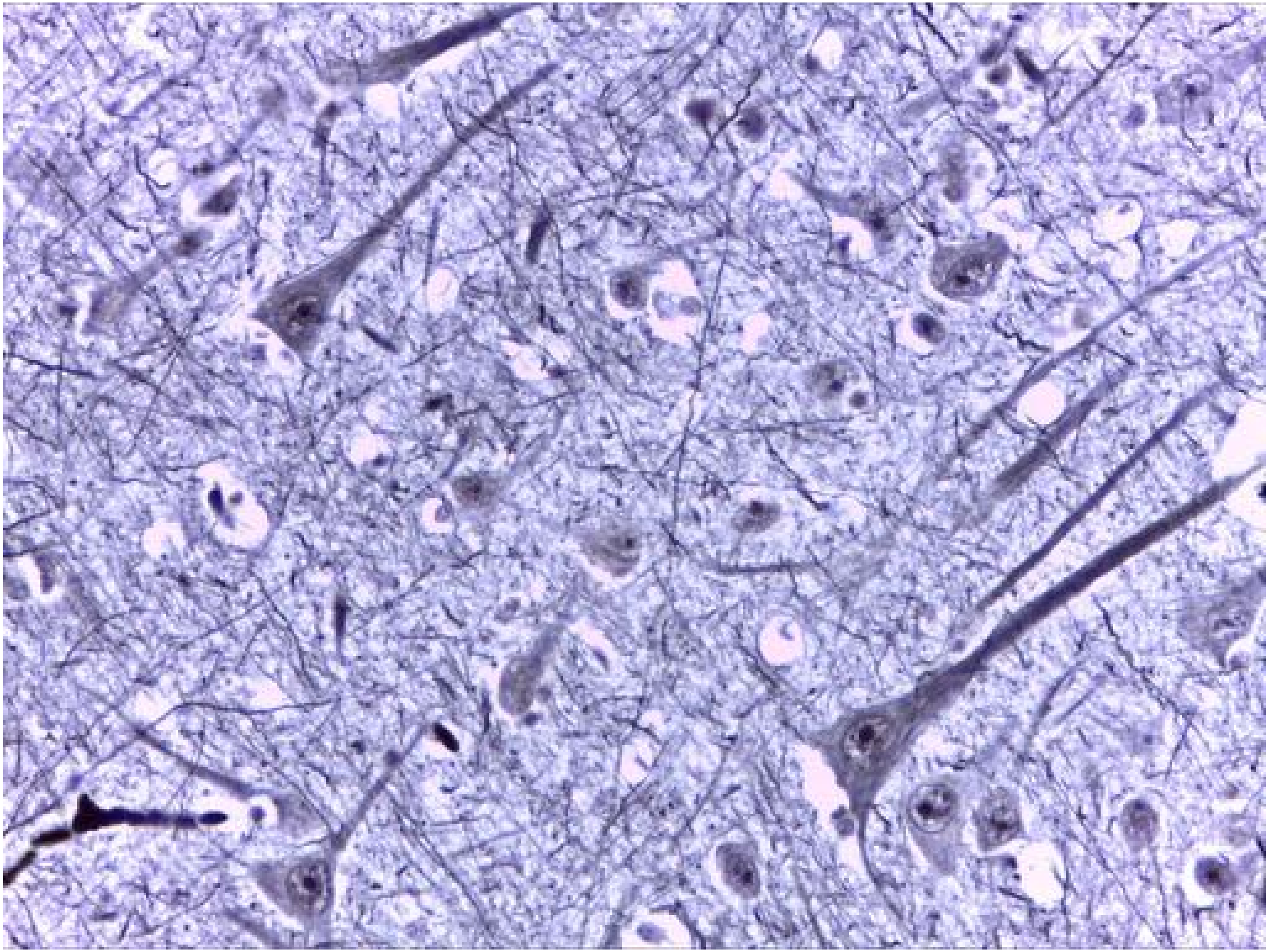
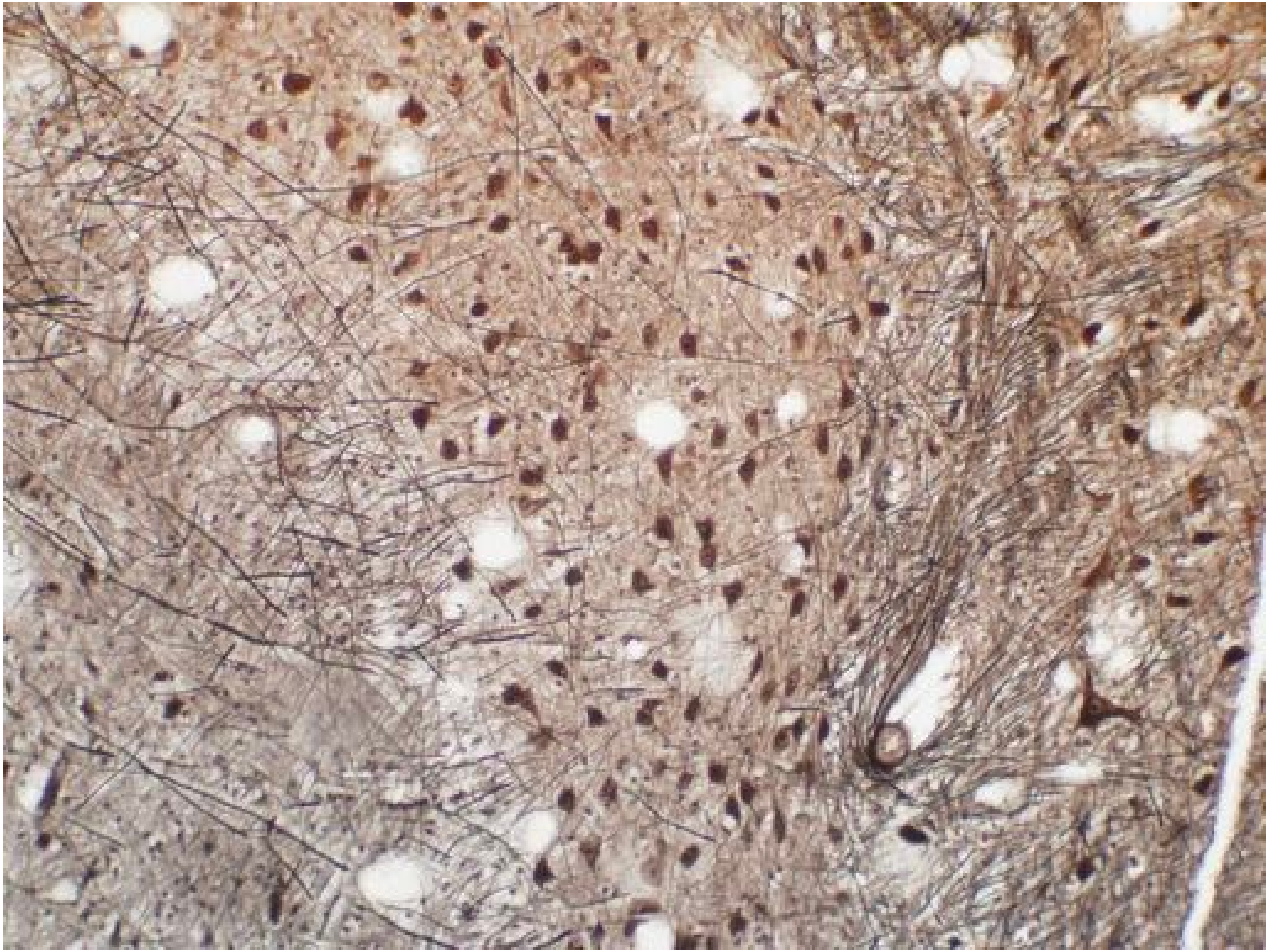
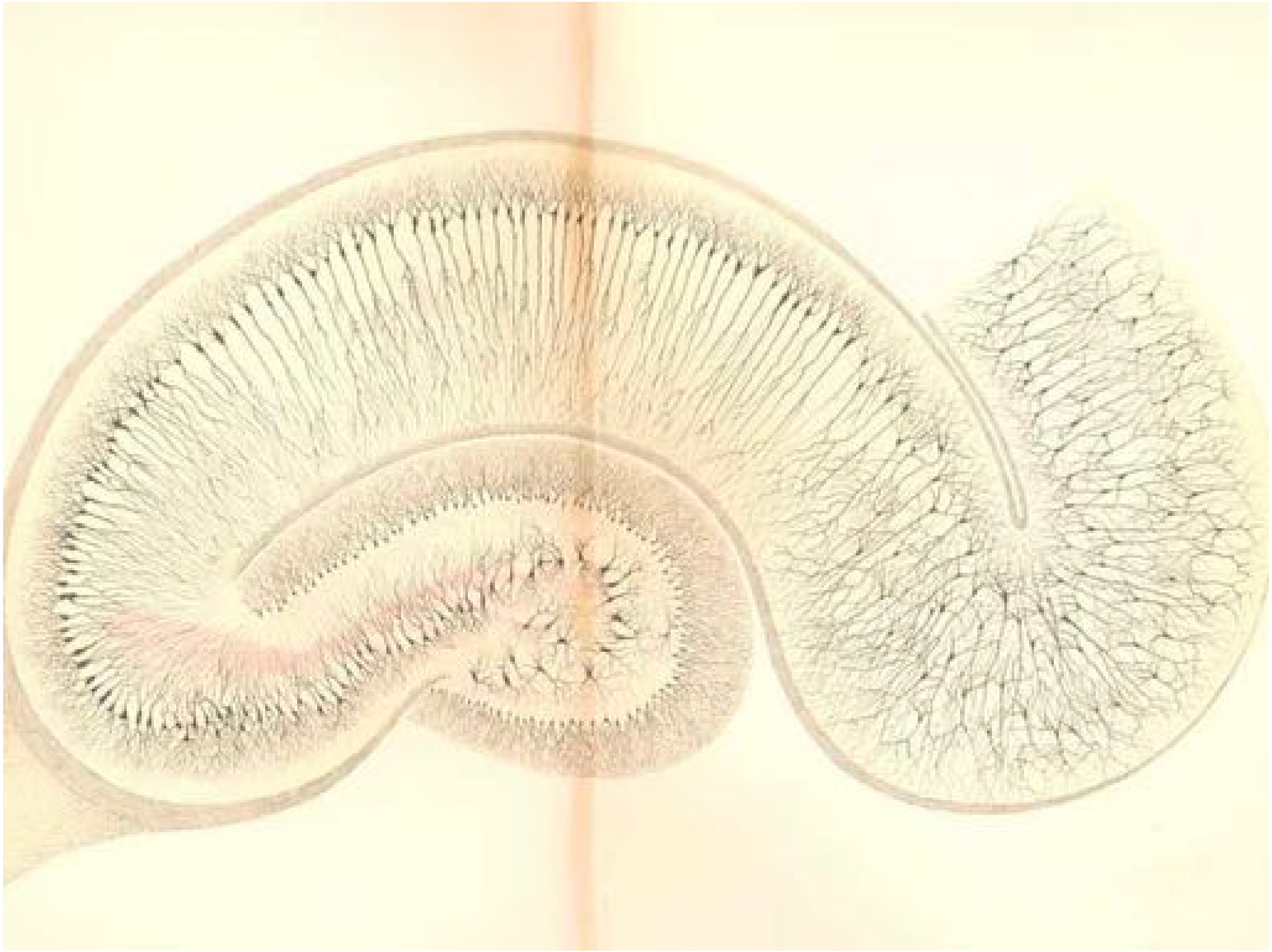
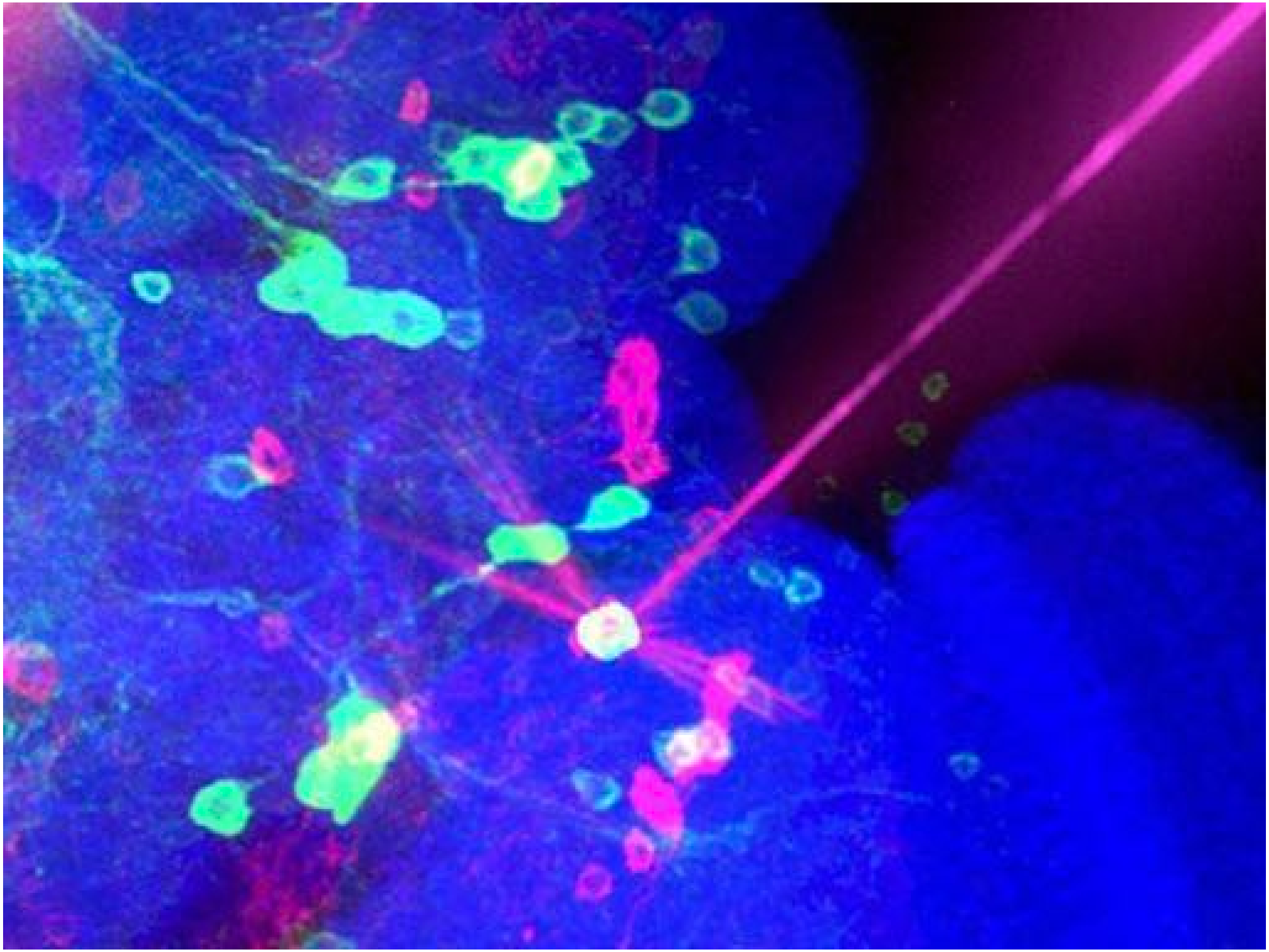
Axon

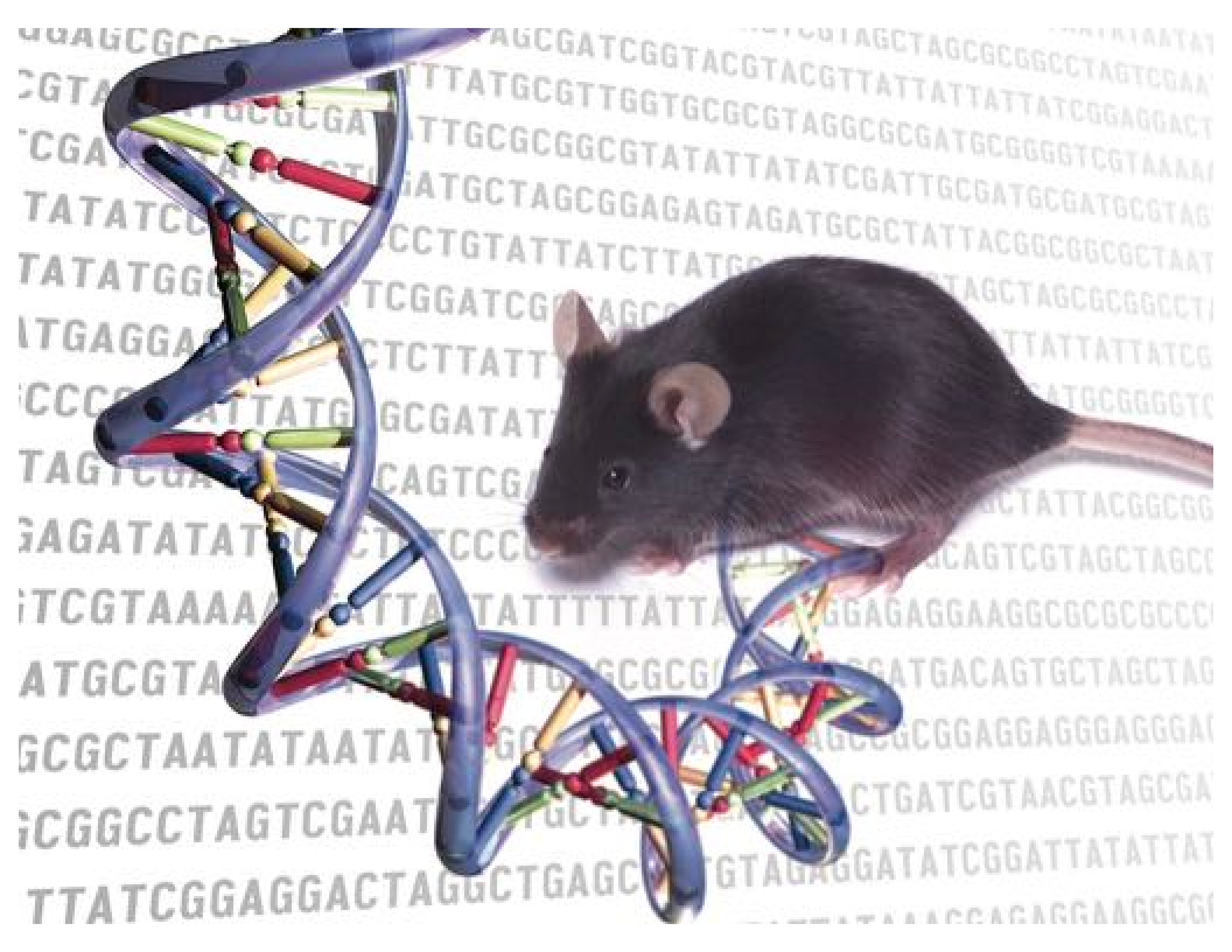


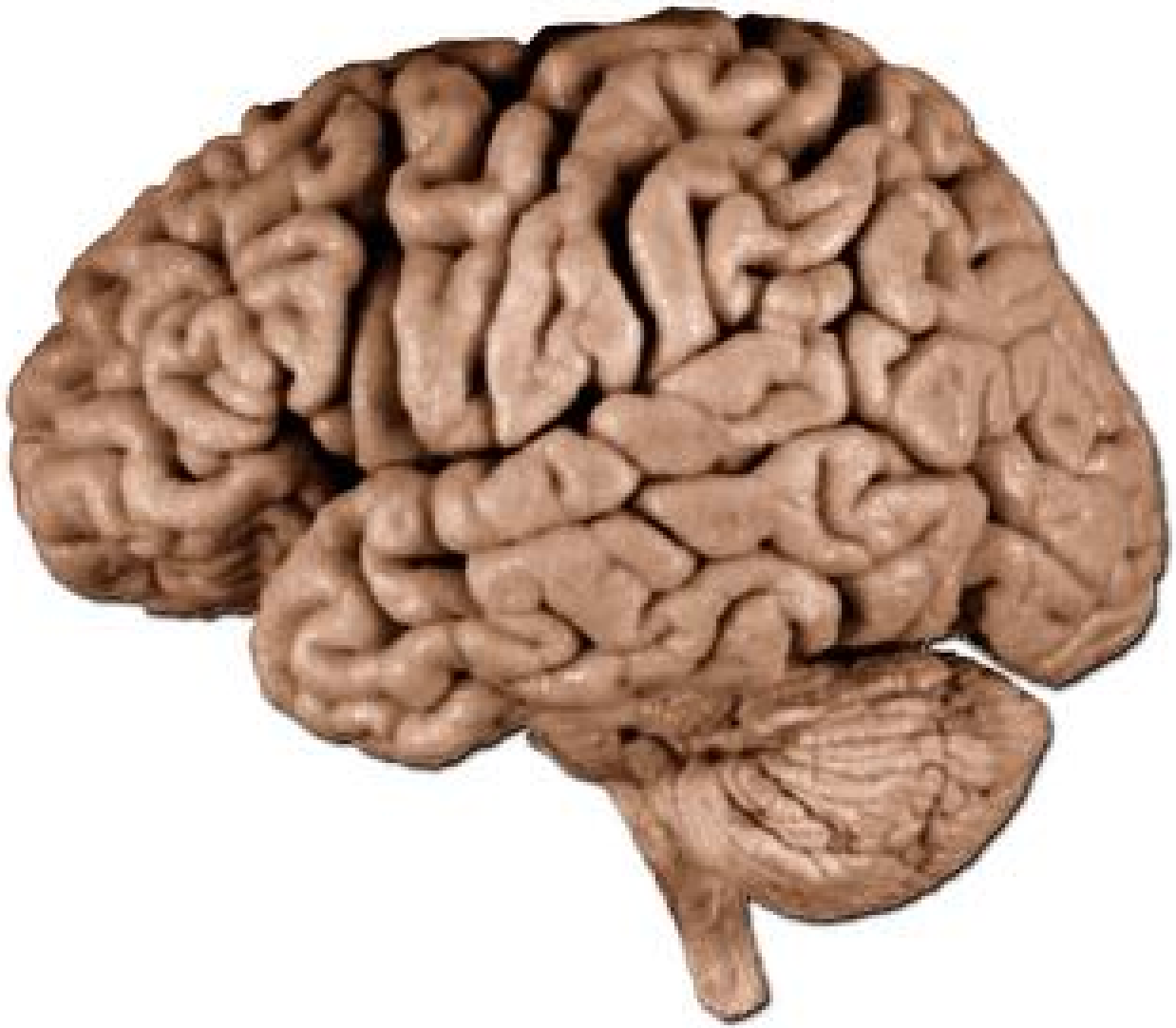


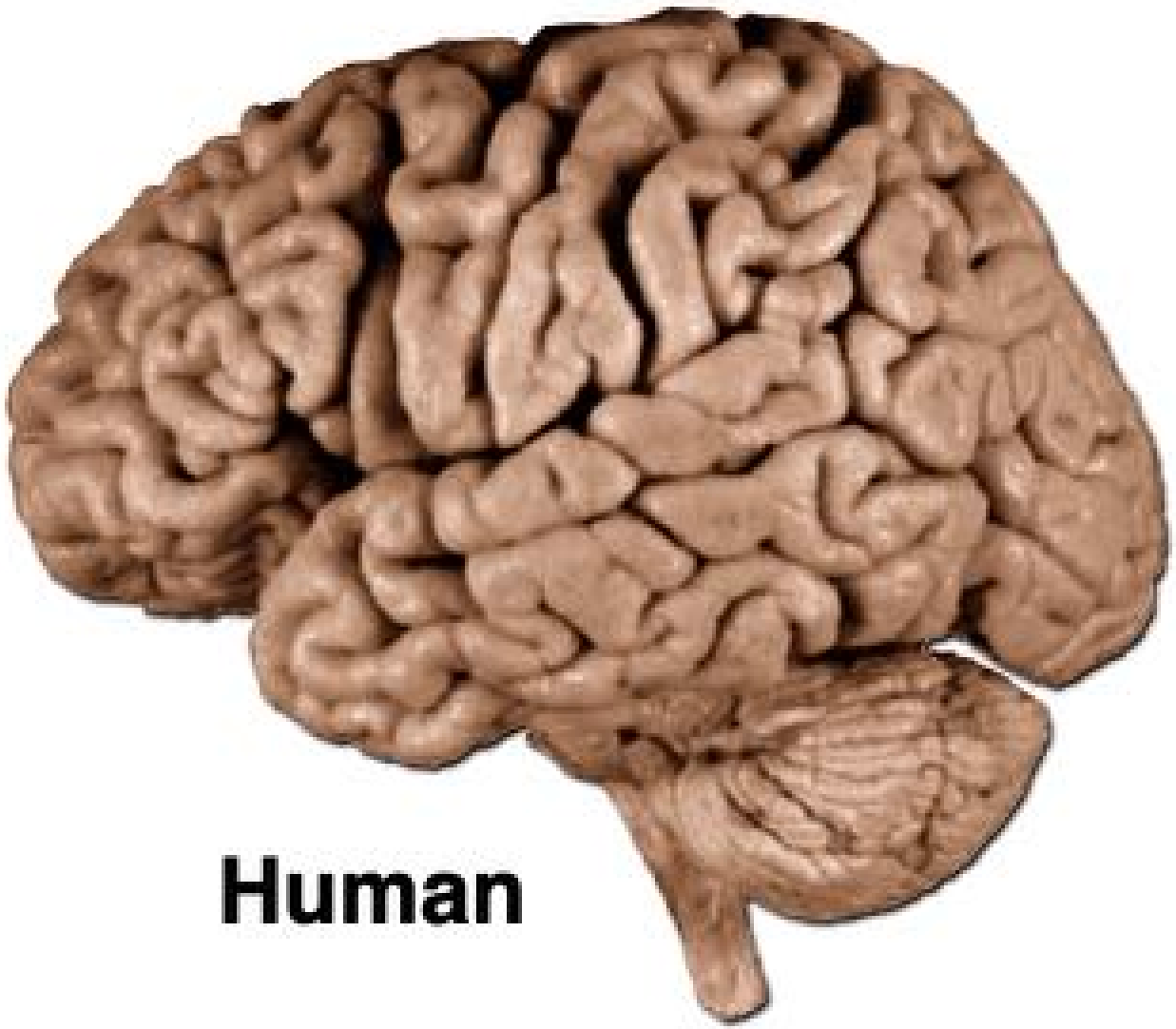












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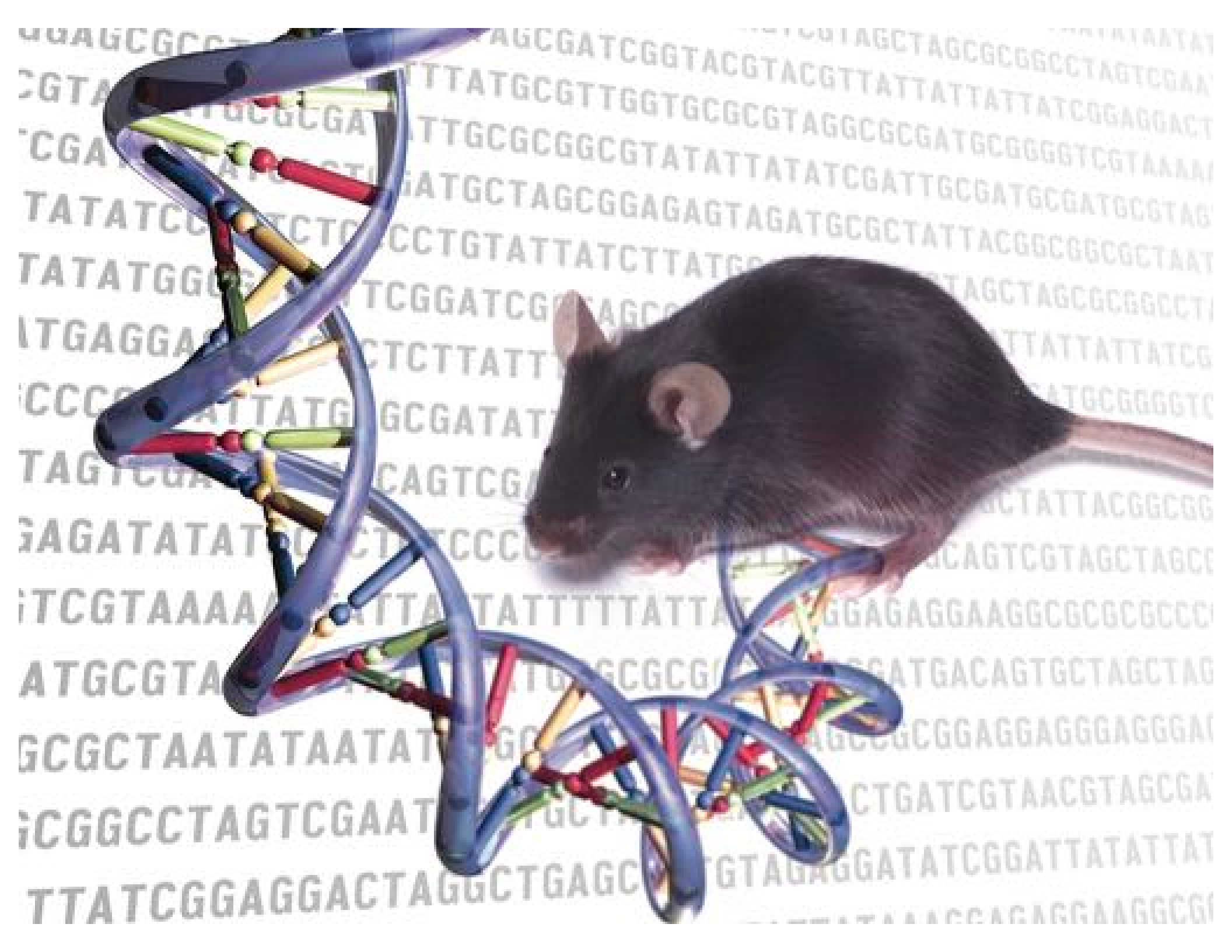

