mouse

Sick as a ~~dog~~: intermittent exposure to pathogens impacts brain and behavior

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Tulane

Disclosures & Acknowledgments

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India Pursell, BS
Kail Citron, BS
Laura Wegrowski
Natasha Barahona, BS
Raul Freitas, PhD
Sam Rawlins
Sharhana Shrestha
Yubin Lee

My Village

Don – Understanding spouse
Isabella – World's best cheerleader
Dialys – Domestic warrior

Mentoring Team

Dr. Greg Bix
Dr. Jim Simpkins
Dr. Ann Stowe
Dr. Courtney DeVries
Dr. David Rothstein
Dr. Eric Nestler
Dr. Jeff Tasker
Dr. Joan Lakoski
Dr. John Barnett
Dr. Scott Russo

Shared Research Instrumentation Resources

Kathy Brundage, PhD & WVU Flow Cytometry Core
Pete Mathers, PhD & WVU Transgenic Animal Core
Liz Engler-Chiurazzi & WVU Rodent Behavior Core
Connie Poretta, BS Tulane Immunology Flow Cytometry Core
Alan Tucker, BS, Tulane Center for Gene Therapy Flow Cytometry Core

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EEC (K01 MH117343; U54 GM104942; WVU Research Office), JWS (start-up funds, P01 AG0225500; P01 AG0227956; P20 GM10998), EEC/JWS (Brain Health Project; WVU College of Medicine Funds, Nestle Purina), EEC Tulane University Start-up funds, Tulane Brain Institute Research Award, Infectious Disease Society of America

WVU Department of Neuroscience, AAAS IF/THEN Mini Grant, Dana Foundation, Tulane Brain Institute

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I consult (no pay) for Amritagen. I have received past support for industry-sponsored projects from Nestle-Purina and Brain Health Project

And …. Mom (Susan Engler)

Hawaii Volcano Eruption 2018
And Wildfires, 2023

Hurricane Isaac, Louisiana 2012

Tennessee Floods, 2010

Puerto Rico Earthquake, 2020