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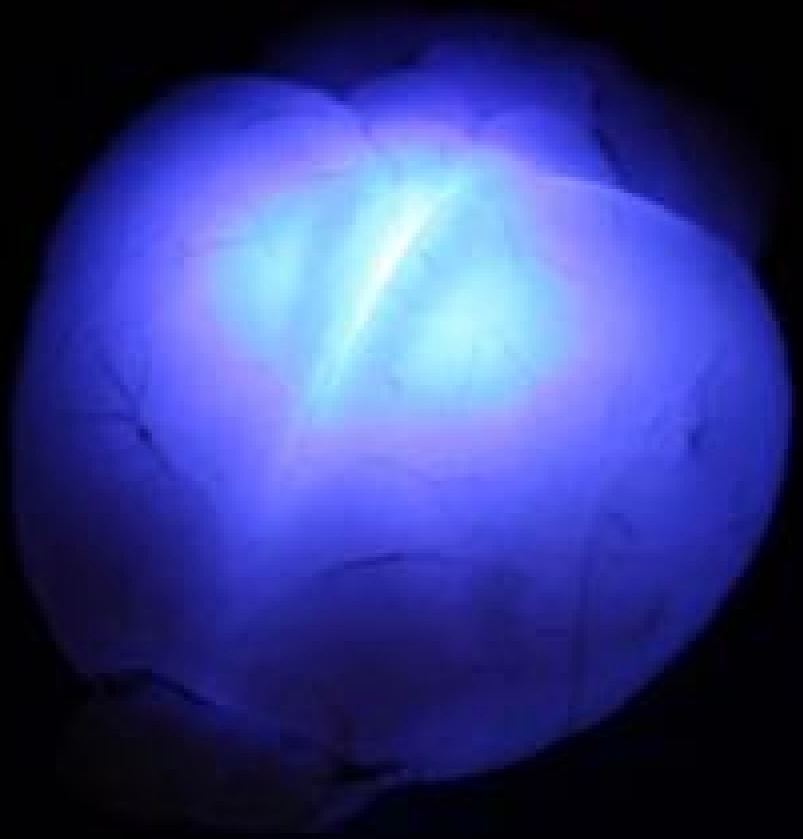

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Neural Structure

Neural Activity

Neuromodulation

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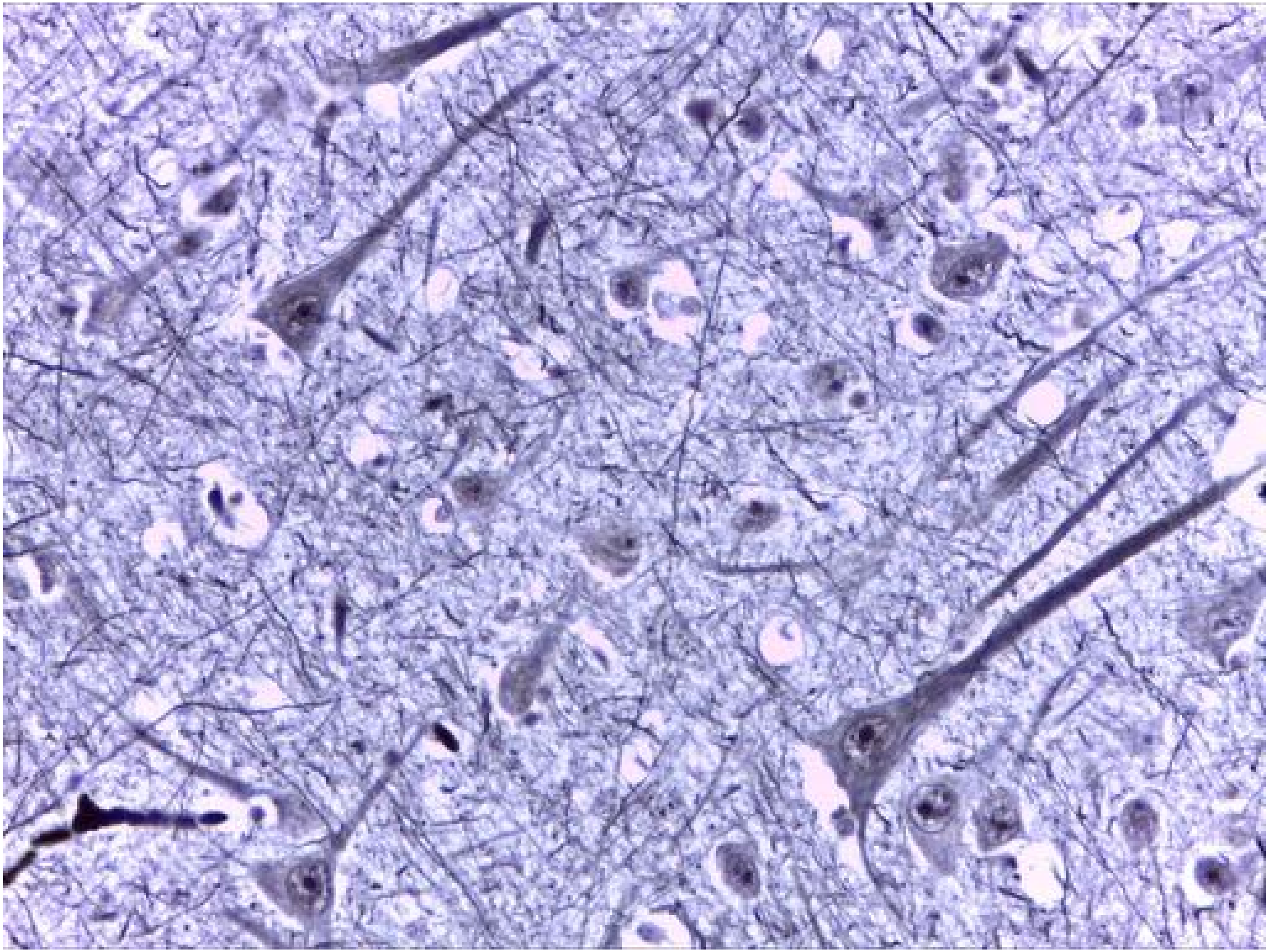
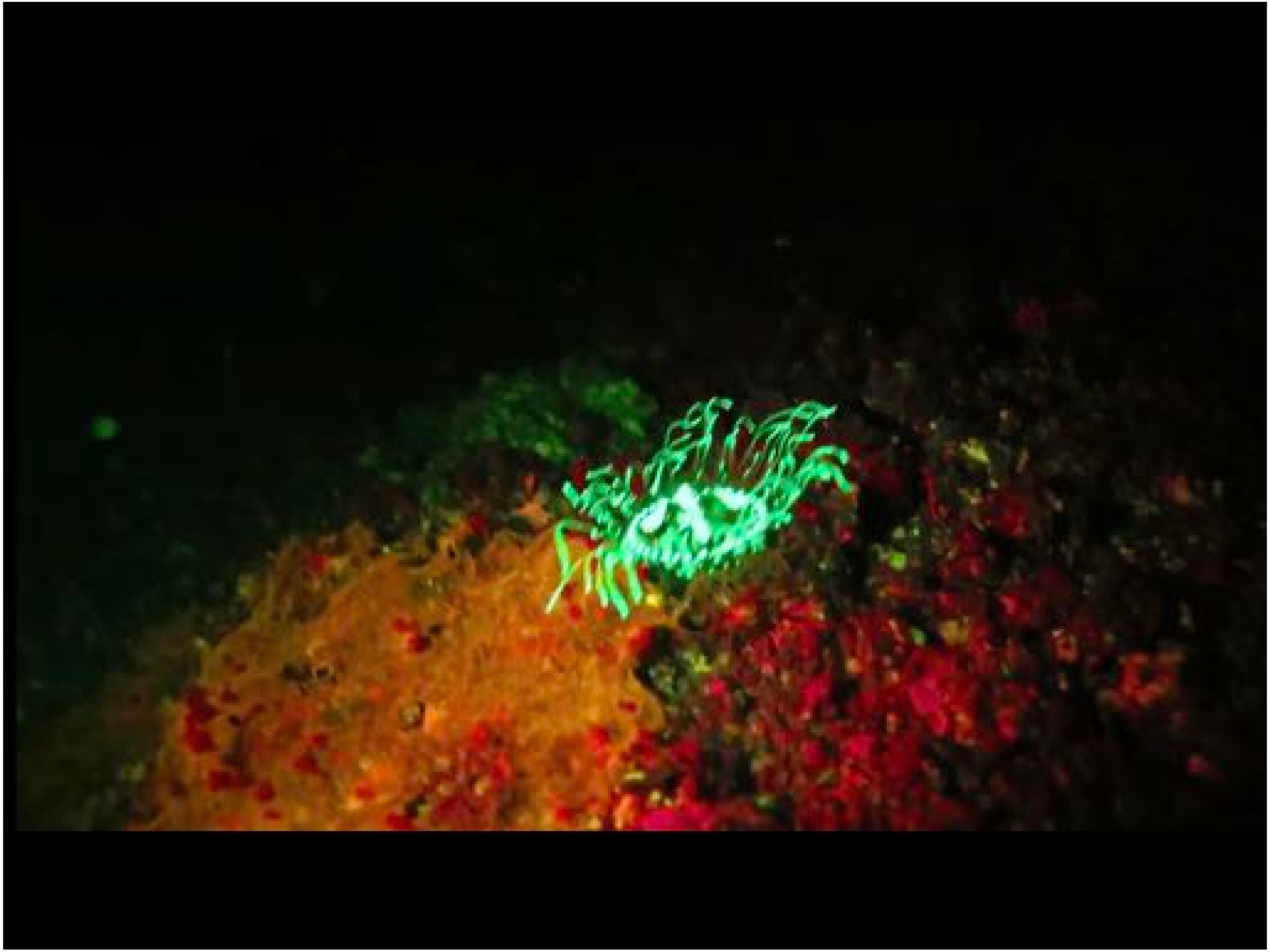
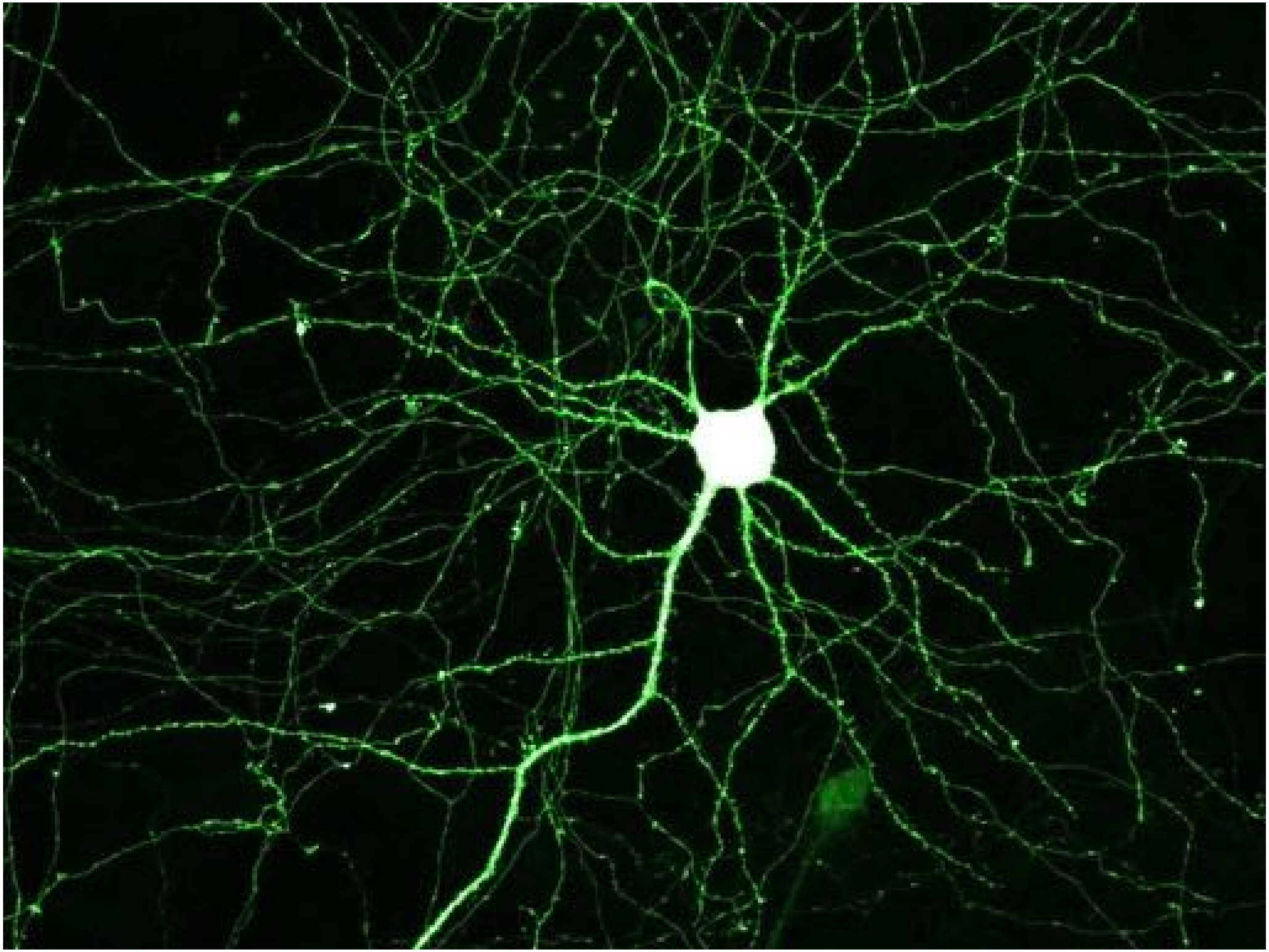
Neural Activity

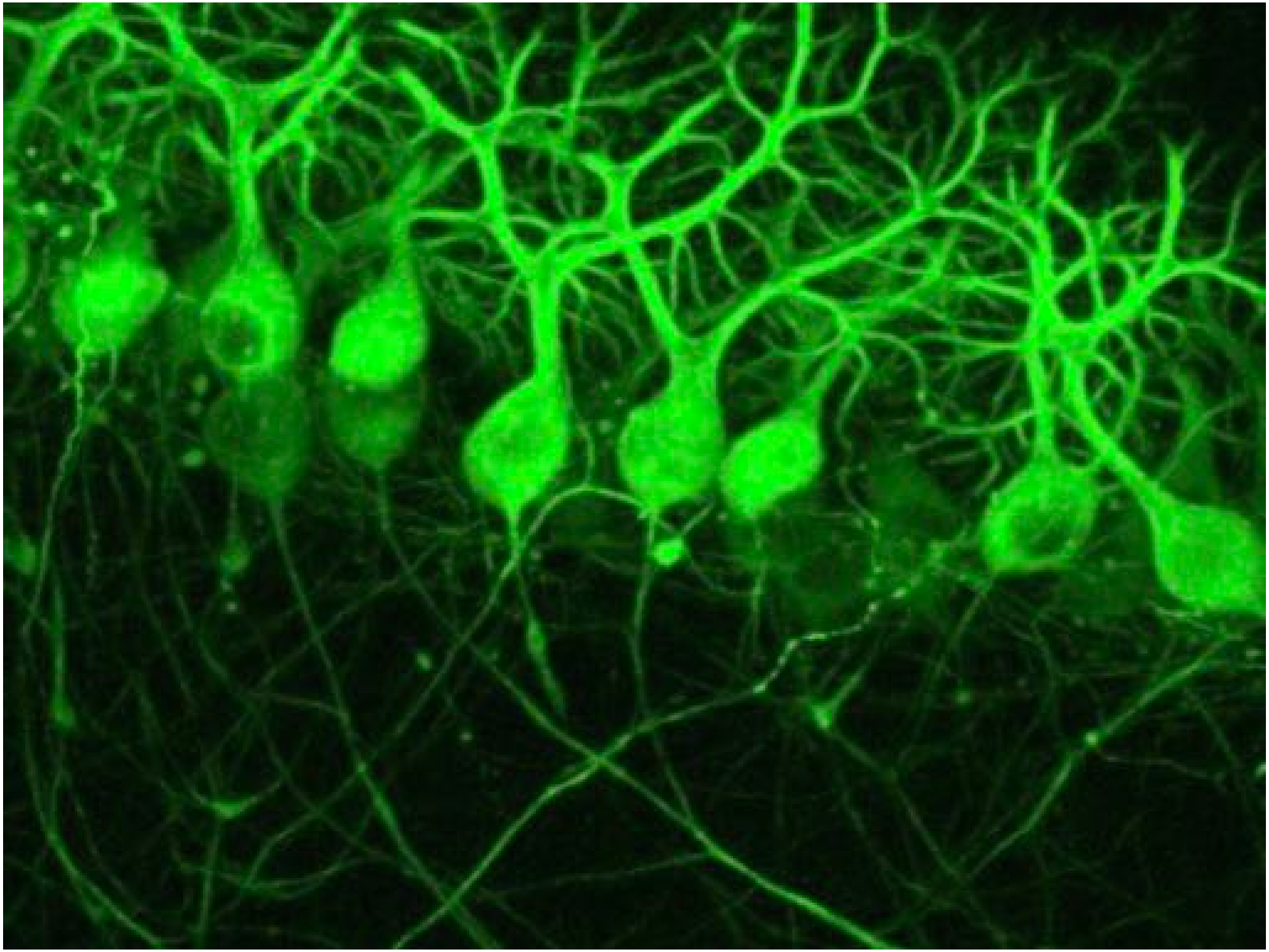
Neuromodulation

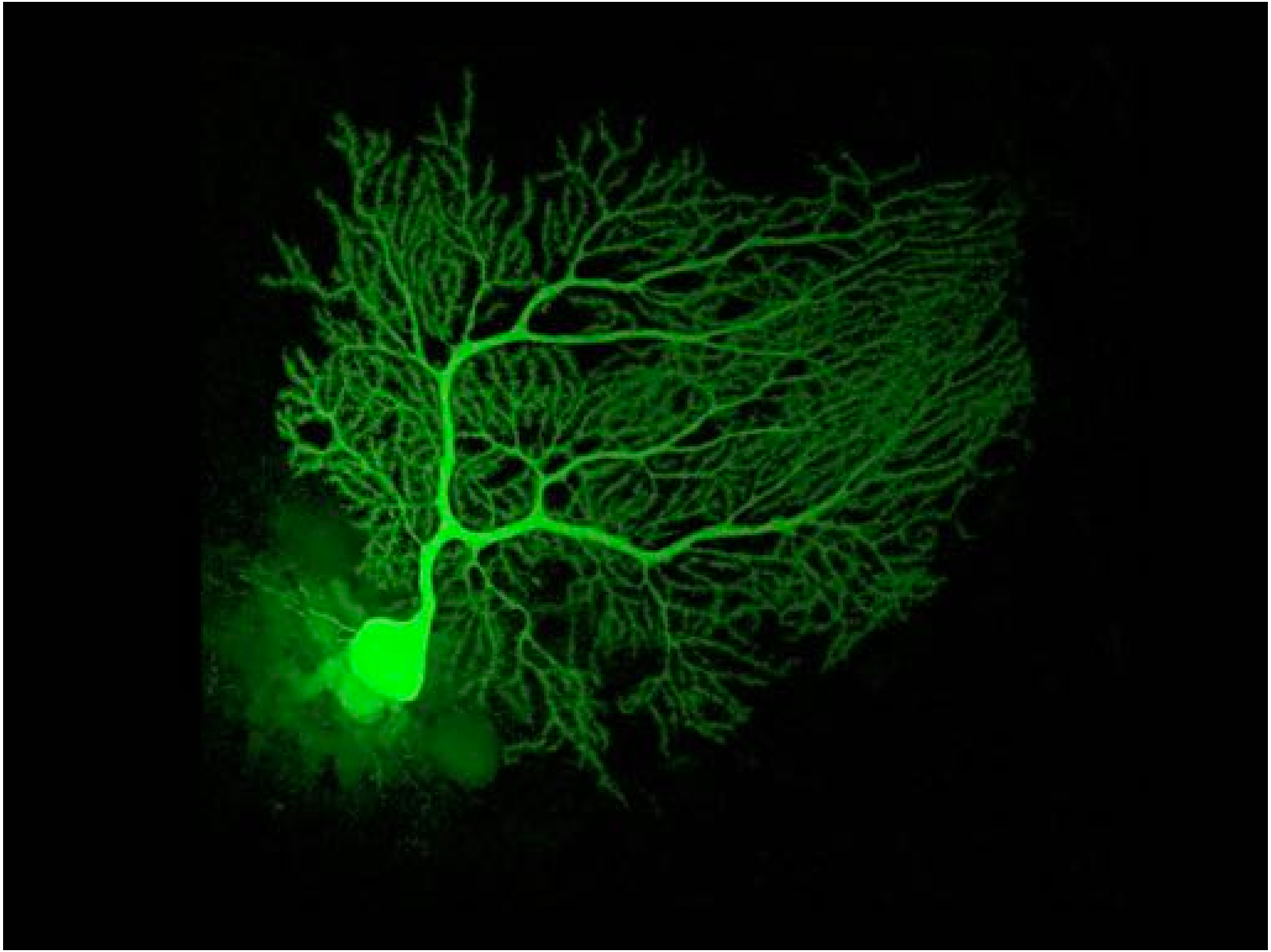


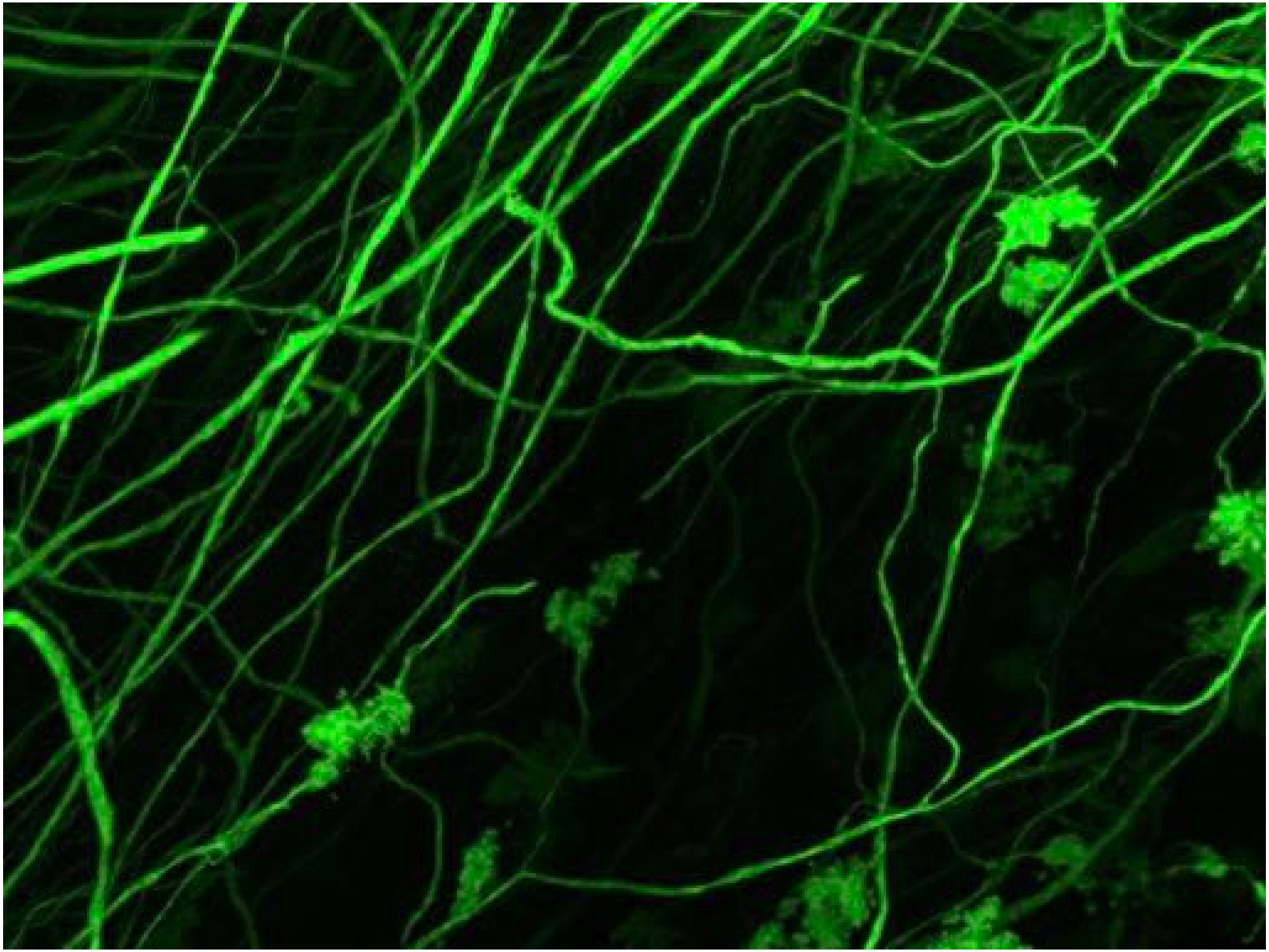


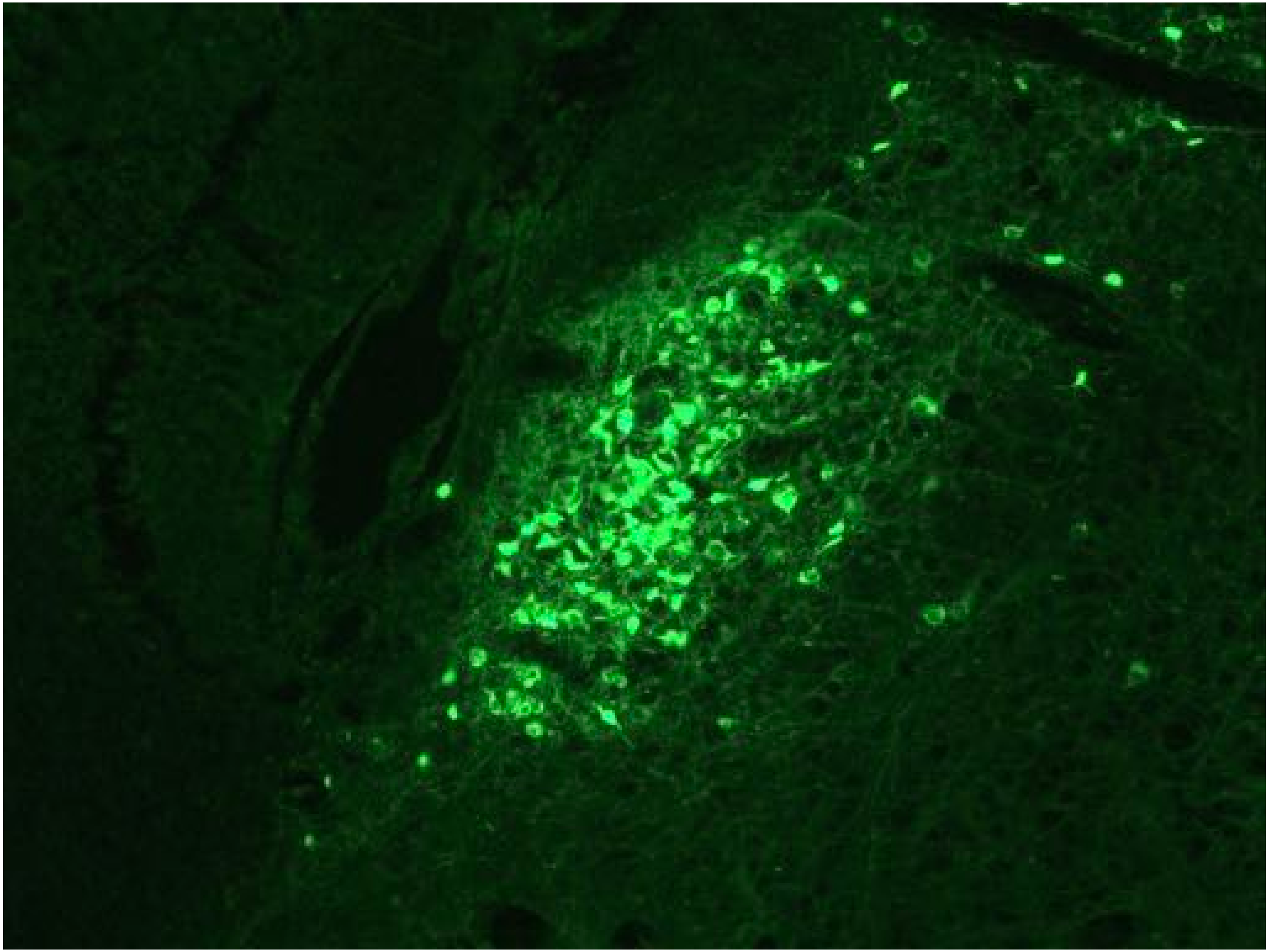
Green Fluorescent Protein (GFP)

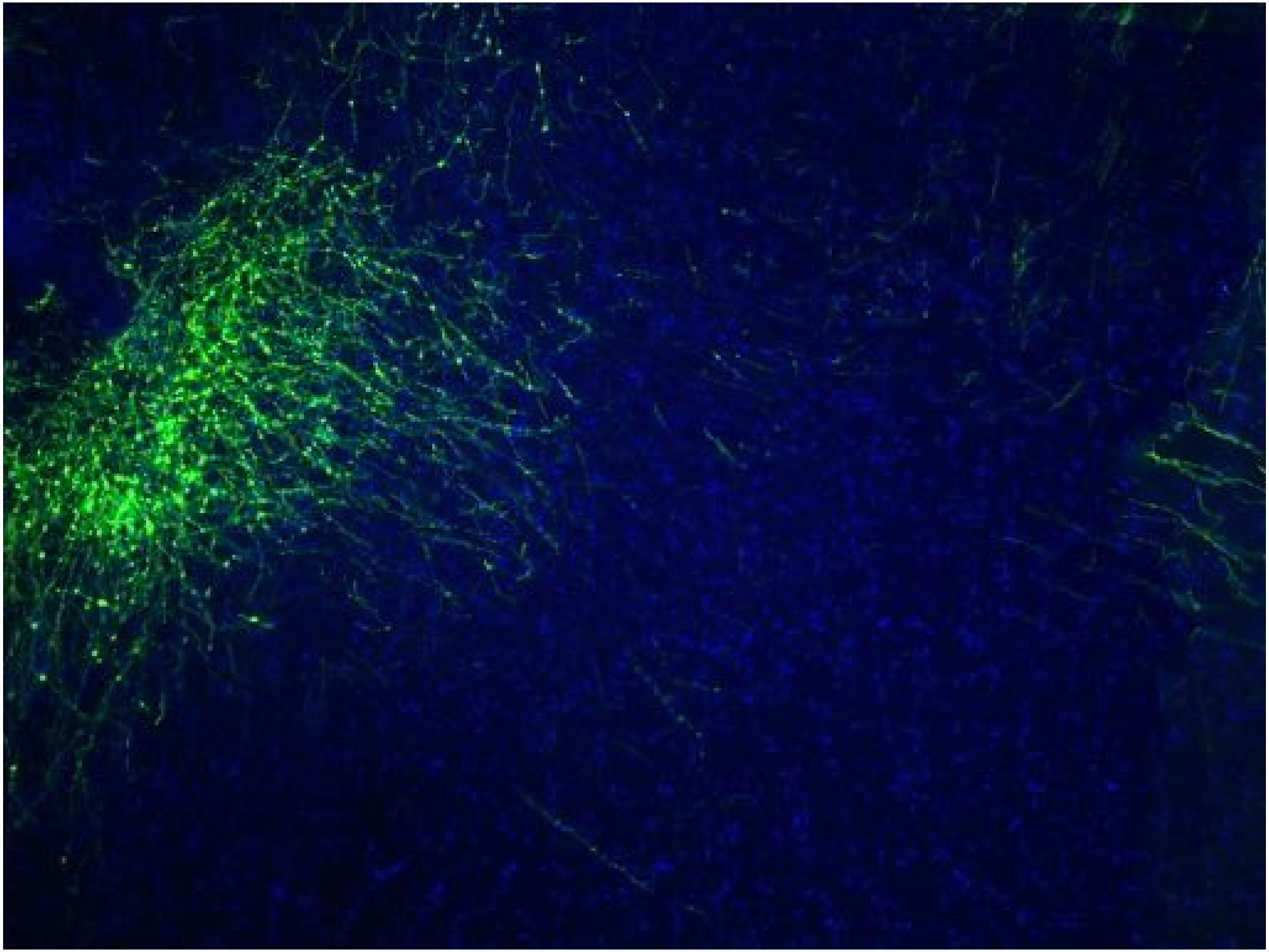


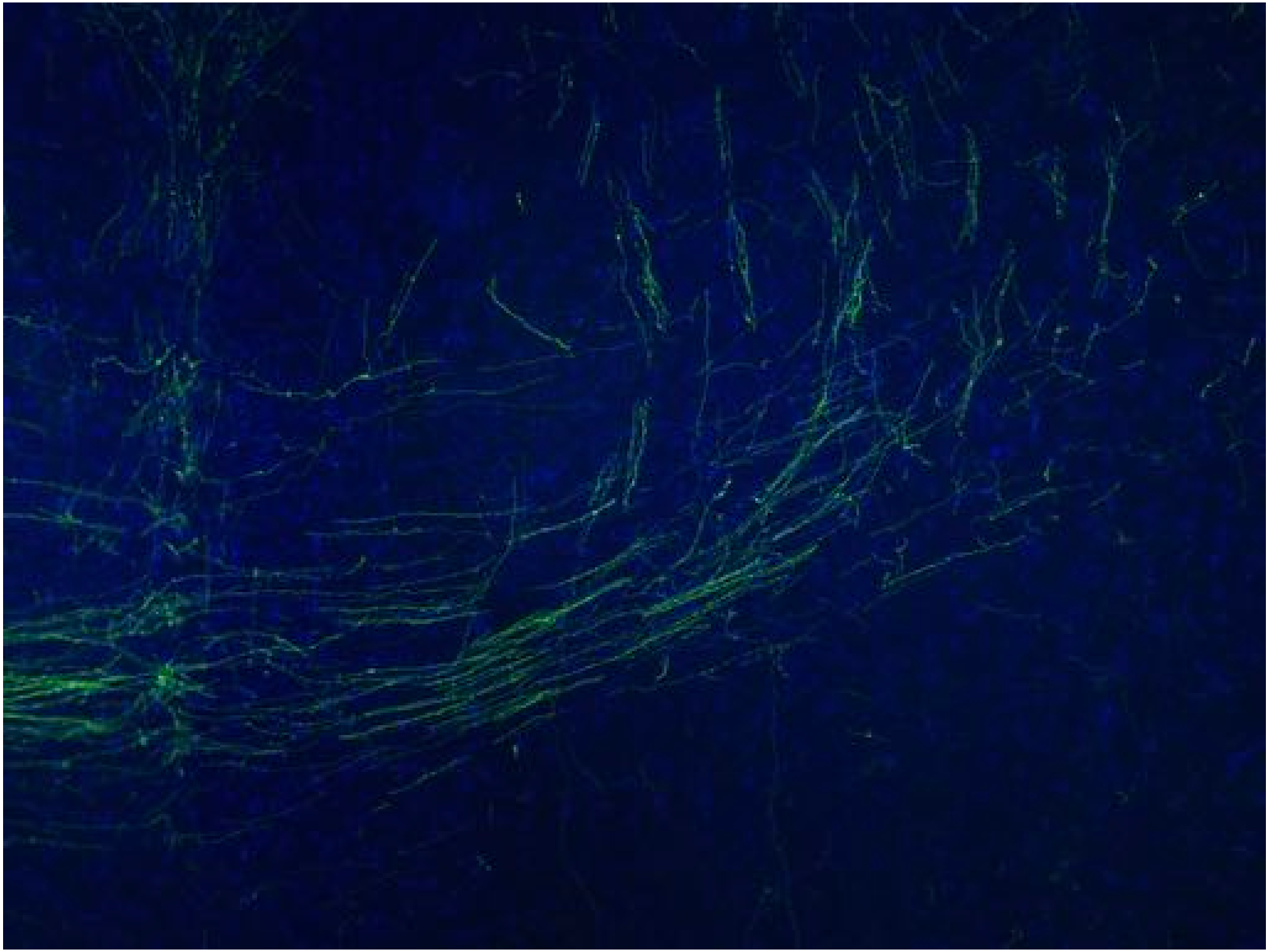


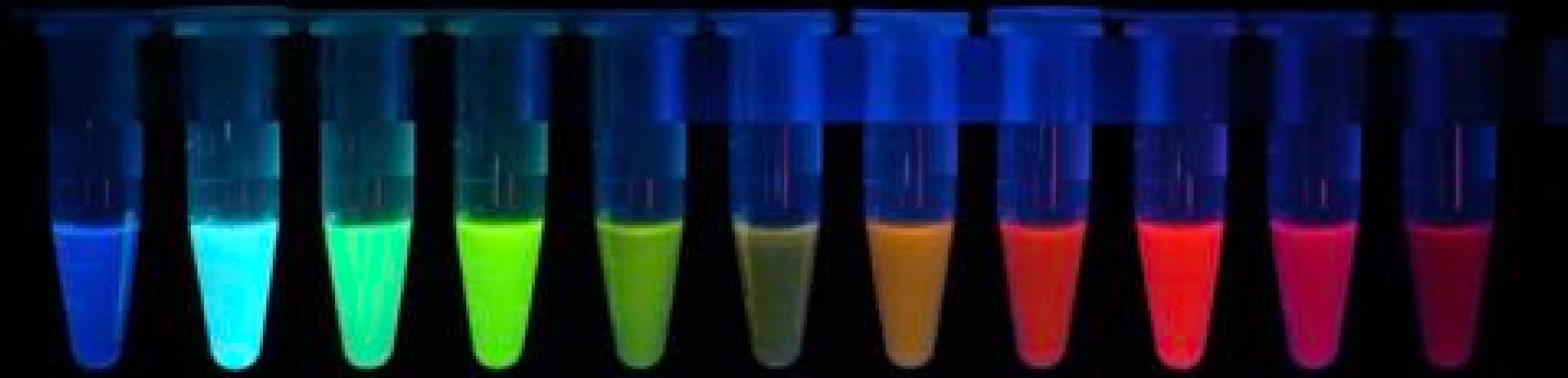


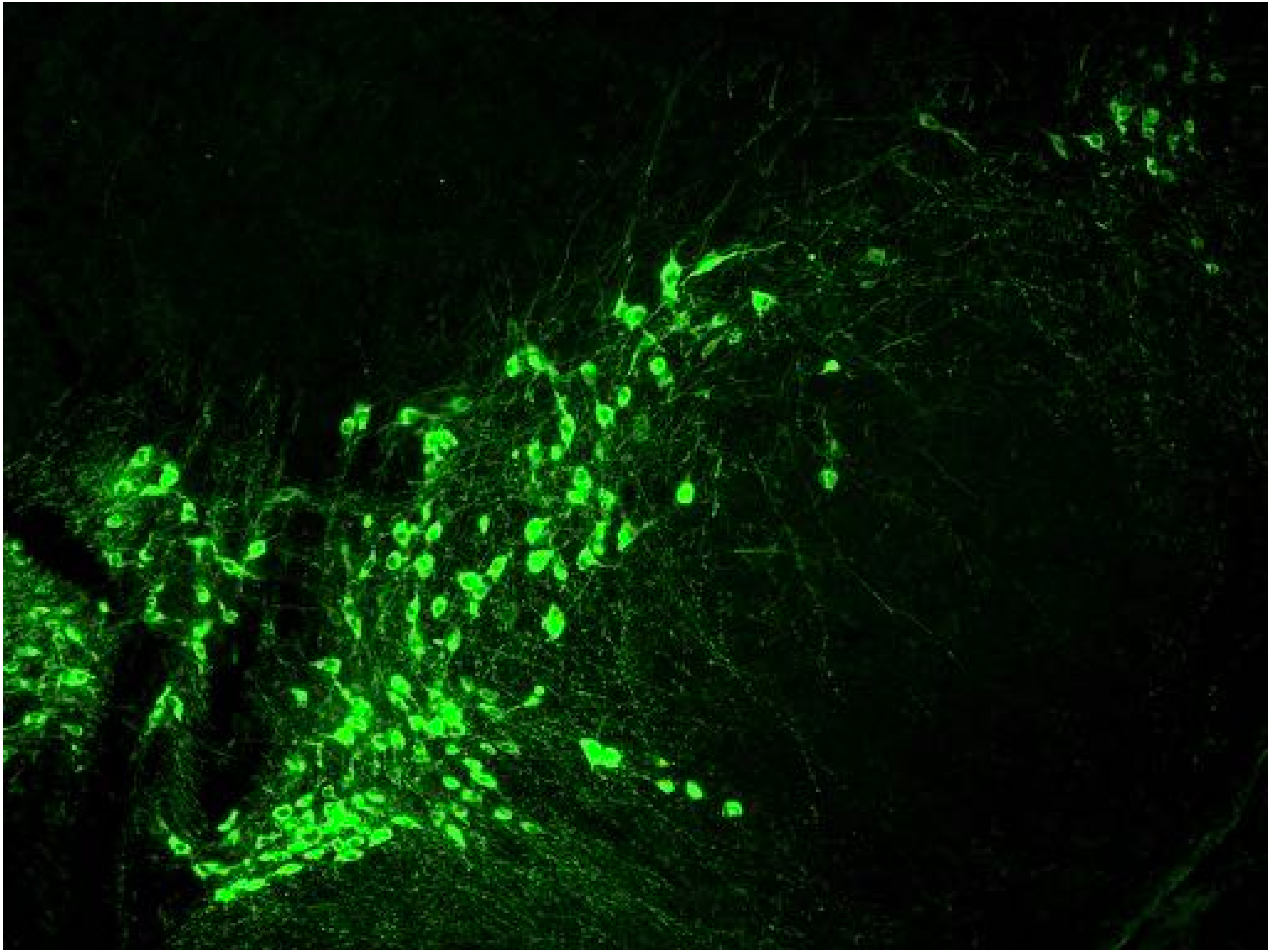


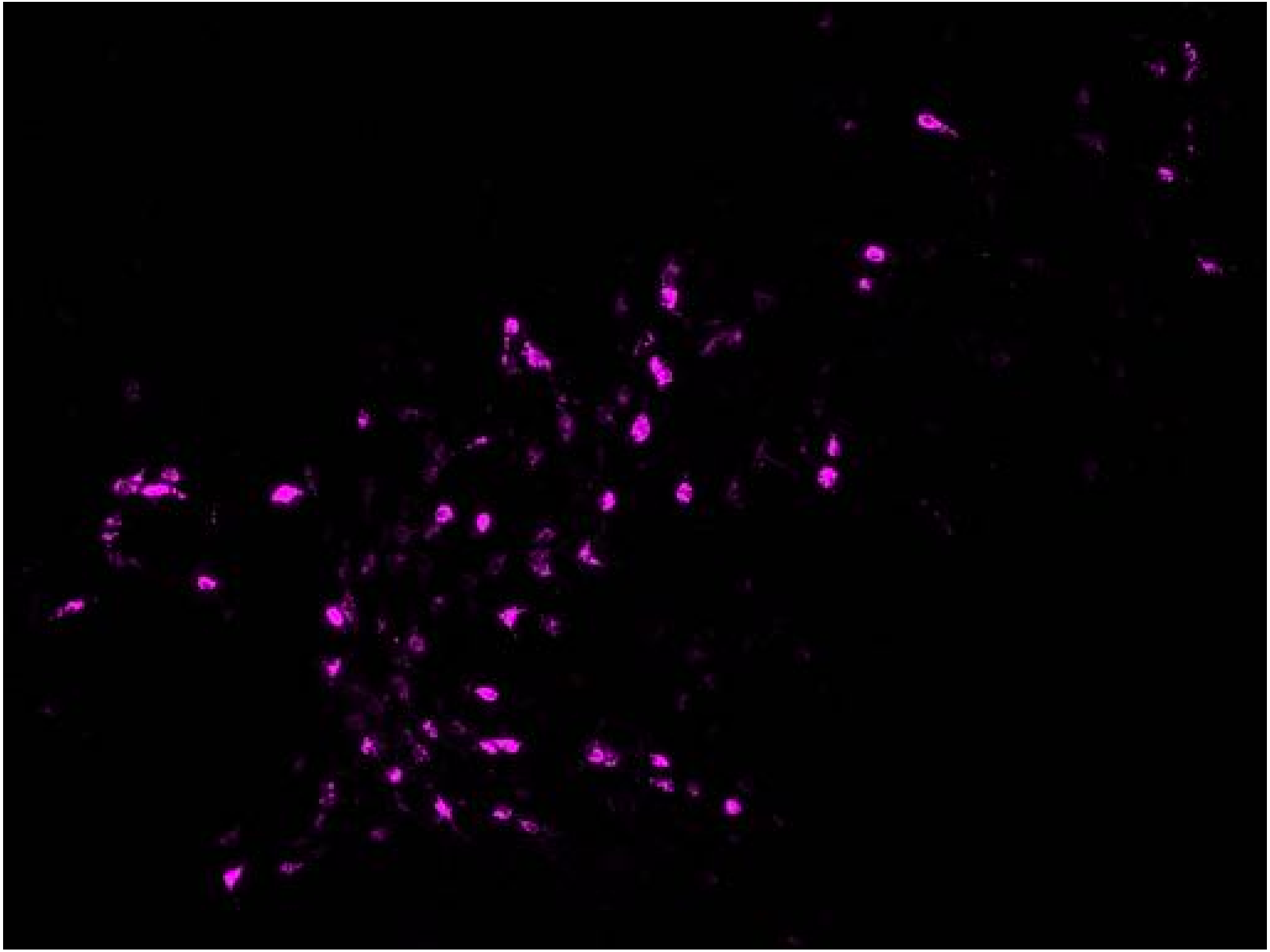


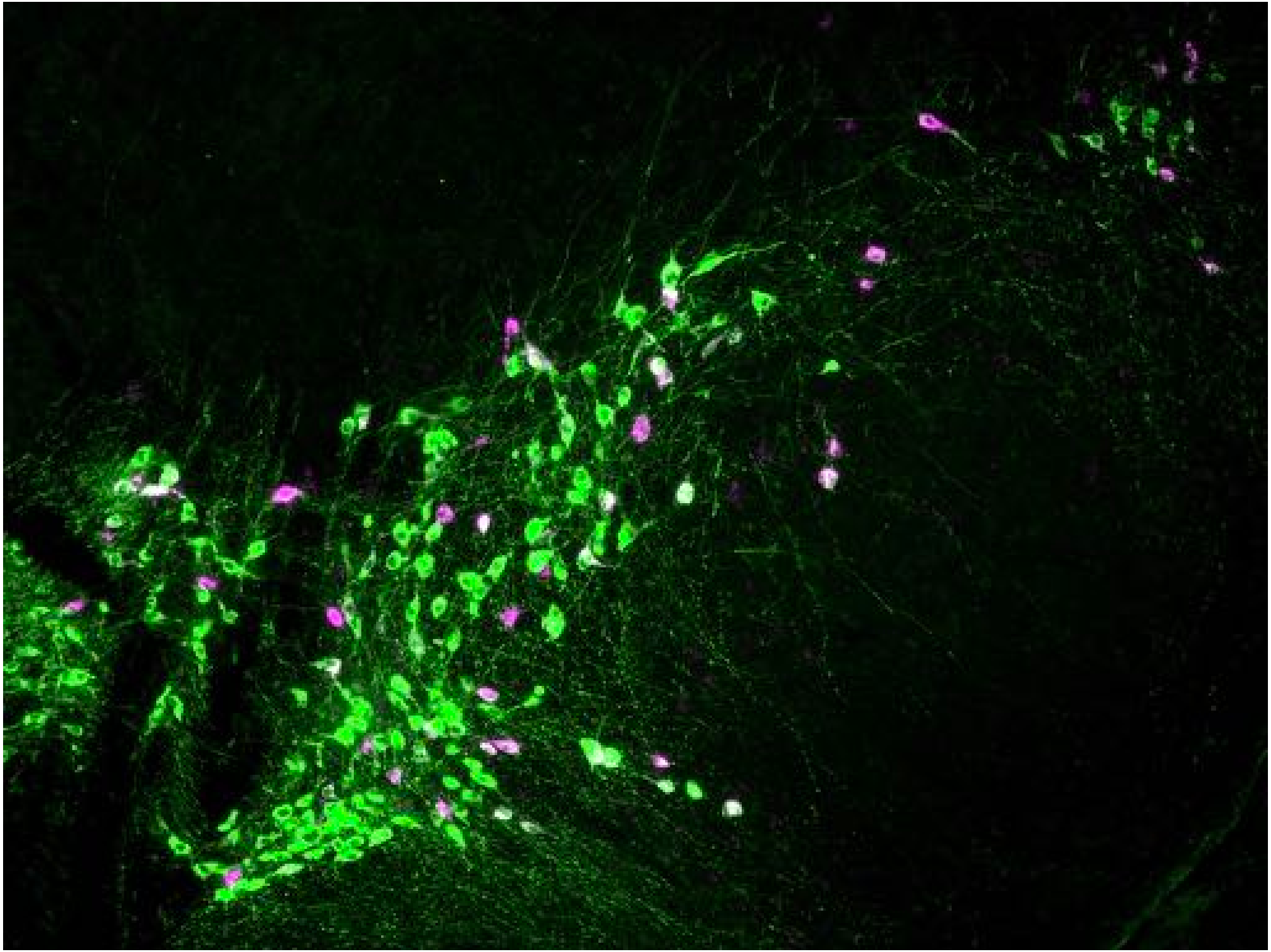


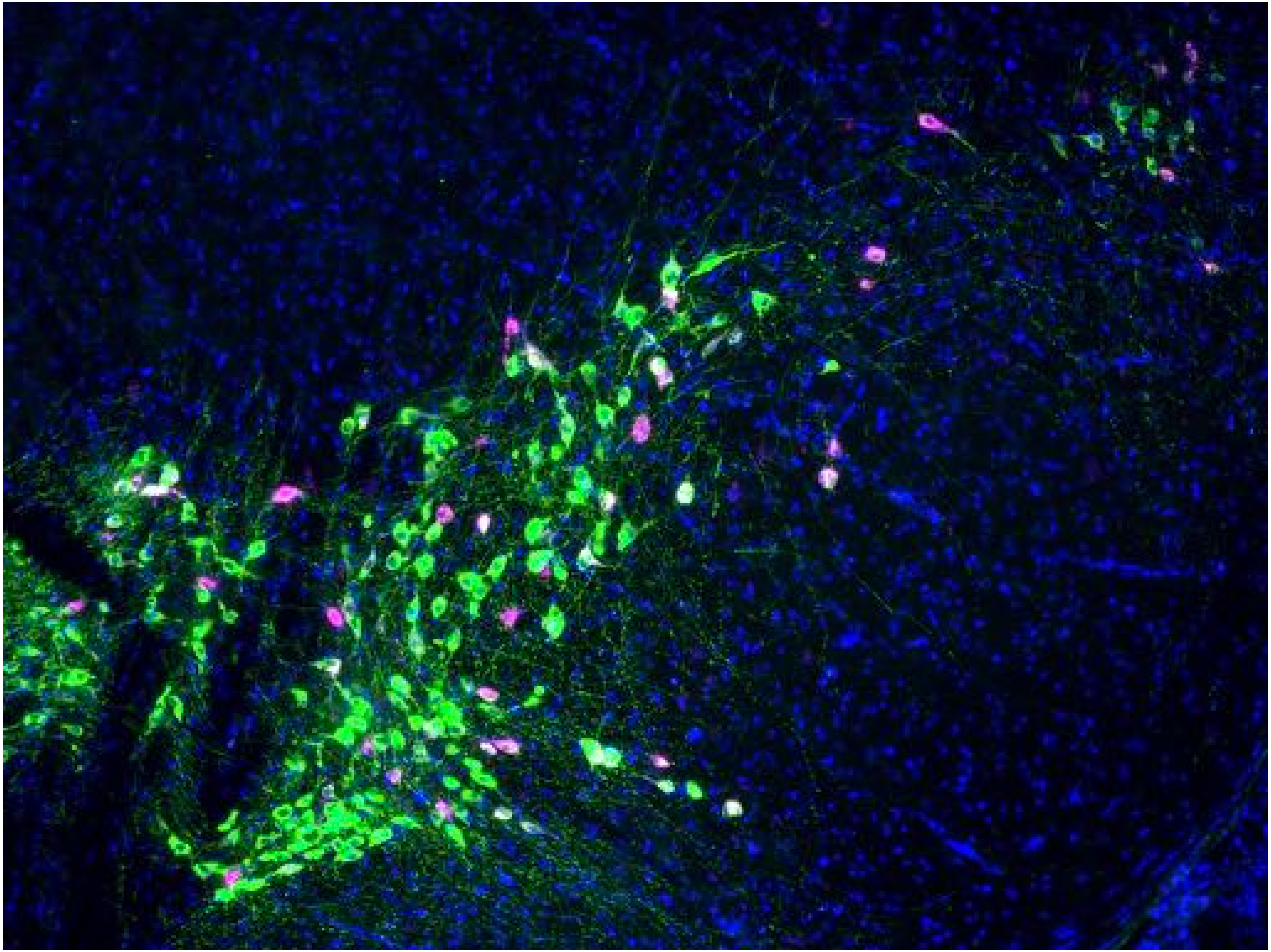


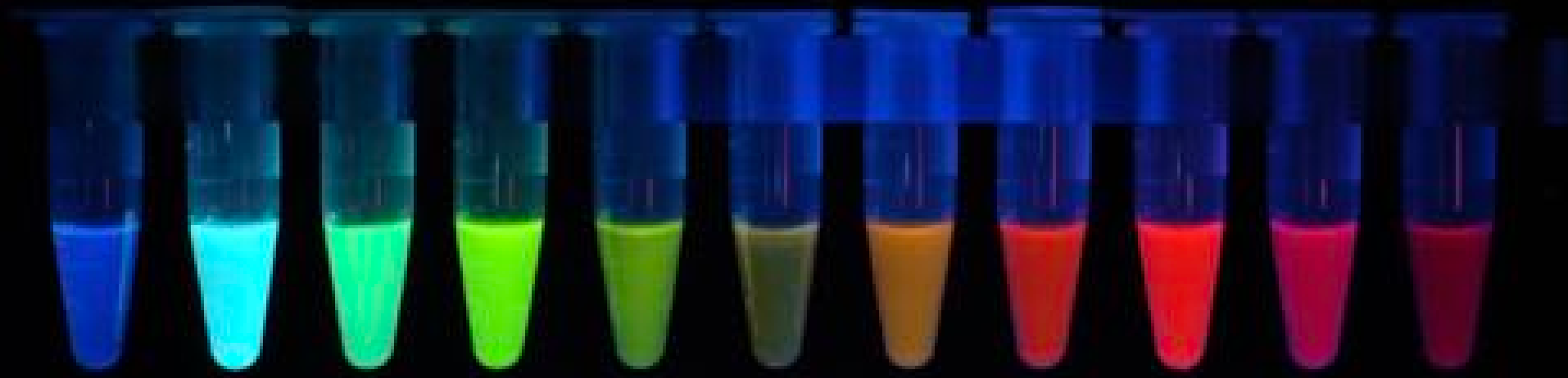


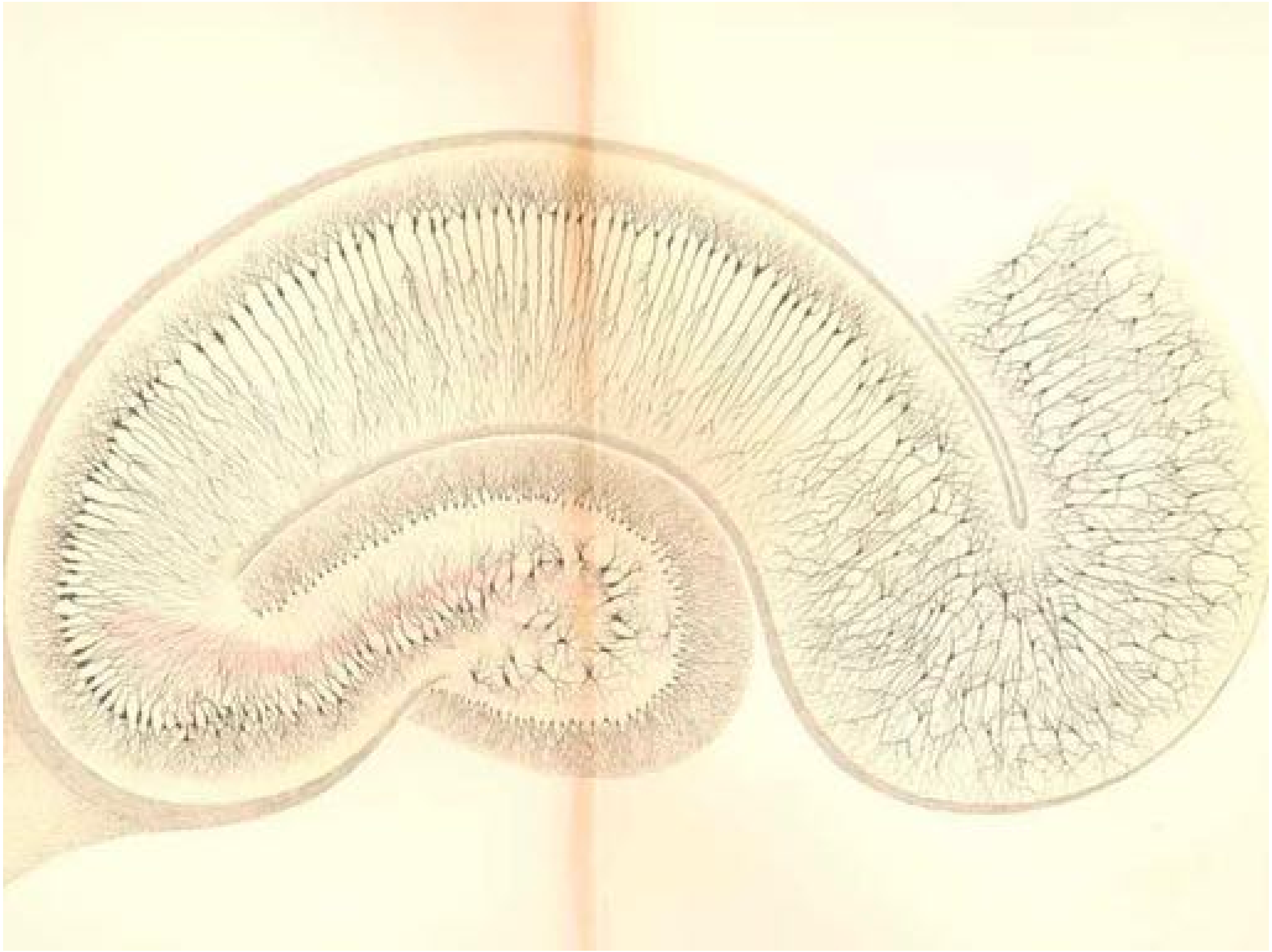


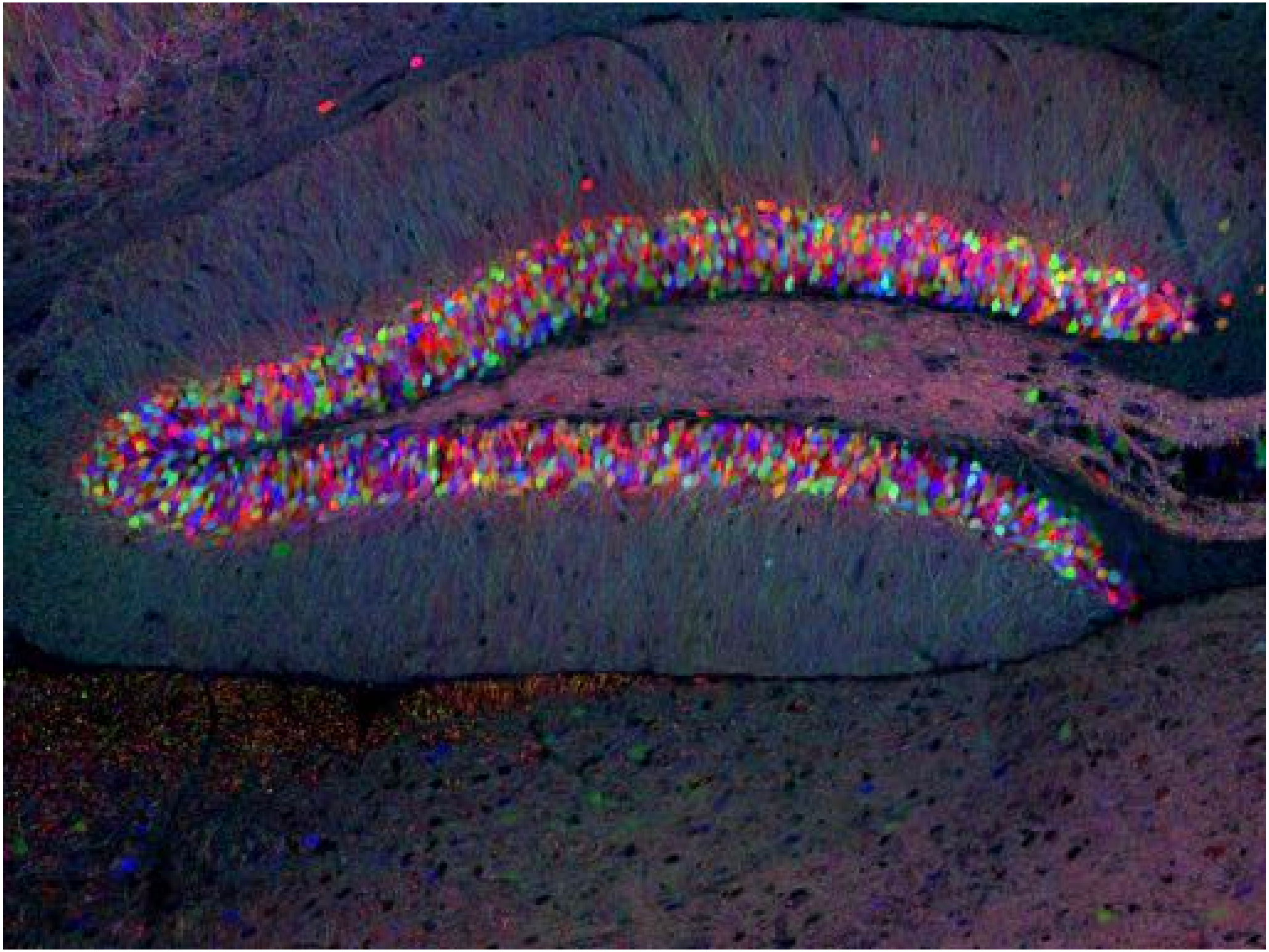


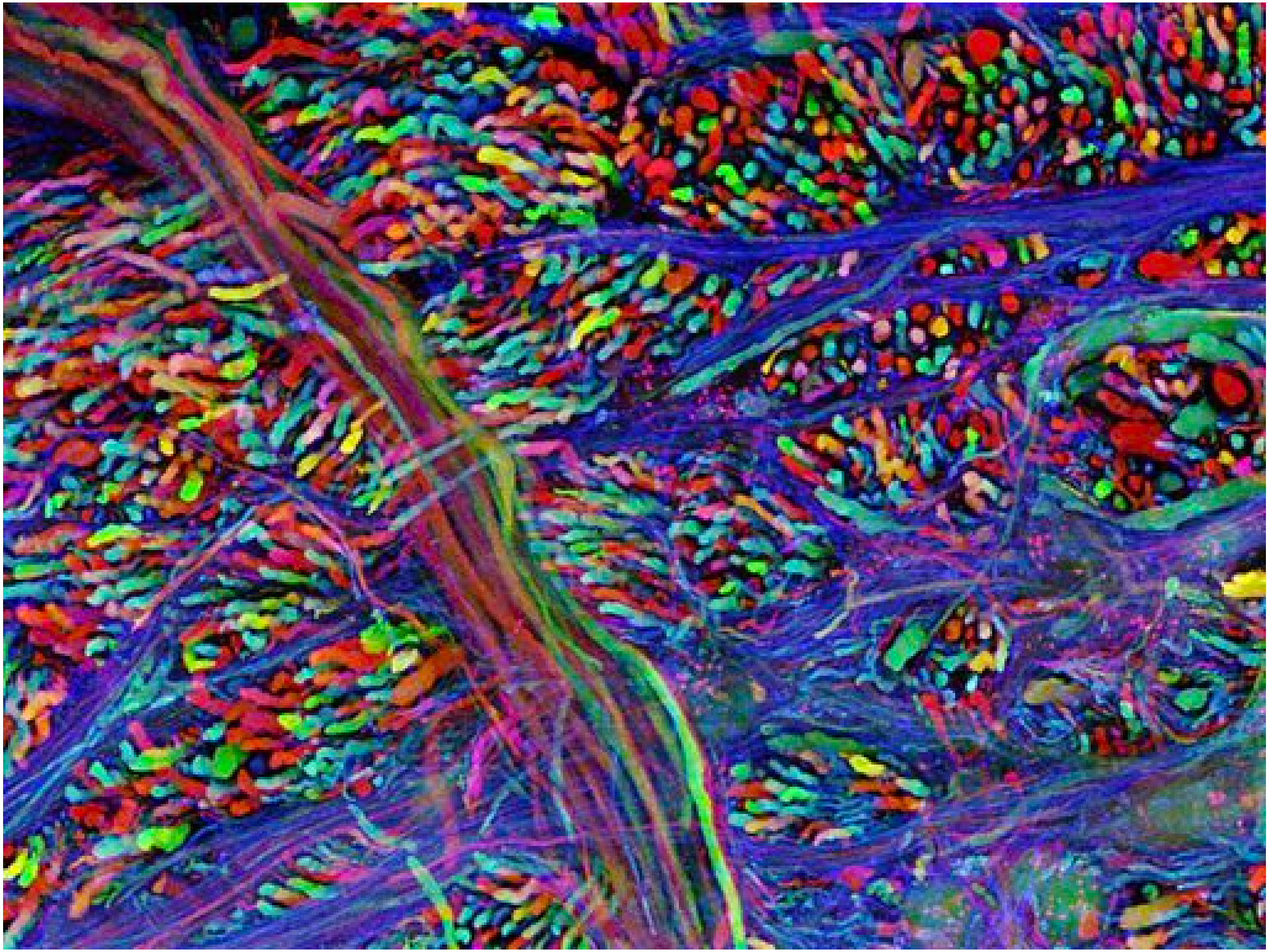


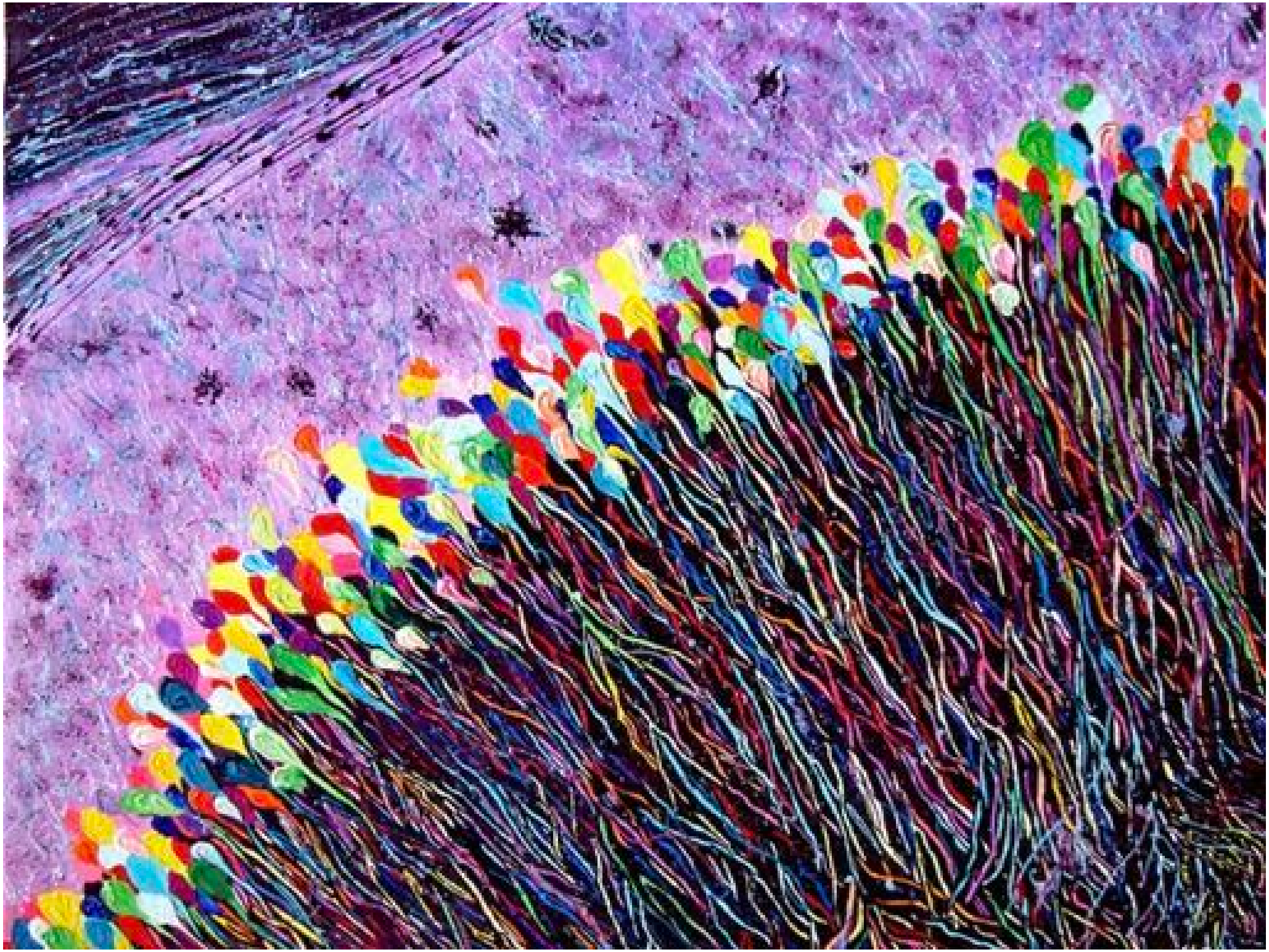


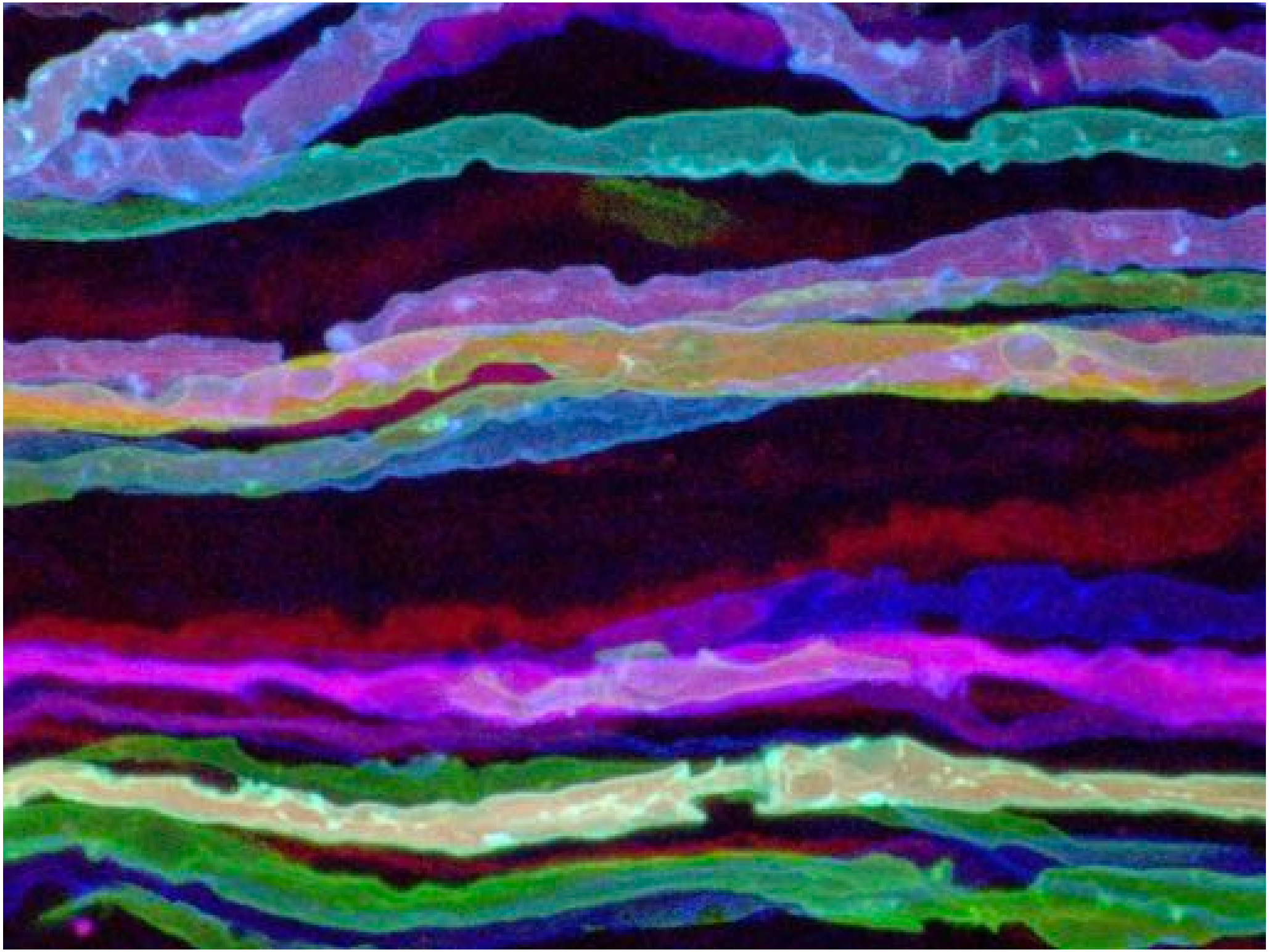


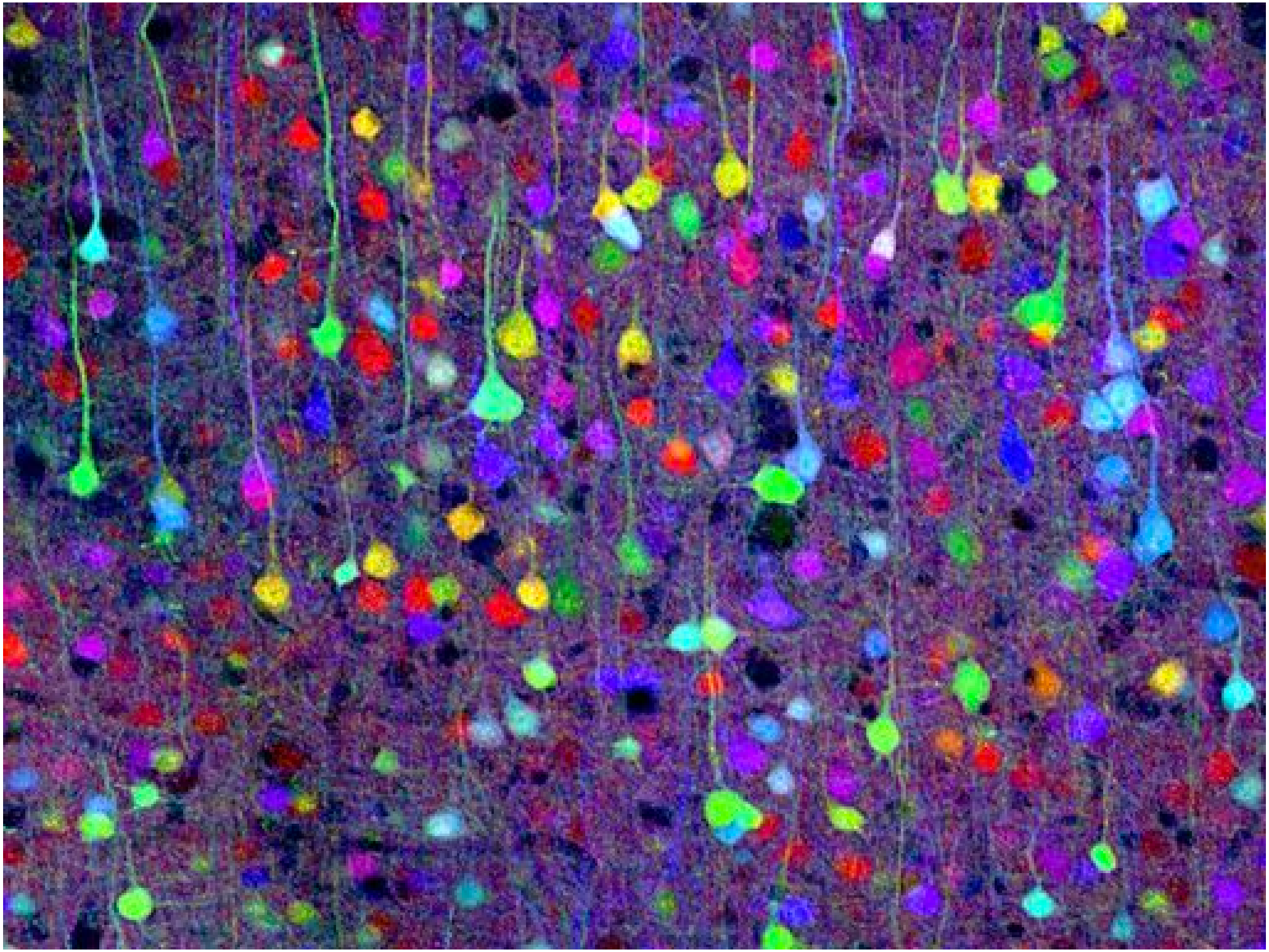


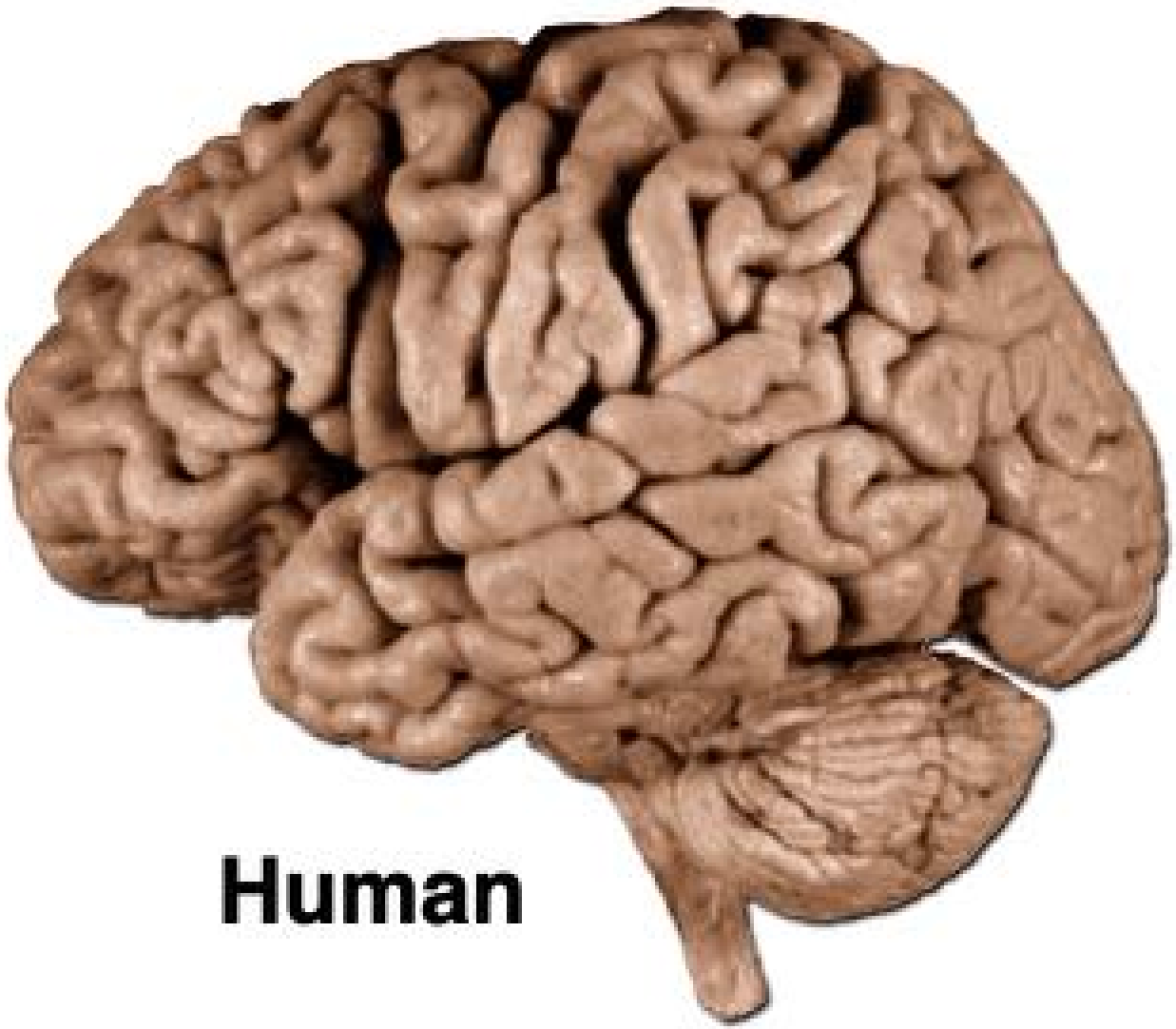








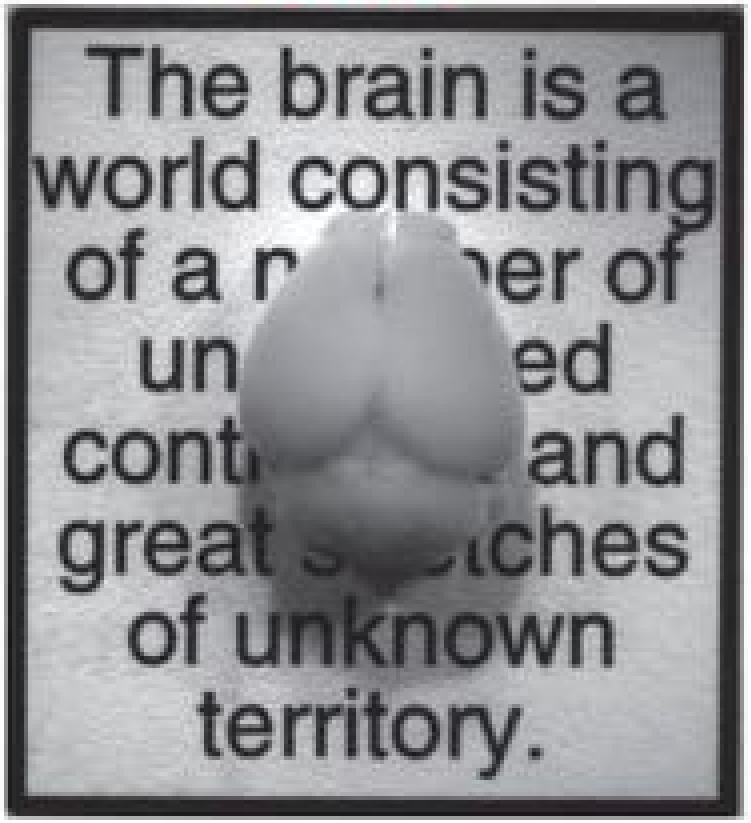




Human

Mouse

Before



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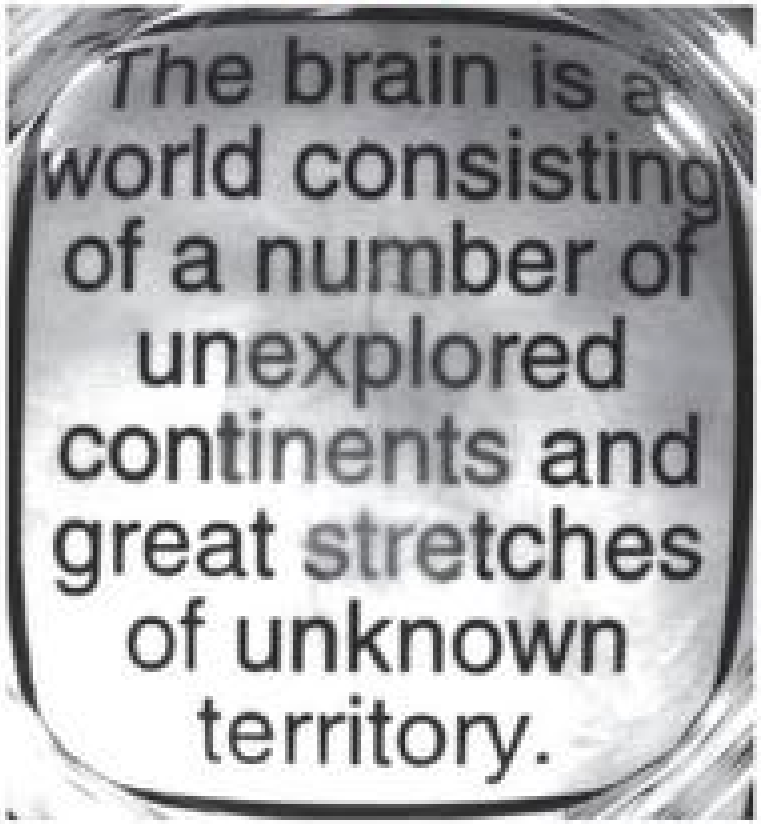

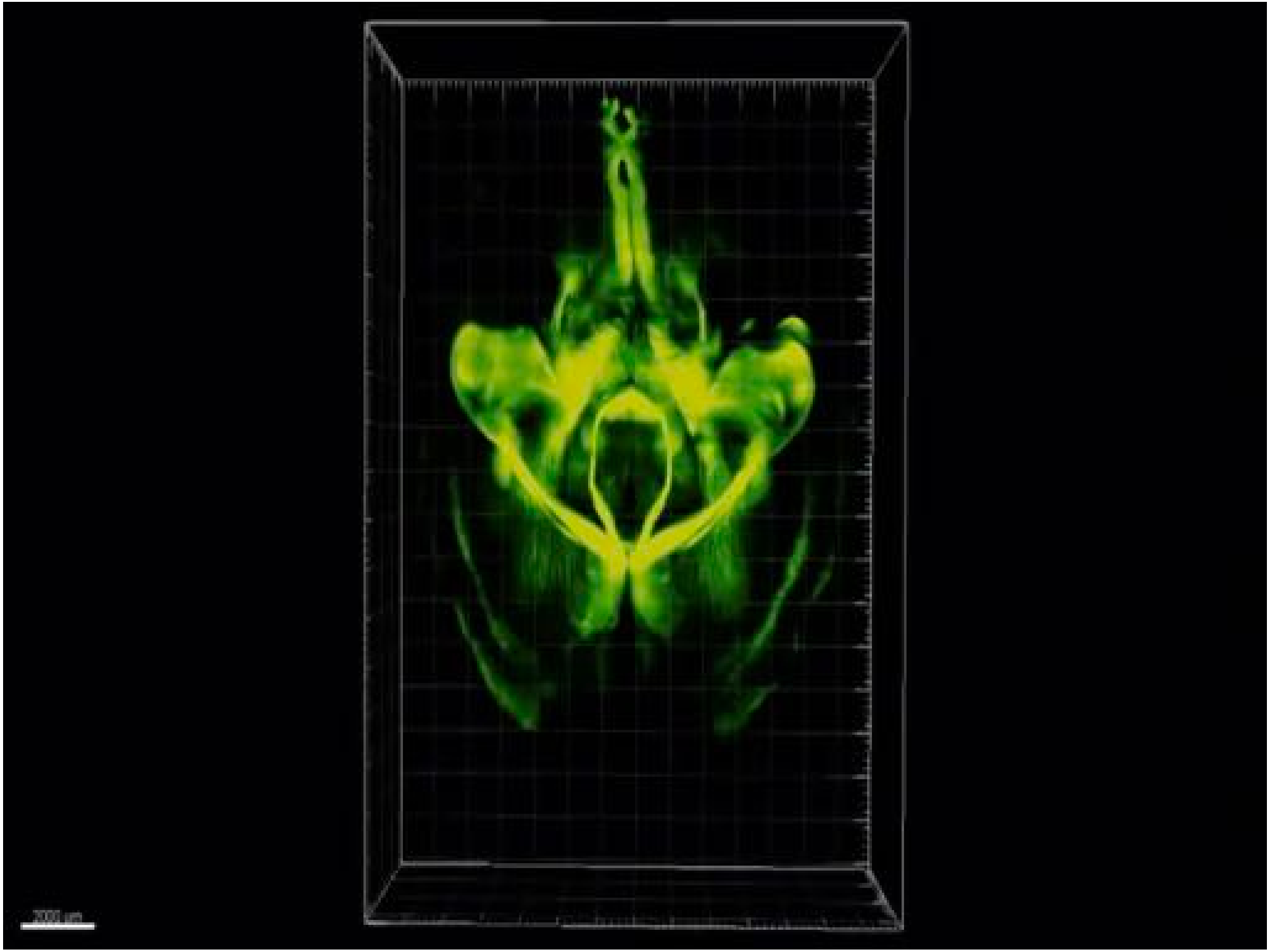

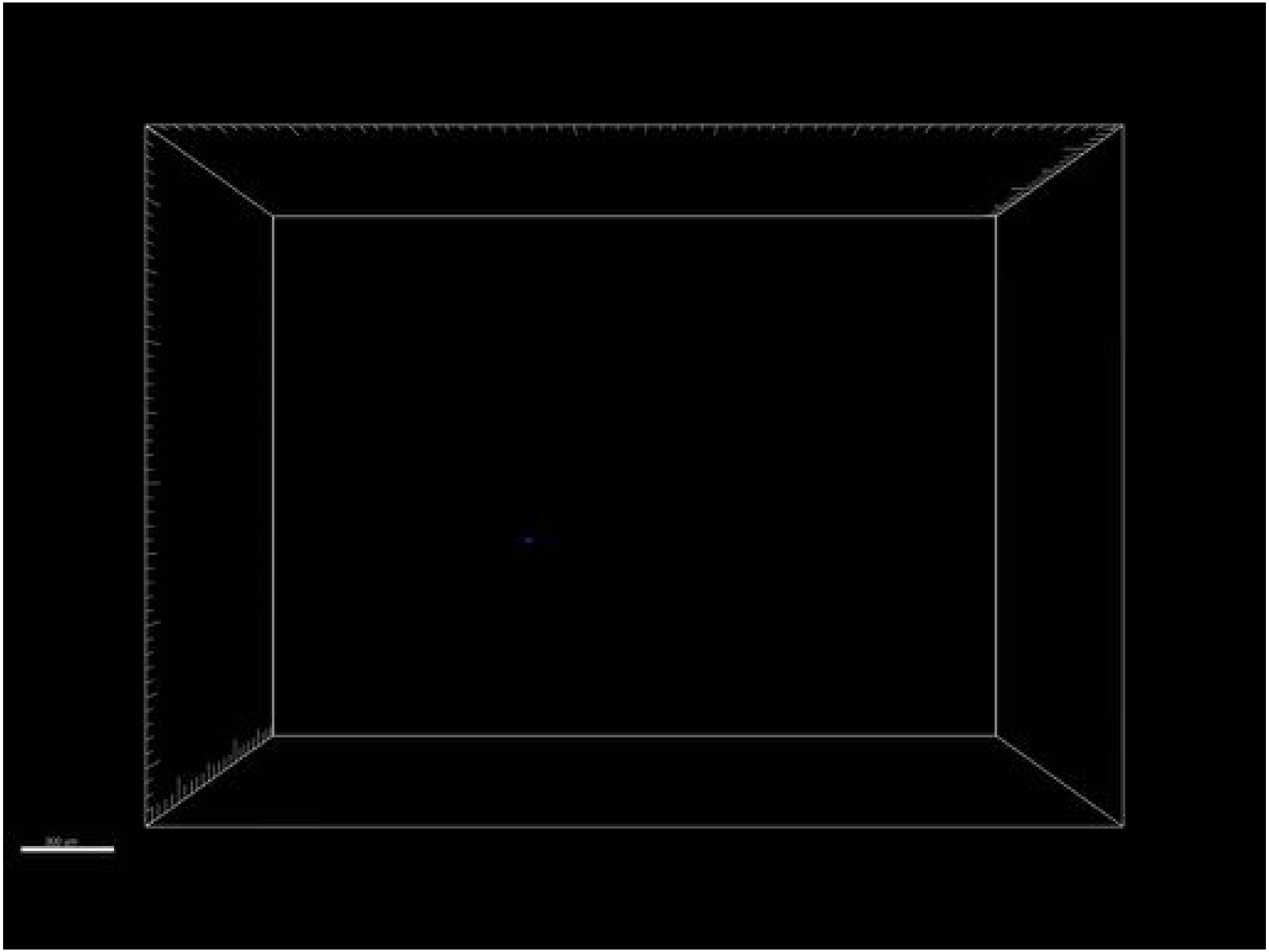

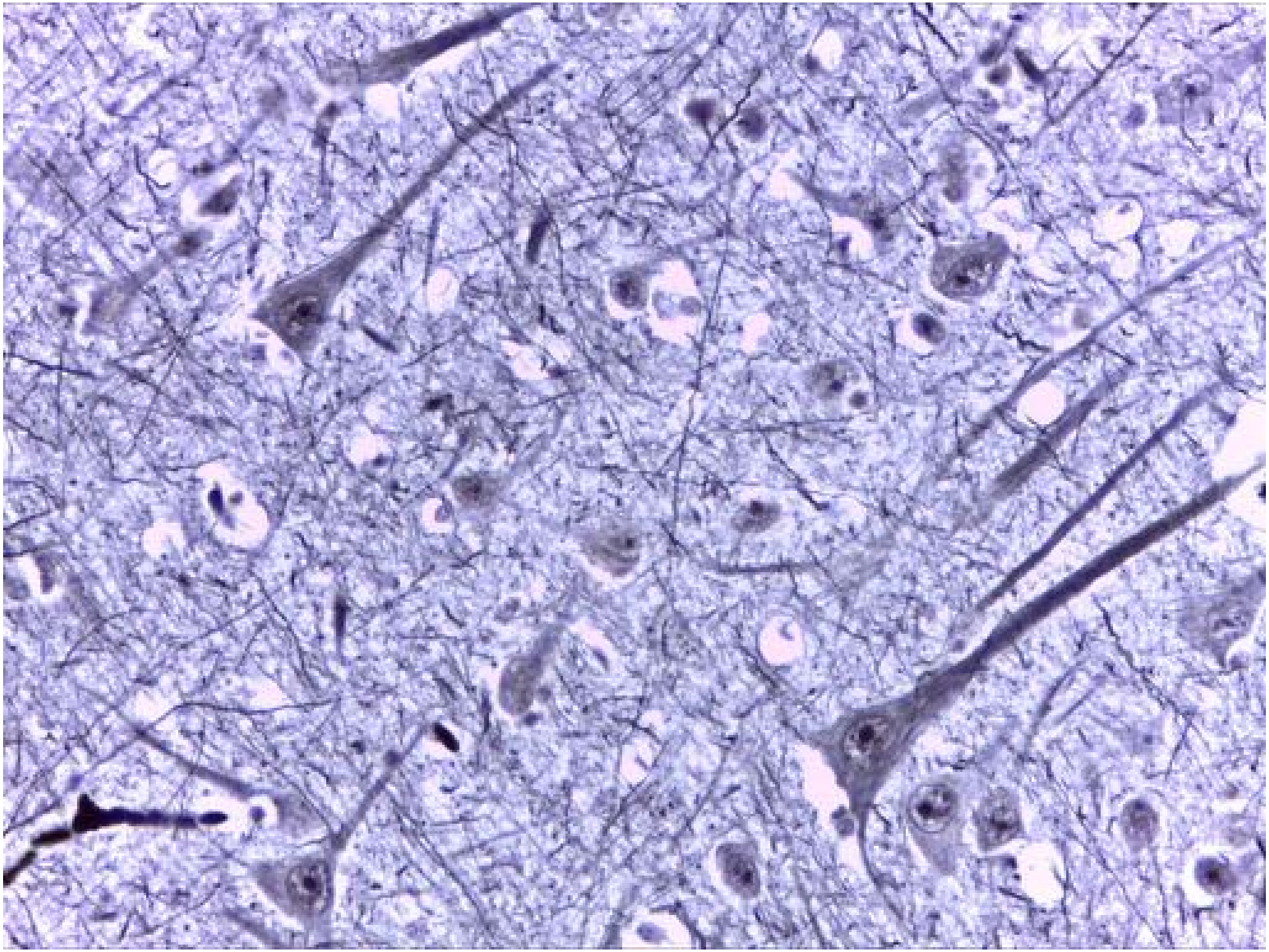

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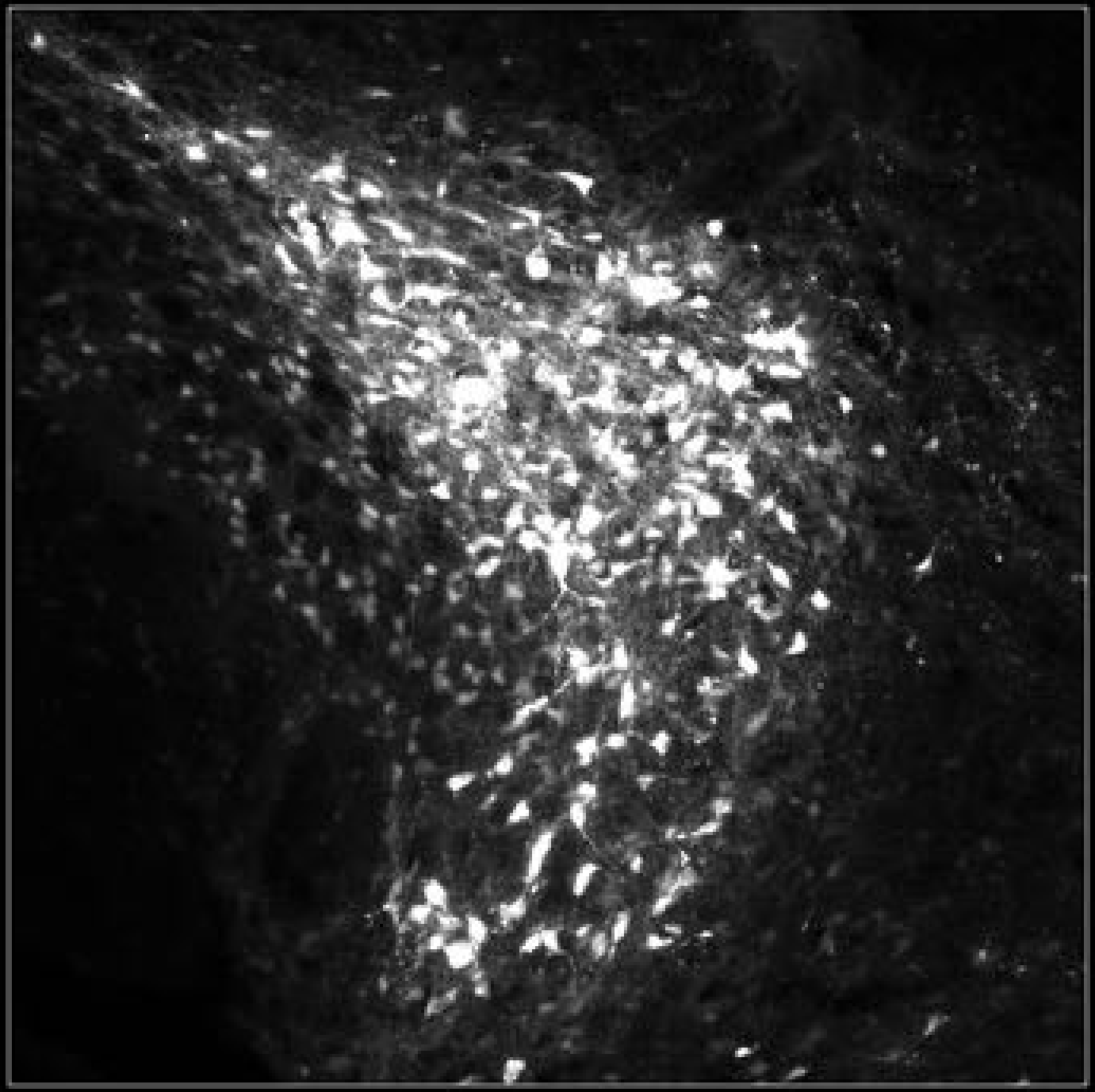
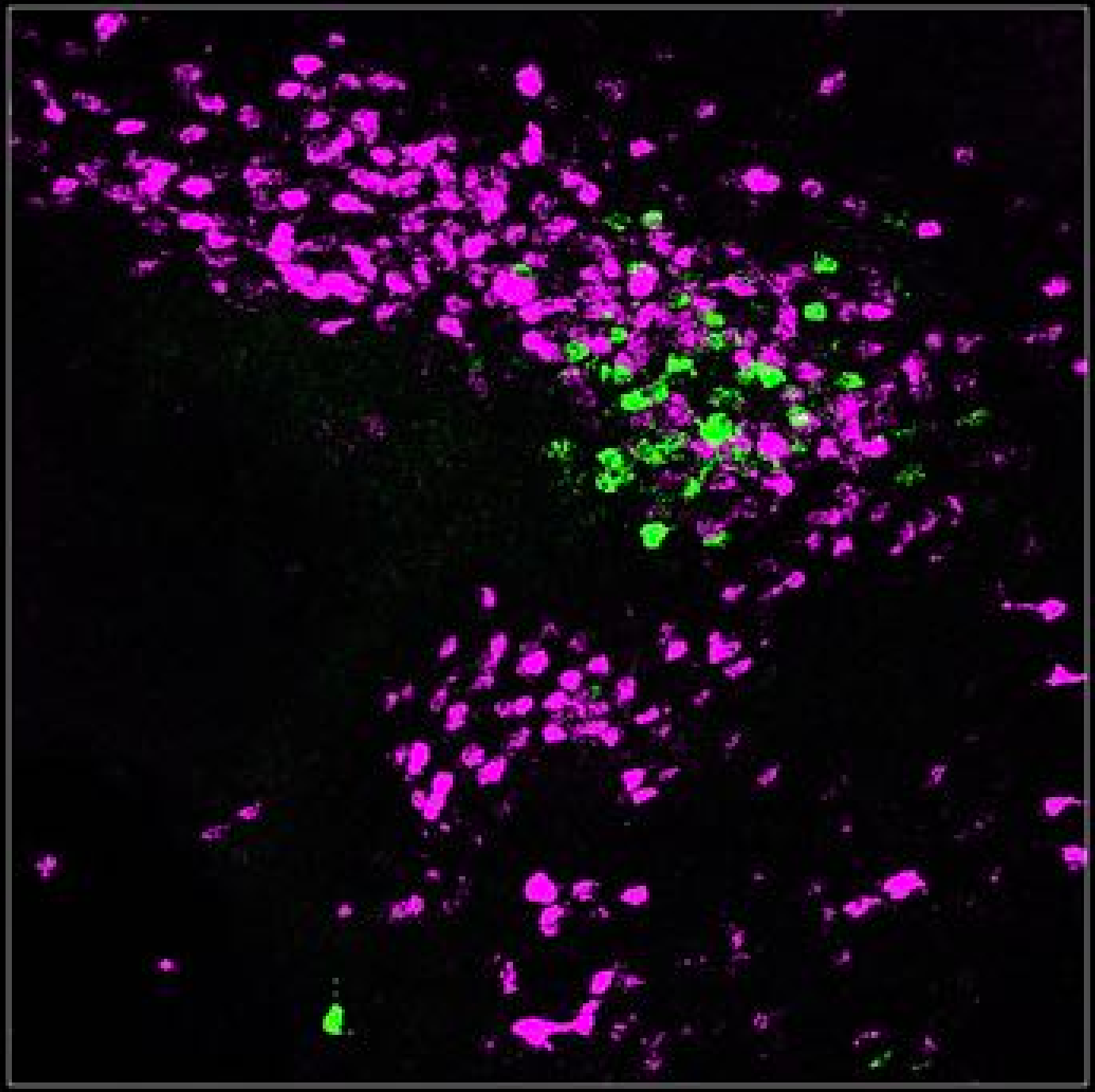
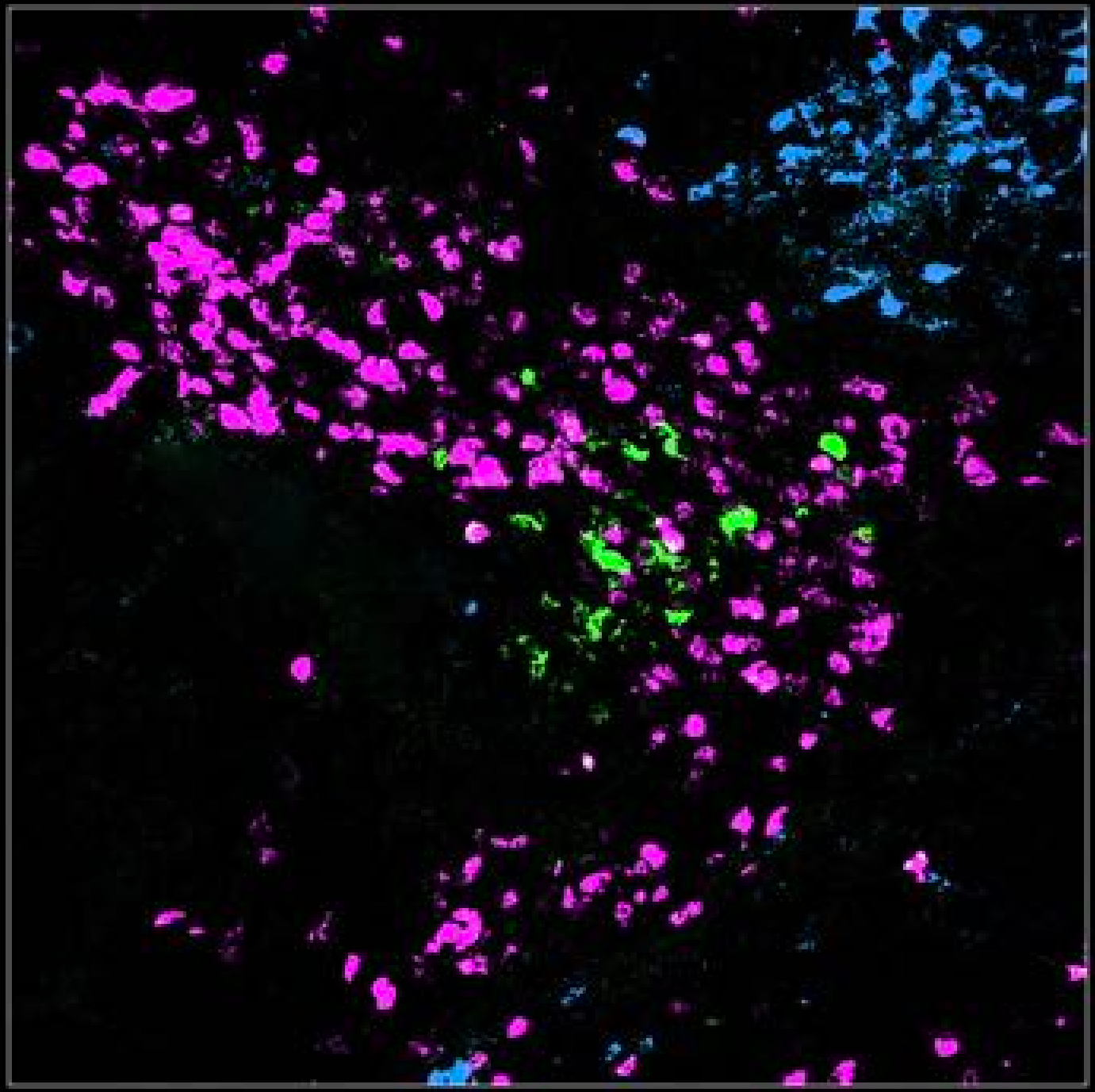
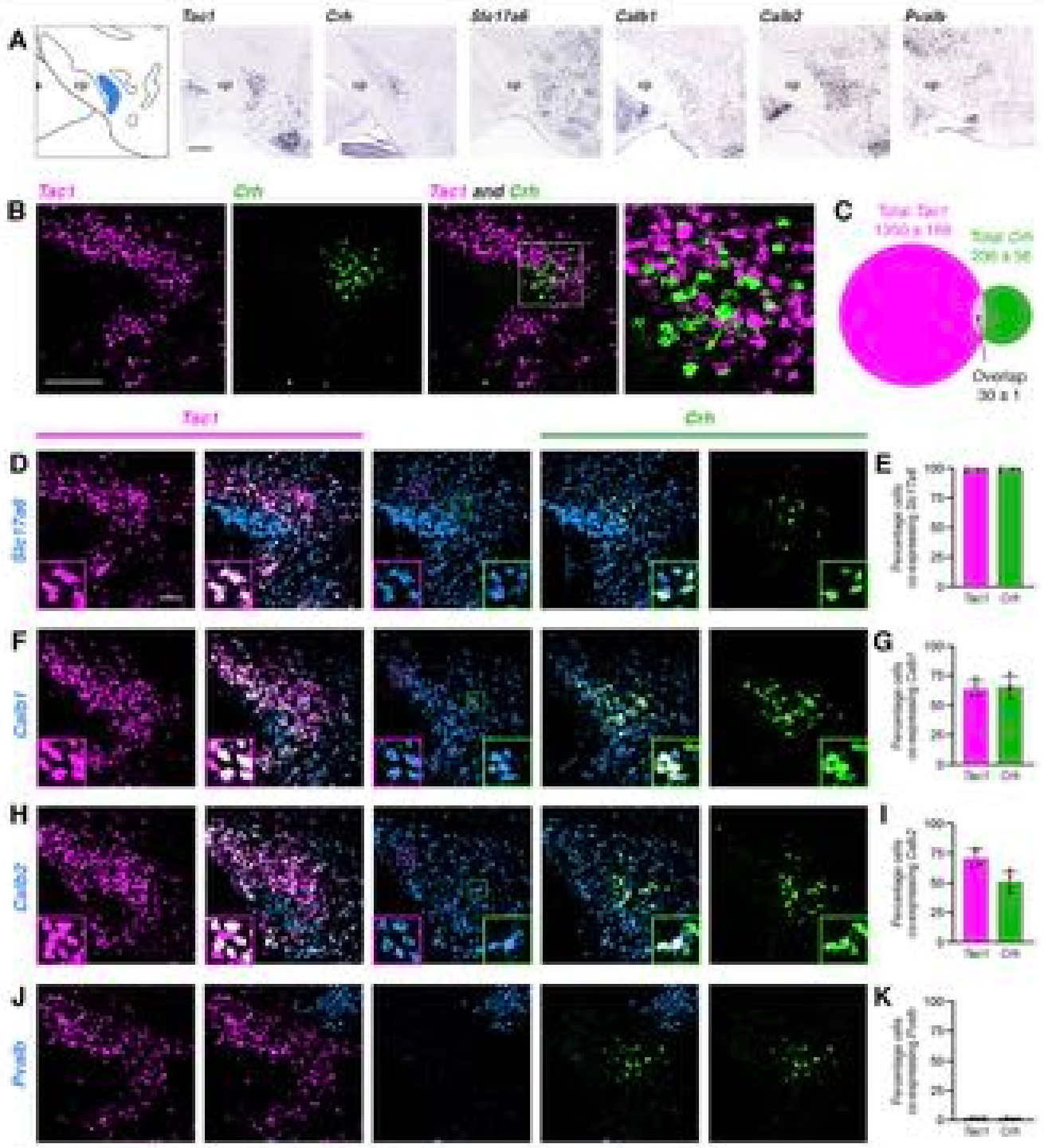
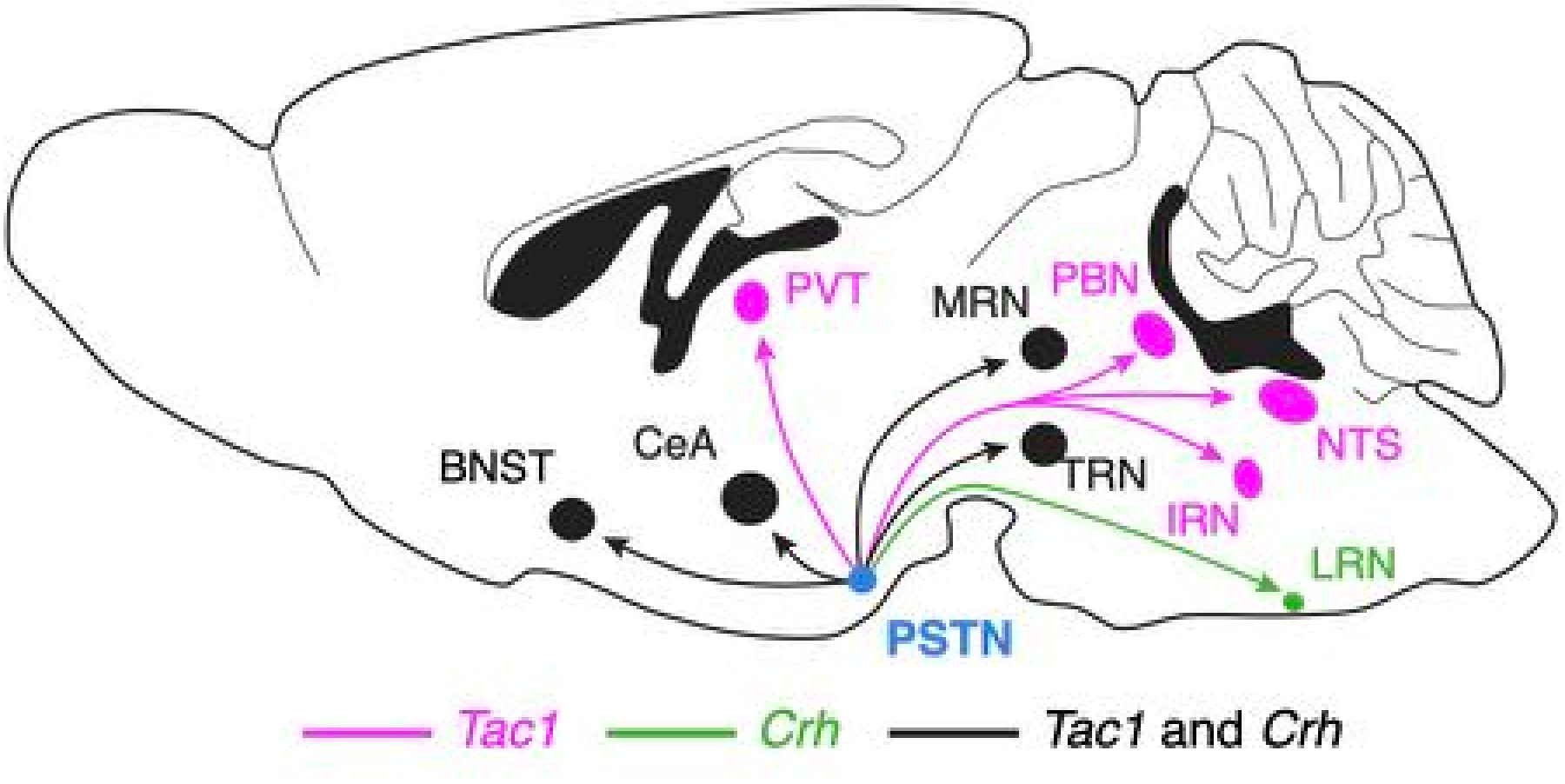







A
Tac1
Crh
Slc17a6
Calb1
Calb2
Pvalb
B
Tac1
Crh
Tac1 and Crh
C
Total Tac1
1350 ± 199
Total Crh
295 ± 56
Overlap
30 ± 1
Tac1
Crh
D
Slc17a6
E
F
Calb1
G
H
Calb2
I
J
Pvalb
K


PVT
MRN
PBN
NTS
BNST
CeA
TRN
IRN
LRN
PSTN
Tac1
Crh
Tac1 and Crh

Adding a bit of color and light to the brain

Neural Structure

Neural Activity

Neuromodulation

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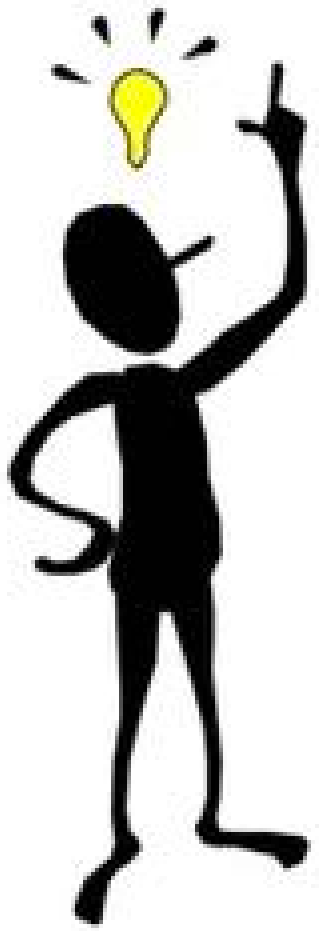
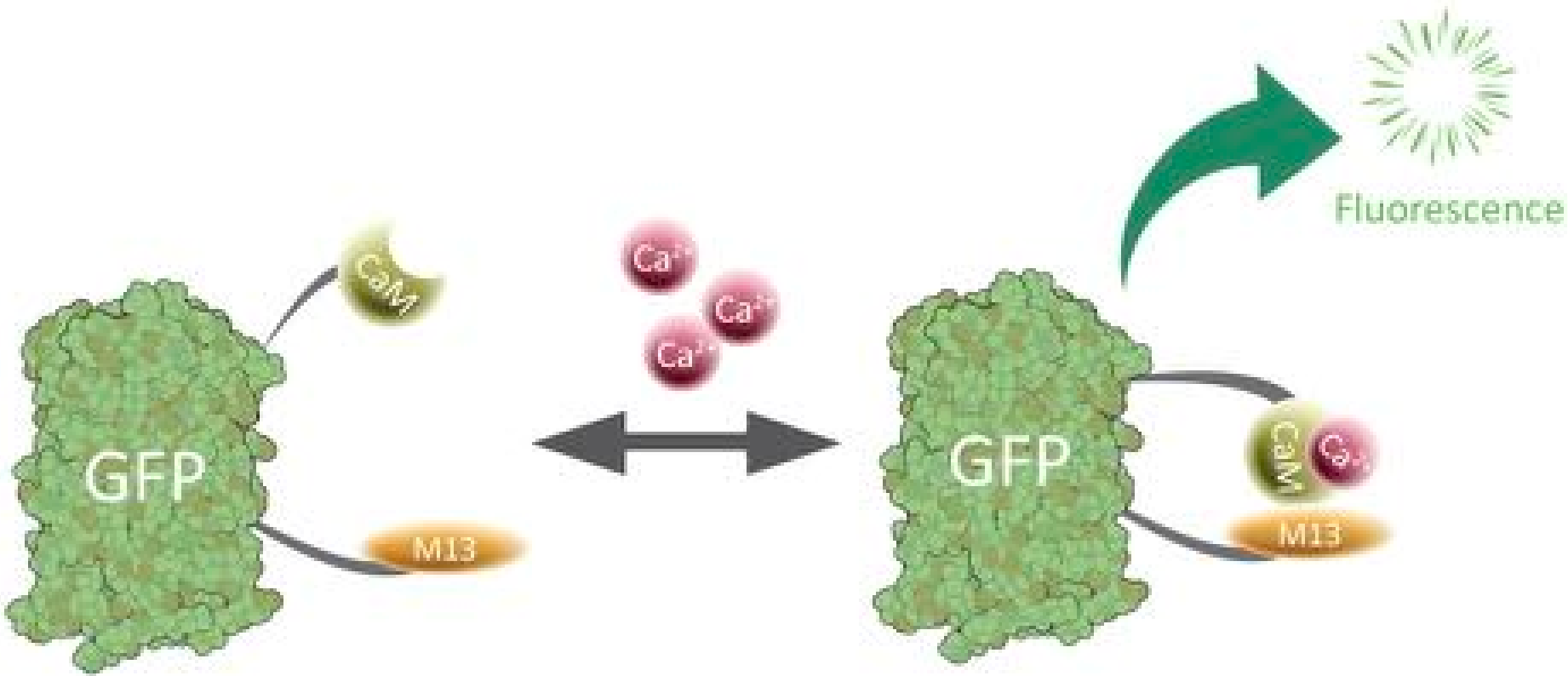
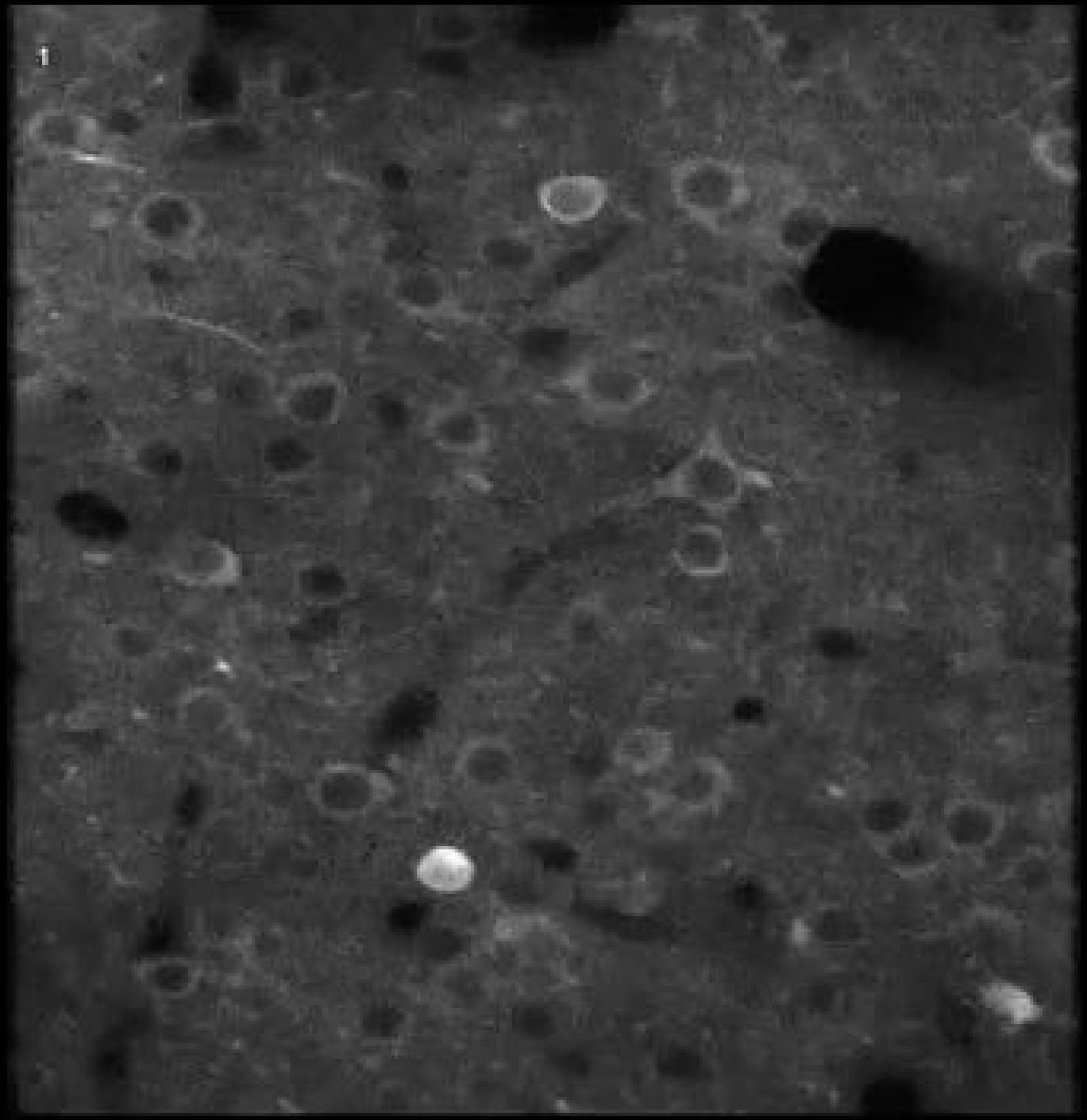
Neural Structure

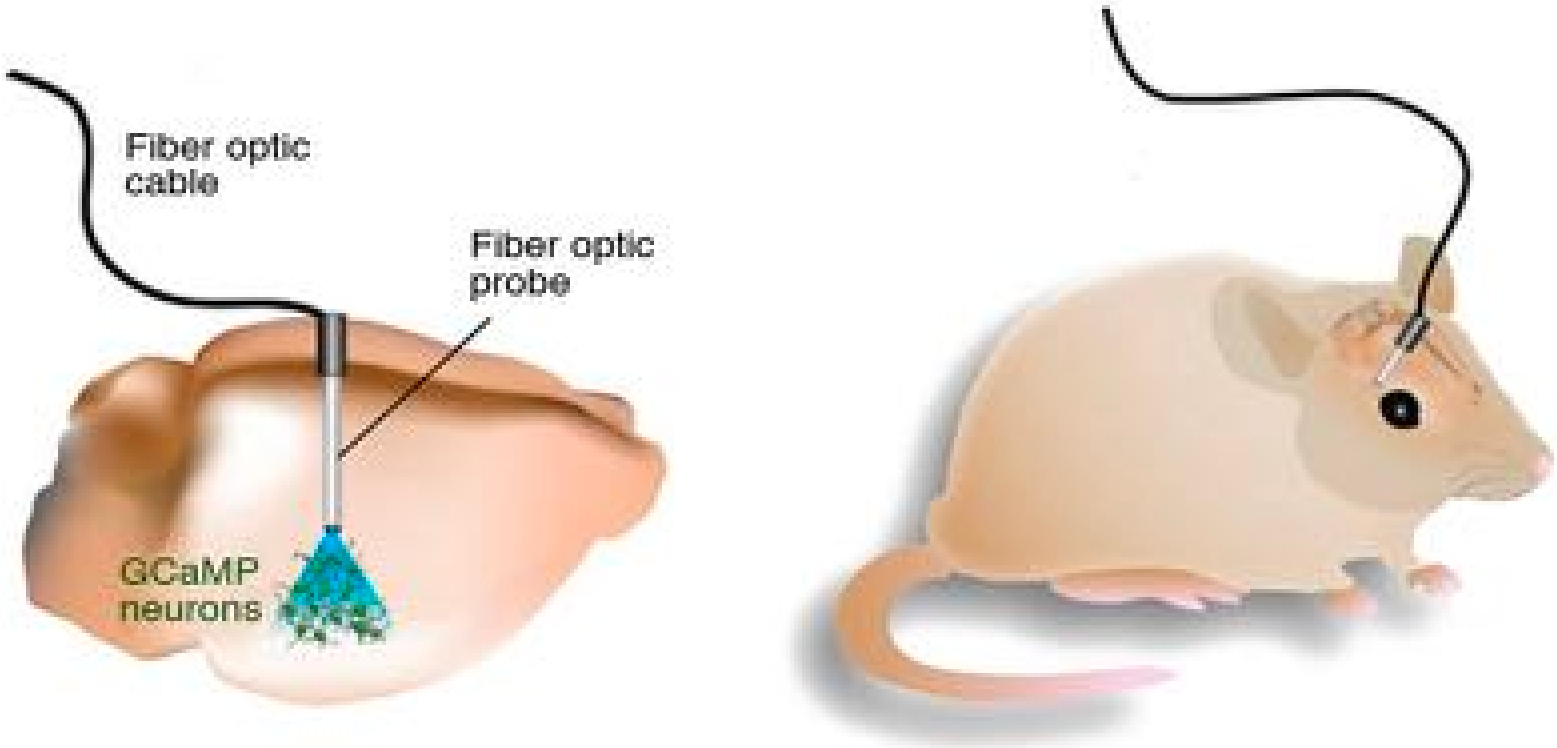
Neural Activity

Neuromodulation




Fluorescence
GFP
CaM
M13
GFP
CaM
M13

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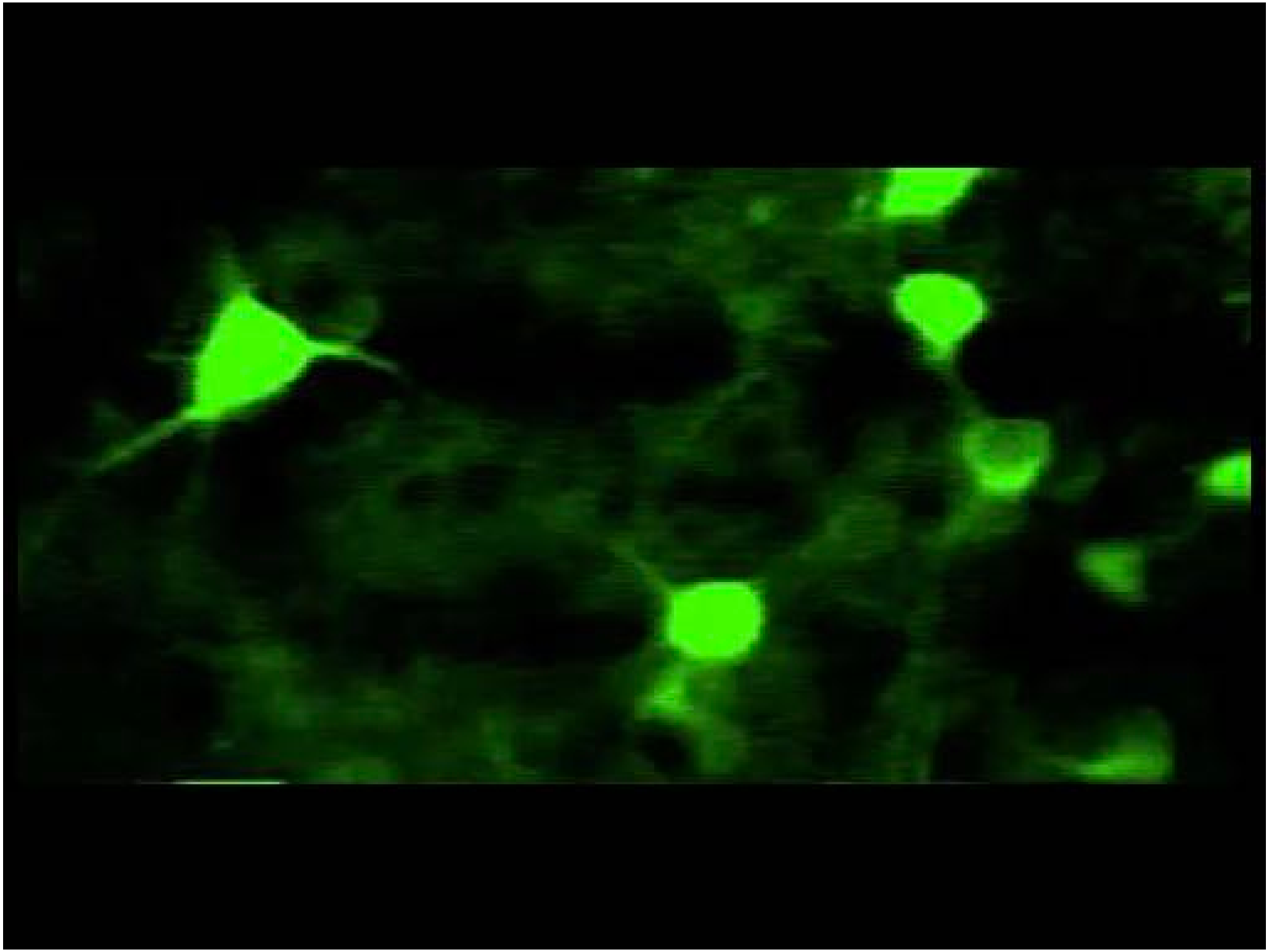
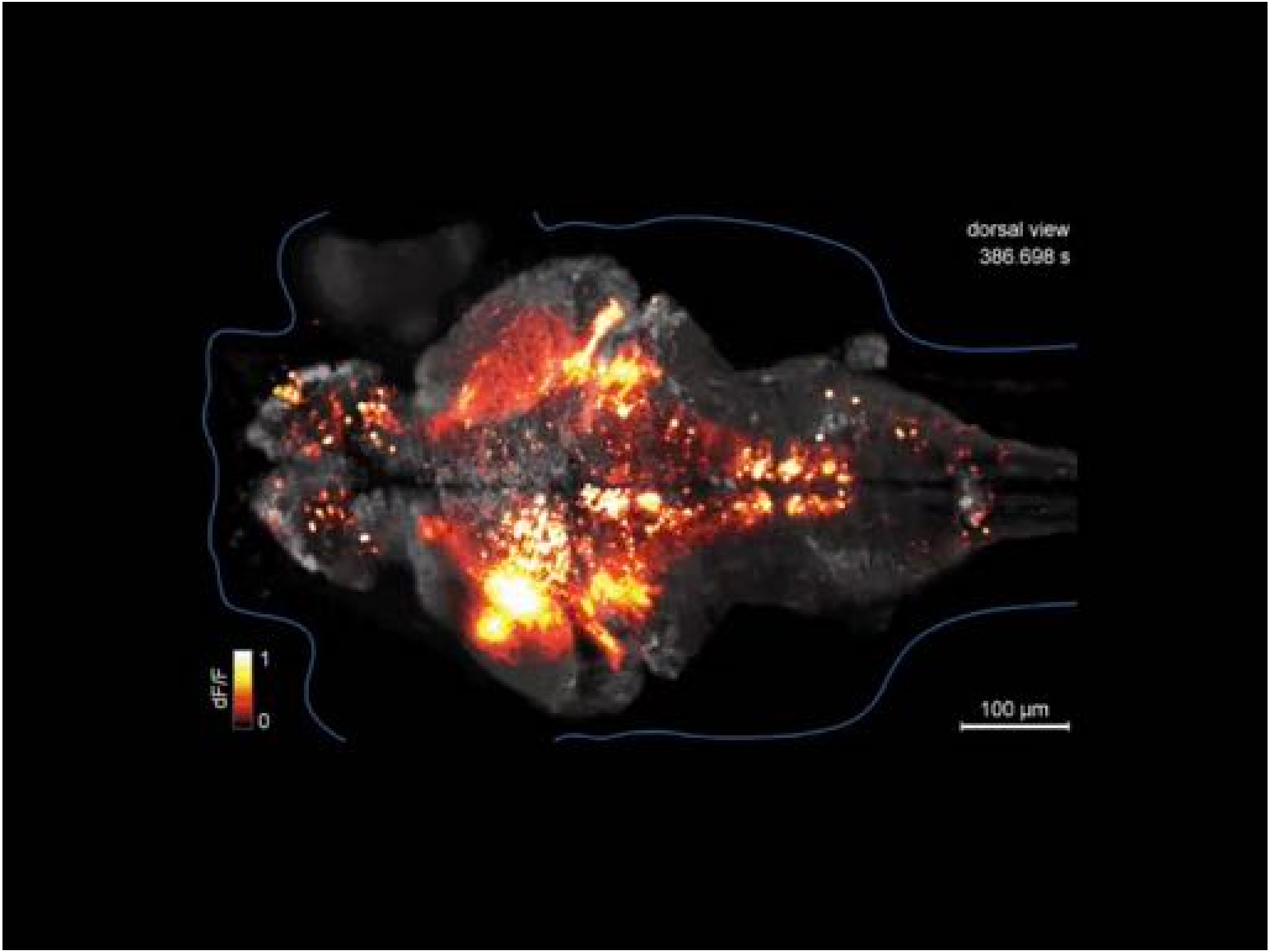
probe
GCaMP
neurons

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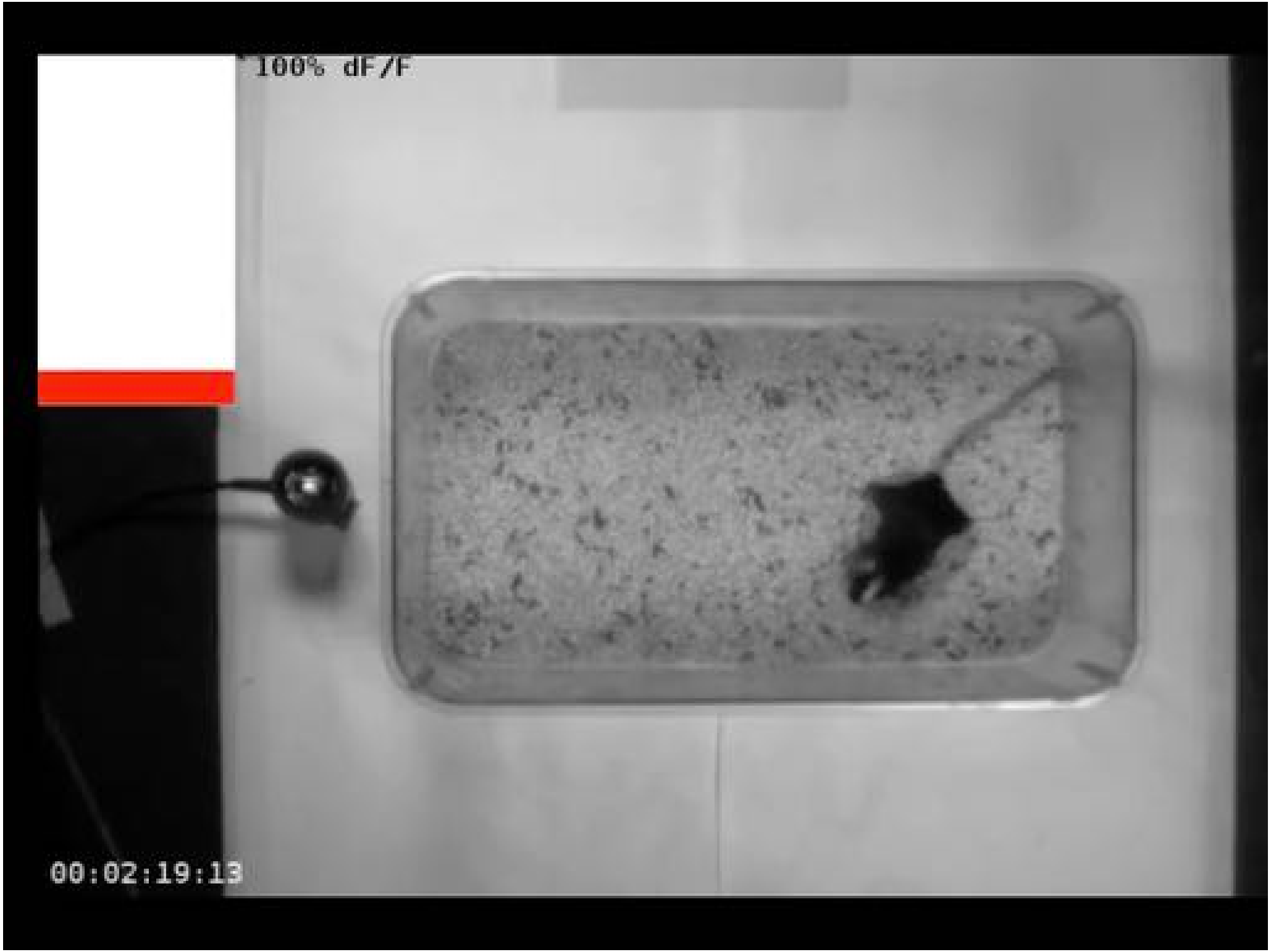
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eLife

RESEARCH ARTICLE

A discrete parasubthalamic nucleus subpopulation plays a critical role in appetite suppression

Jessica H Kim[1†], Grace H Kromm[1†], Olivia K Barnhill[1†], Jacob Sperber[1], Lauren B Heuer[1], Sierra Loomis[1], Matthew C Newman[1], Kenneth Han[1], Faris F Gulamali[1], Theresa B Logan[1], Katherine E Jansen[1], Samuel C Funderburk[2], Michael J Krashes[3], Matthew E Carter[1]*

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[†]These authors contributed equally to this work

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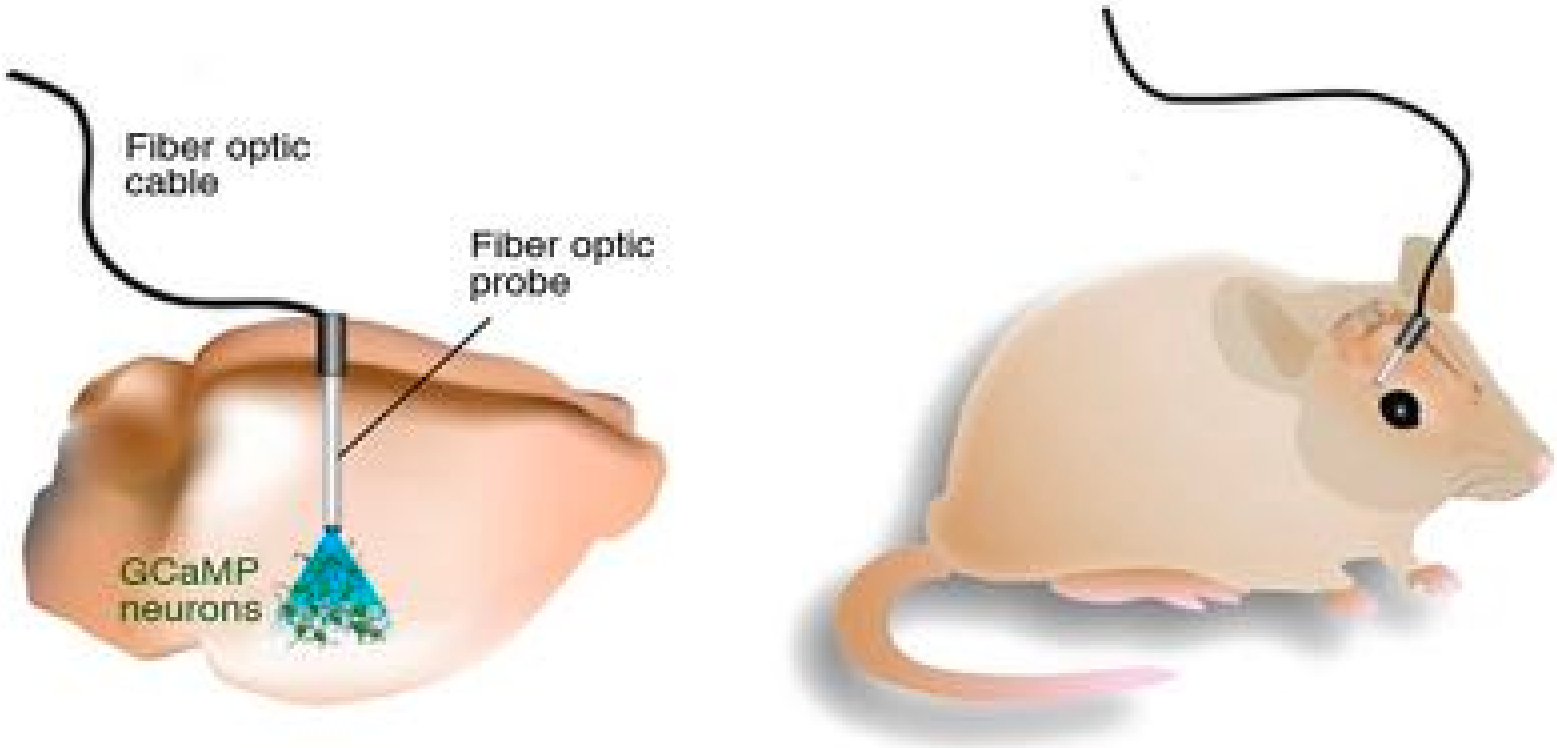
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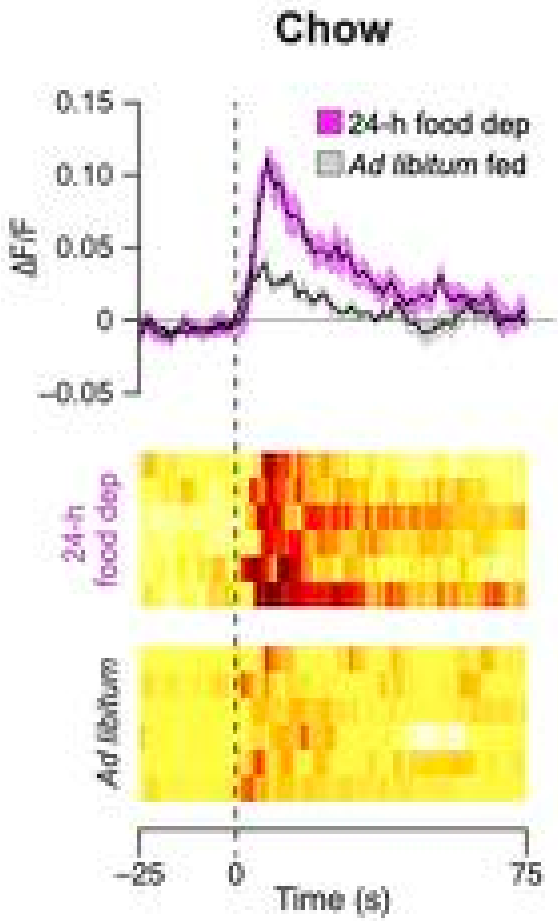
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0.15
0.10
0.05
0
−0.05
ΔF/F
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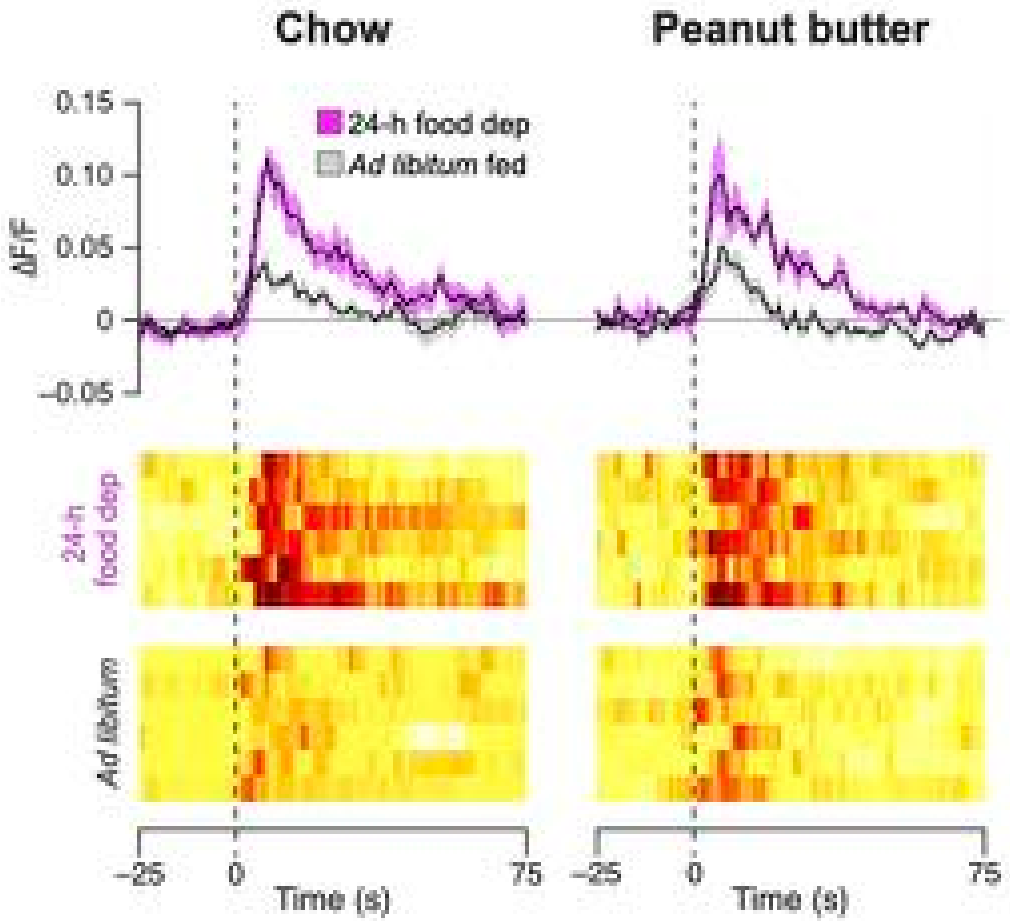
Ad libitum fed
24-h food dep
Ad libitum
−25
0
75
Time (s)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Peanut butter
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Ad libitum fed
ΔF/F
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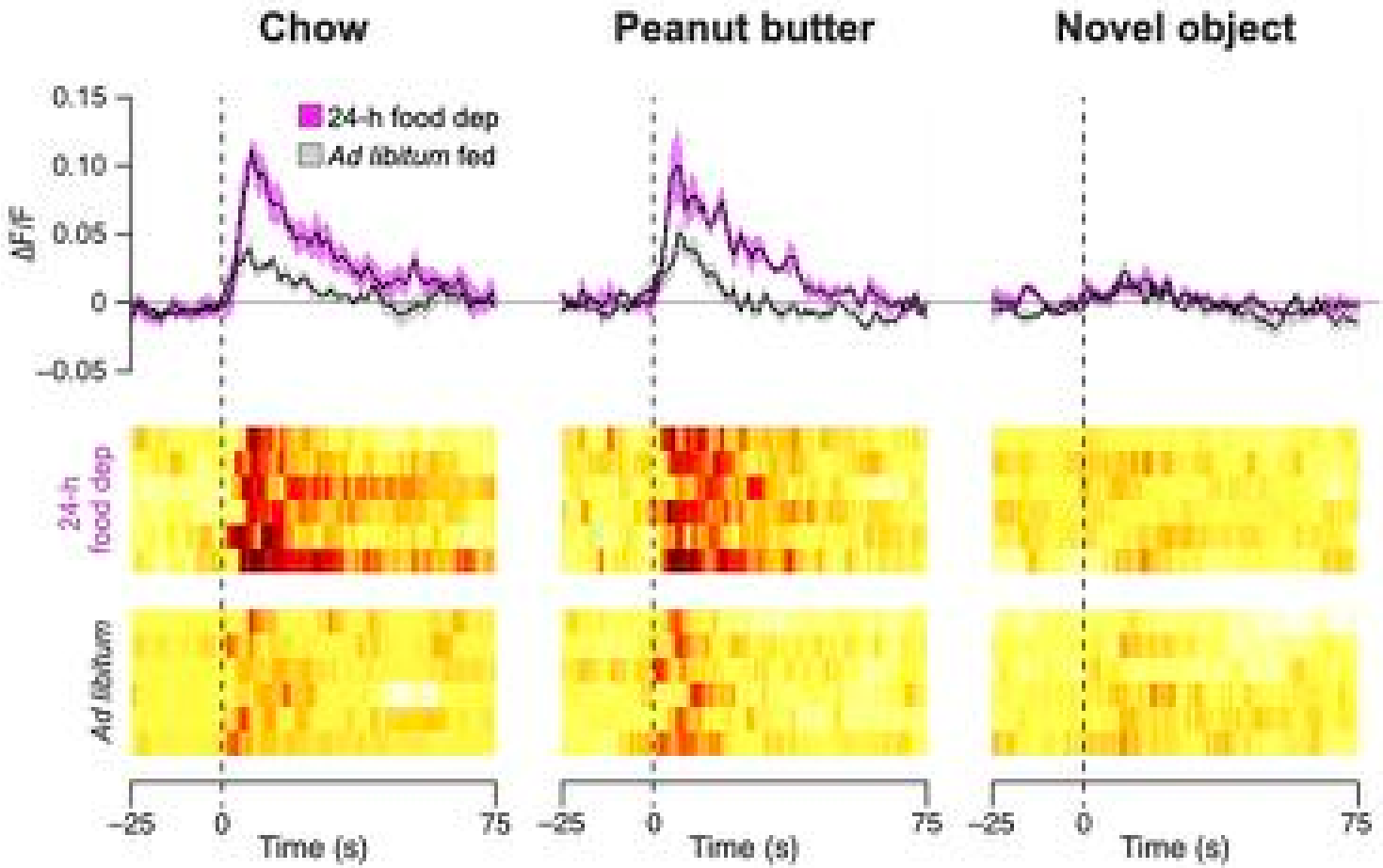
0.10
0.05
0
−0.05
24-h food dep
Ad libitum
−25
0
75
Time (s)
−25
0
75
Time (s)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Peanut butter
Novel object
24-h food dep
Ad libitum fed
ΔF/F
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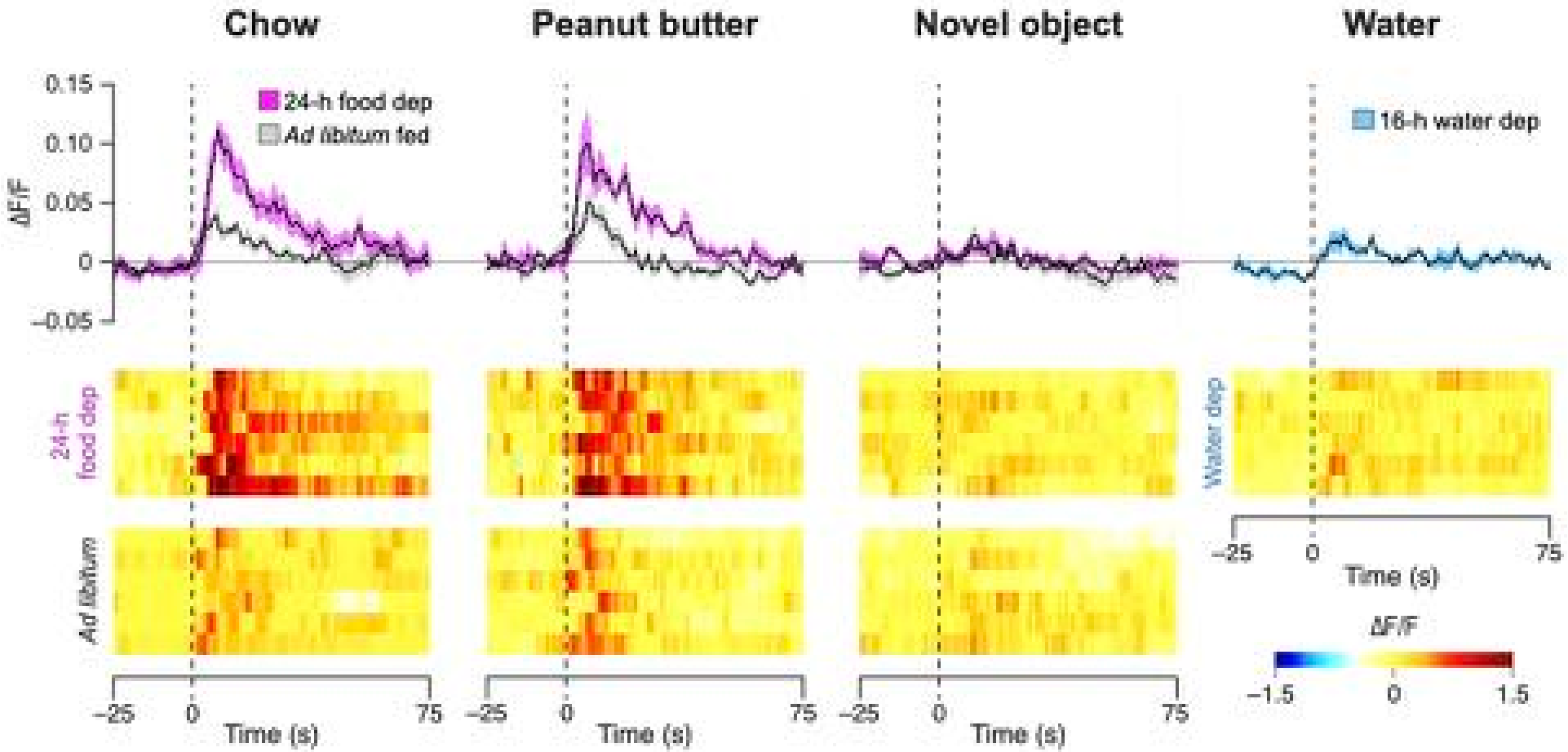
0.10
0.05
0
−0.05
24-h food dep
Ad libitum
−25
0
75
Time (s)


Chow
Peanut butter
Novel object
Water
24-h food dep
Ad libitum fed
16-h water dep
ΔF/F
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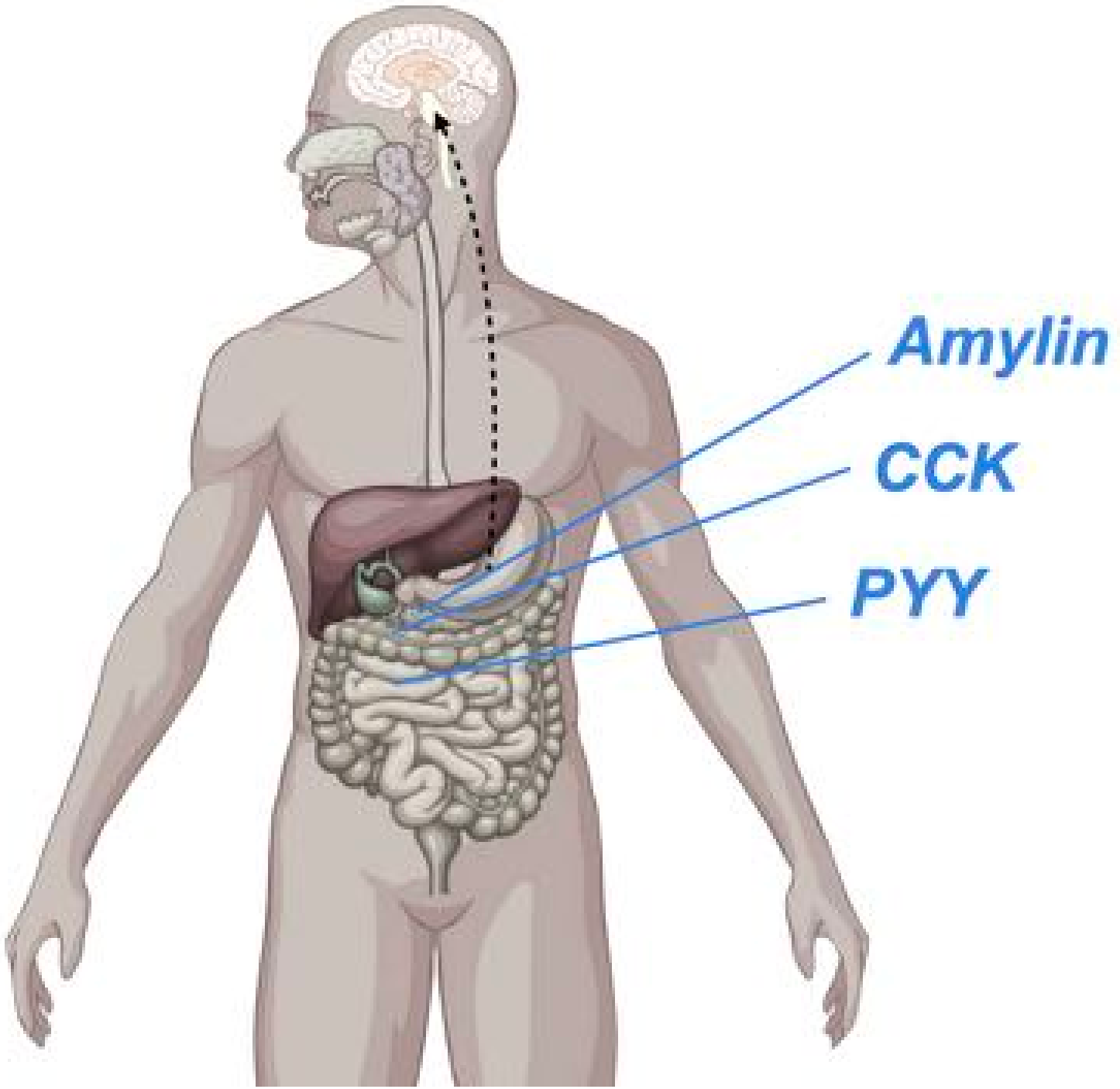
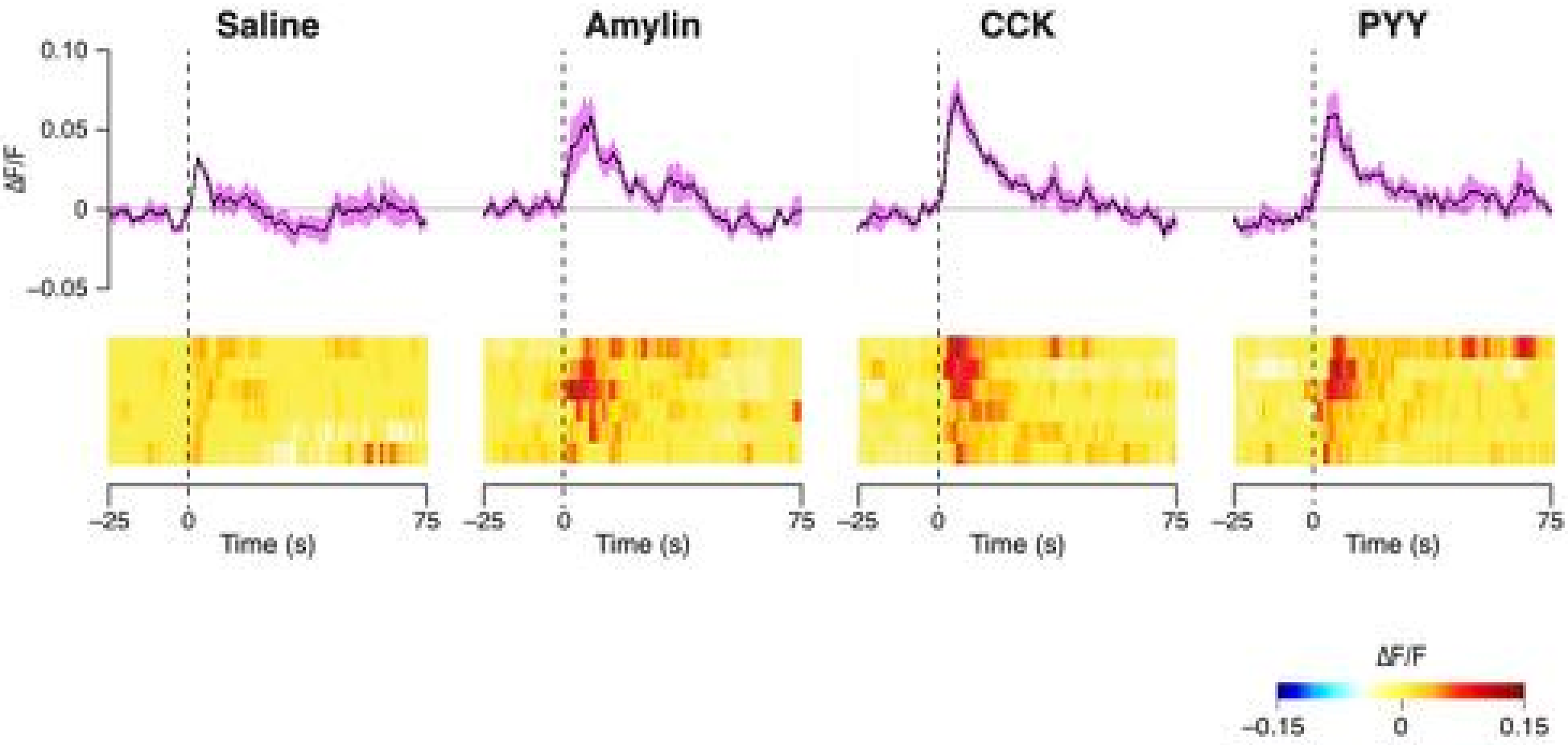
0.10
0.05
0
−0.05
24-h food dep
Ad libitum
Water dep
−25
0
75
Time (s)
ΔF/F
−1.5
0
1.5


Amylin
CCK
PYY


Saline
Amylin
CCK
PYY
0.10
0.05
0
−0.05
ΔF/F
−25
0
75
Time (s)
ΔF/F
−0.15
0
0.15

Adding a bit of color and light to the brain

Neural Structure

Neural Activity

Neuromodulation

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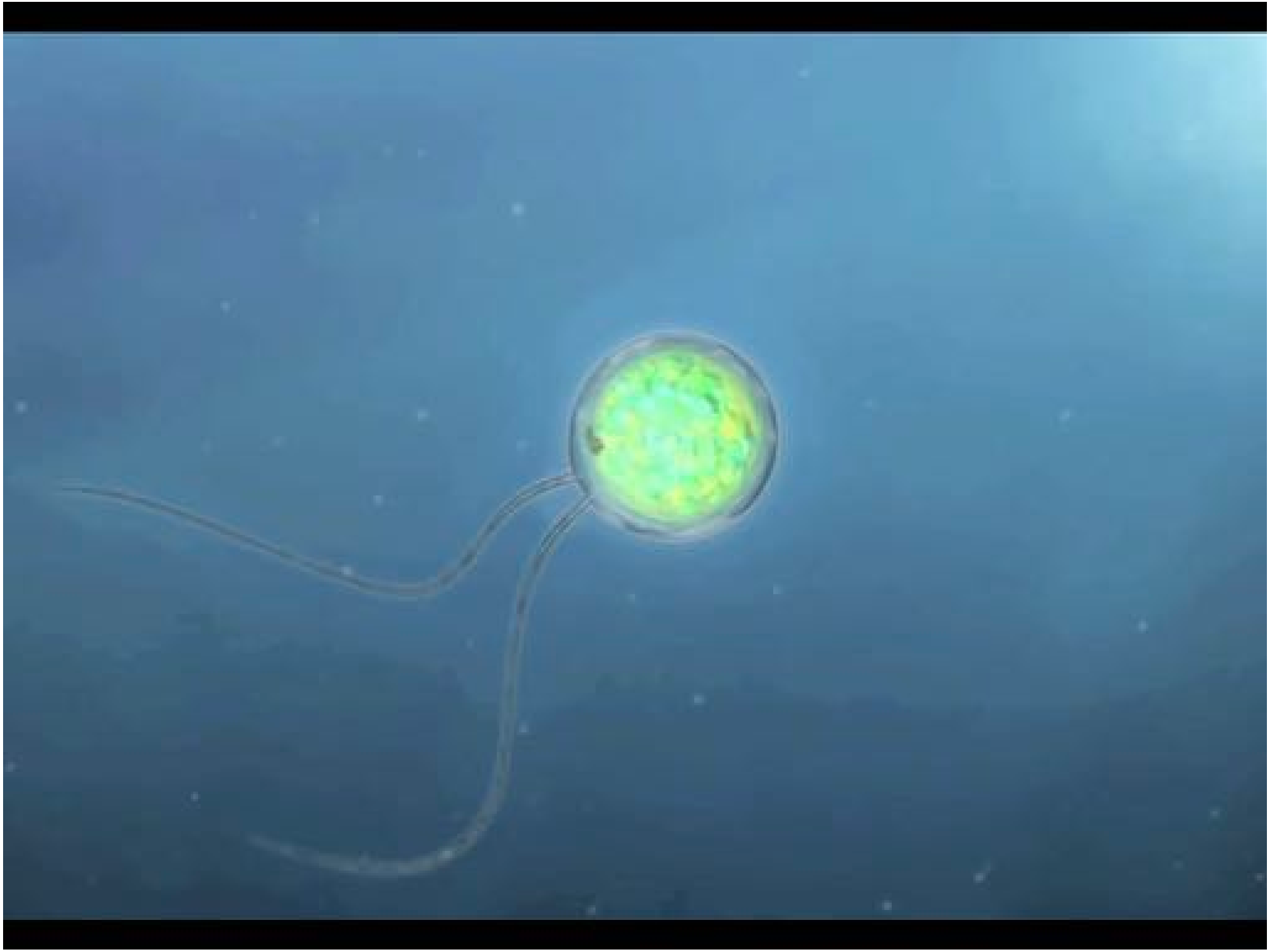

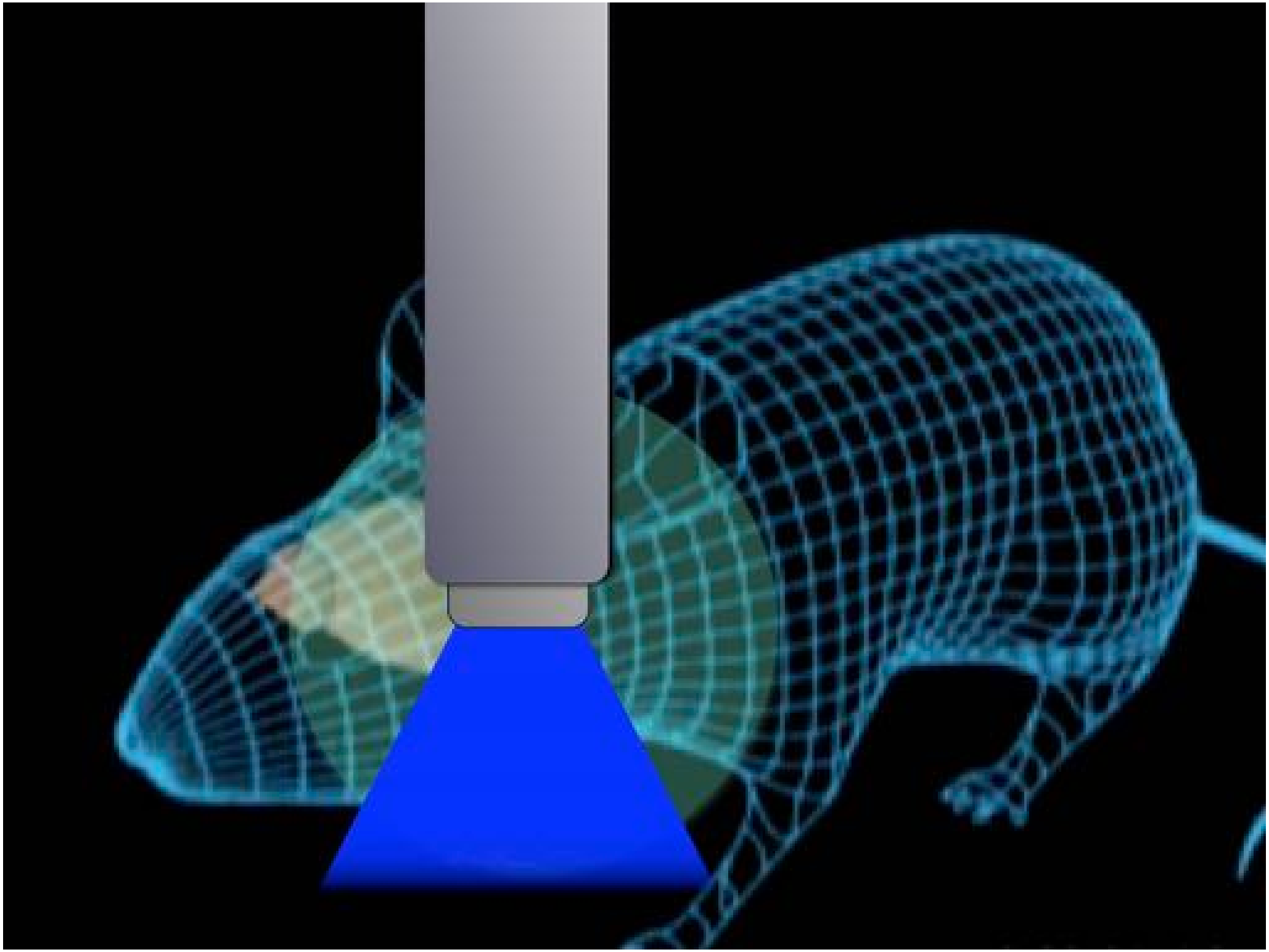

Fiberoptic Control of Locomotion in ChR2 Mouse

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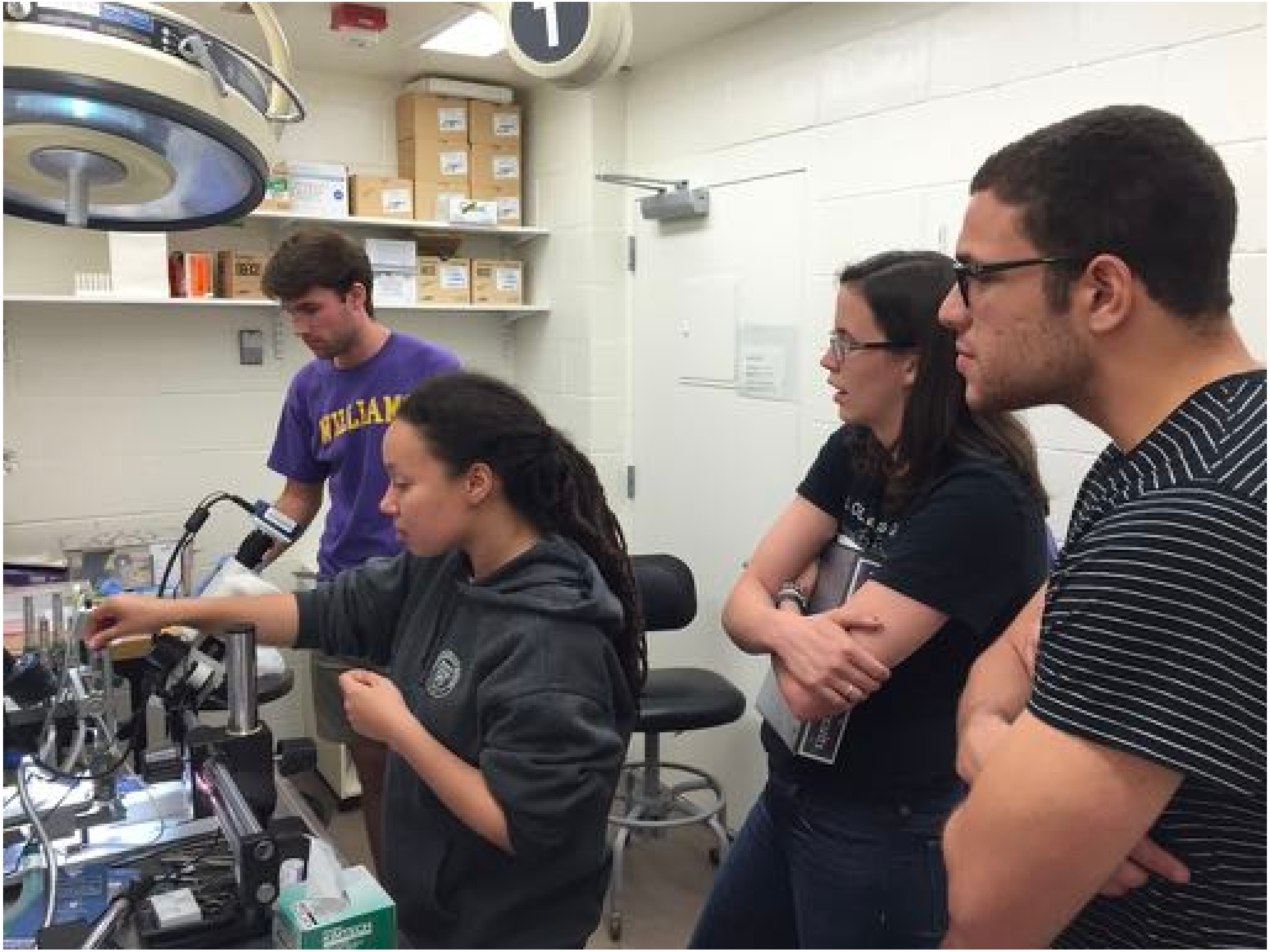
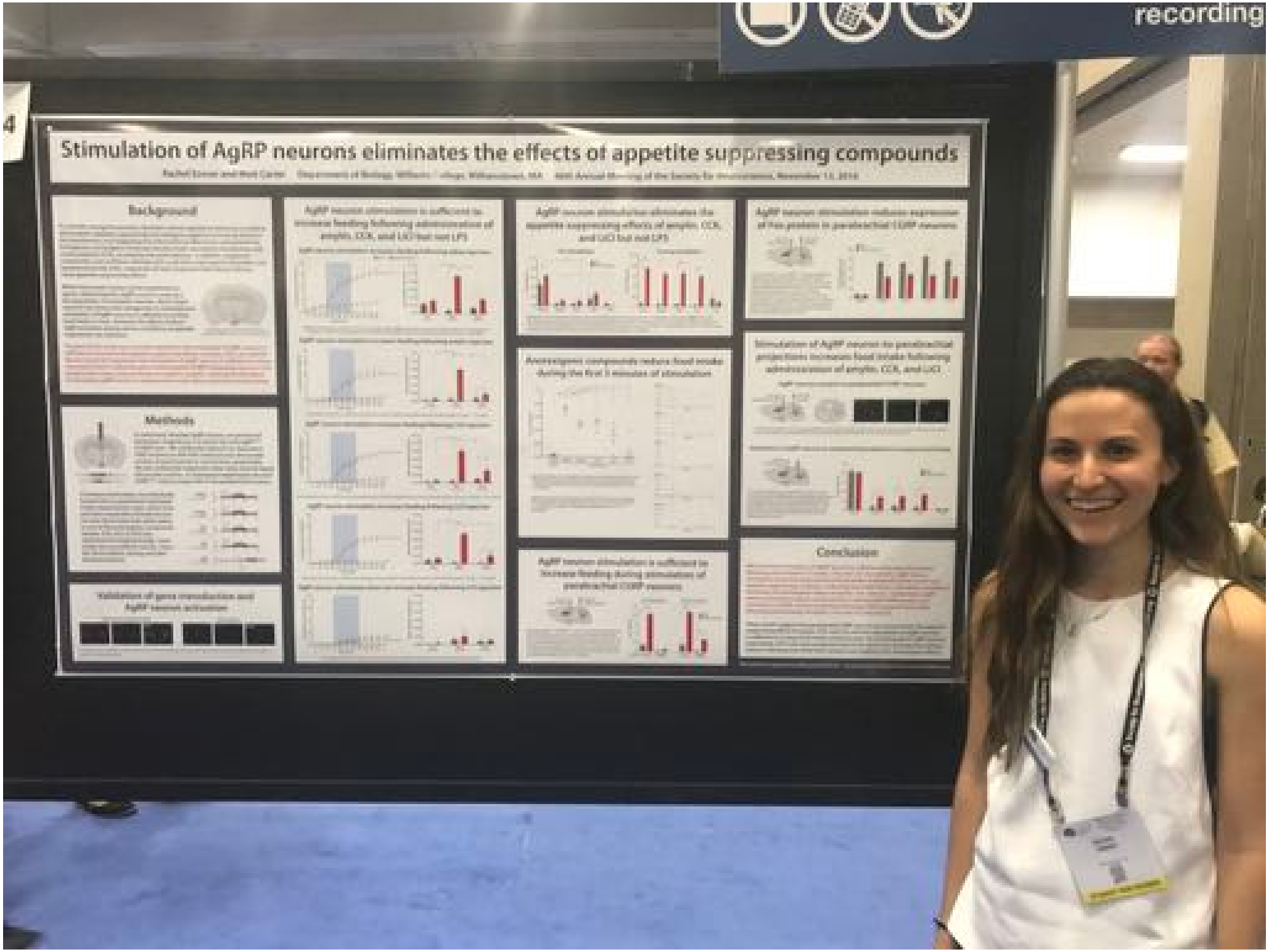
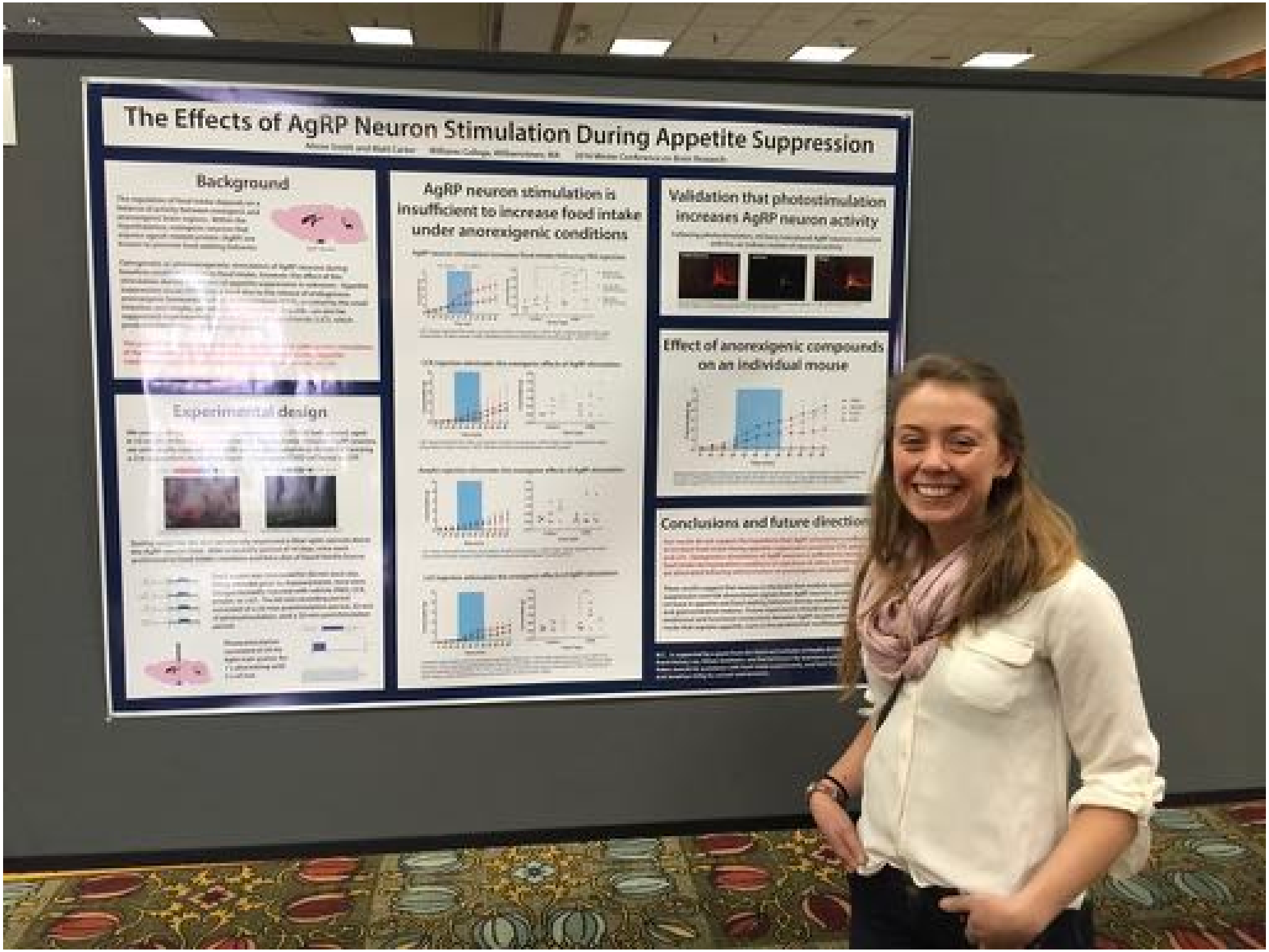
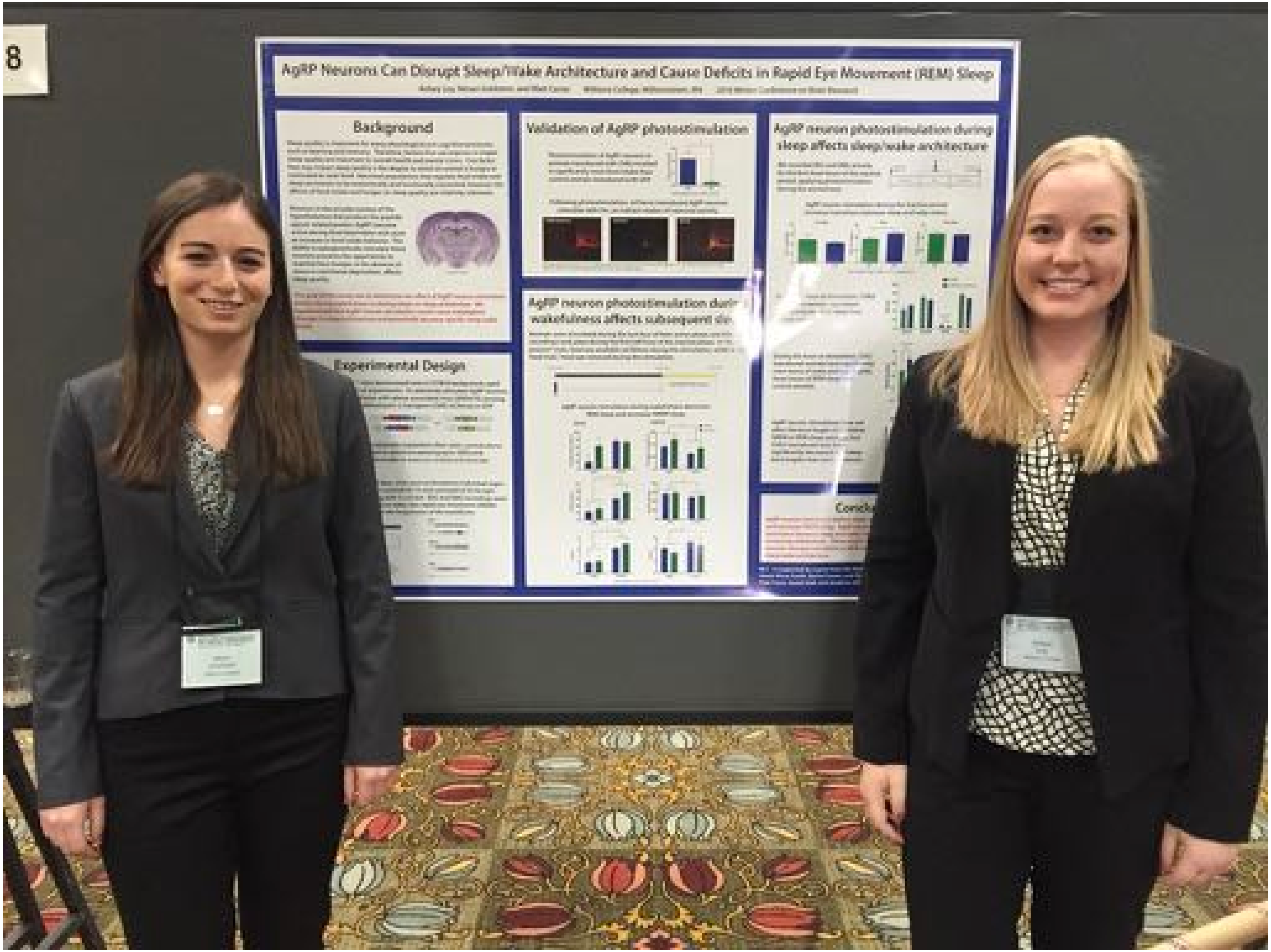
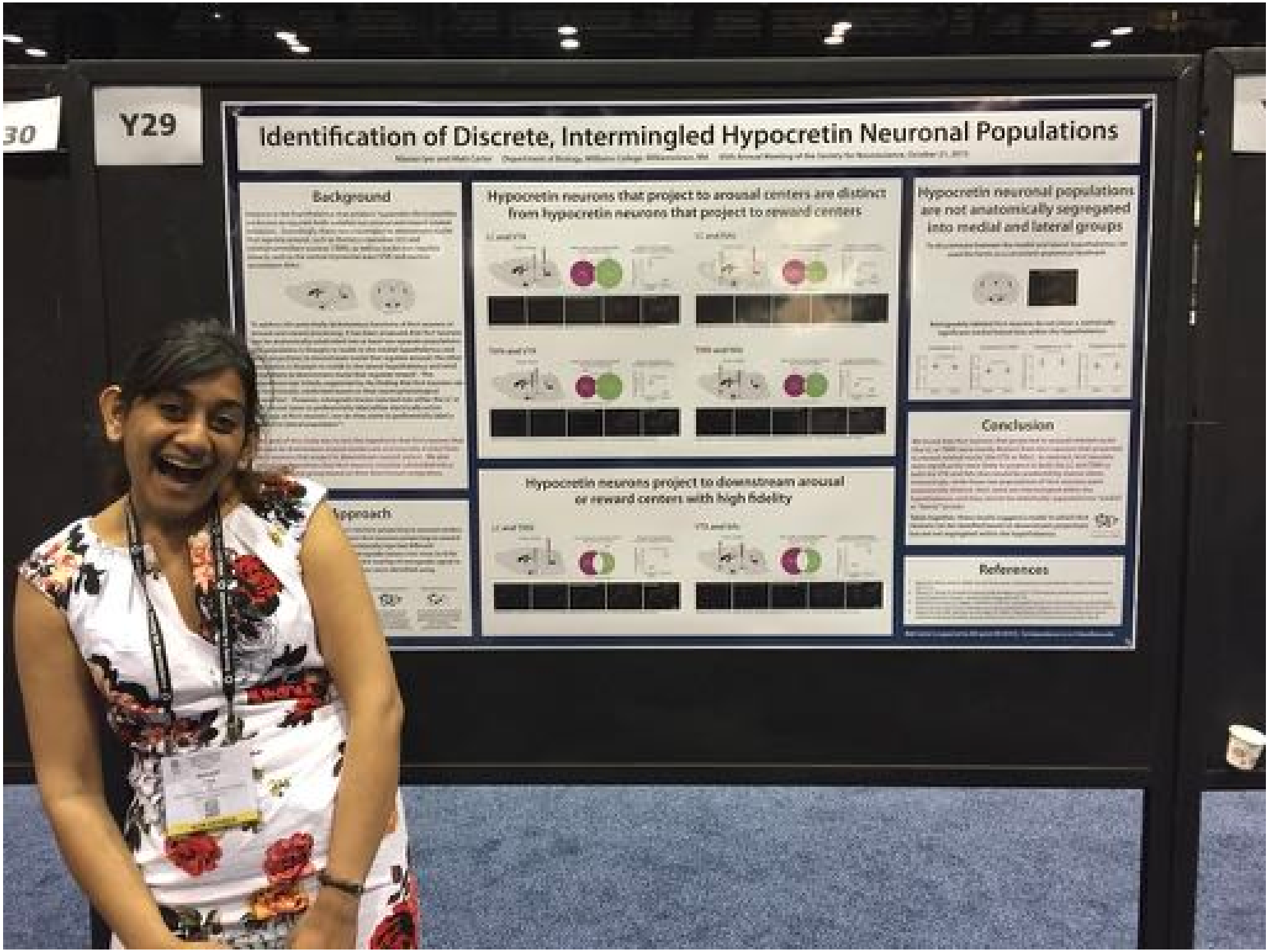
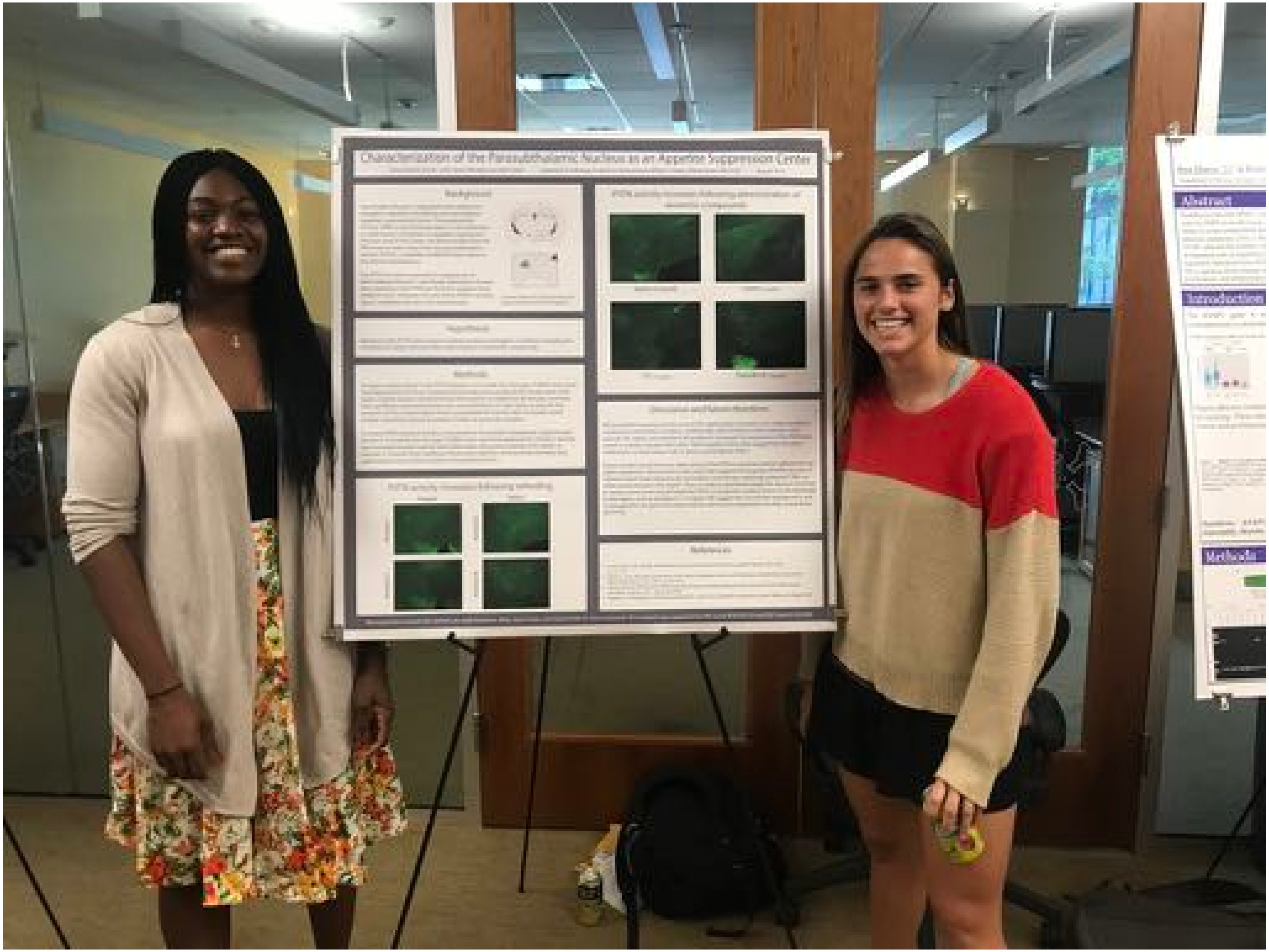



recording
Stimulation of AgRP neurons eliminates the effects of appetite suppressing compounds
Background
Methods
Conclusion


The Effects of AgRP Neuron Stimulation During Appetite Suppression
Background
Experimental design
AgRP neuron stimulation is insufficient to increase food intake under anorexigenic conditions
Validation that photostimulation increases AgRP neuron activity
Effect of anorexigenic compounds on an individual mouse
Conclusions and future direction


AgRP Neurons Can Disrupt Sleep/Wake Architecture and Cause Deficits in Rapid Eye Movement (REM) Sleep
Background
Validation of AgRP photostimulation
AgRP neuron photostimulation during sleep affects sleep/wake architecture
Experimental Design


Y29
Identification of Discrete, Intermingled Hypocretin Neuronal Populations
Background
Hypocretin neurons that project to arousal centers are distinct from hypocretin neurons that project to reward centers
Hypocretin neuronal populations are not anatomically segregated into medial and lateral groups
Hypocretin neurons project to downstream arousal or reward centers with high fidelity
Conclusion
References


Characterization of the Parasubthalamic Nucleus as an Appetite Suppression Center
Background
Introduction
Abstract
Methods

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Matt Carter
Department of Biology
Williams College

August 8, 2022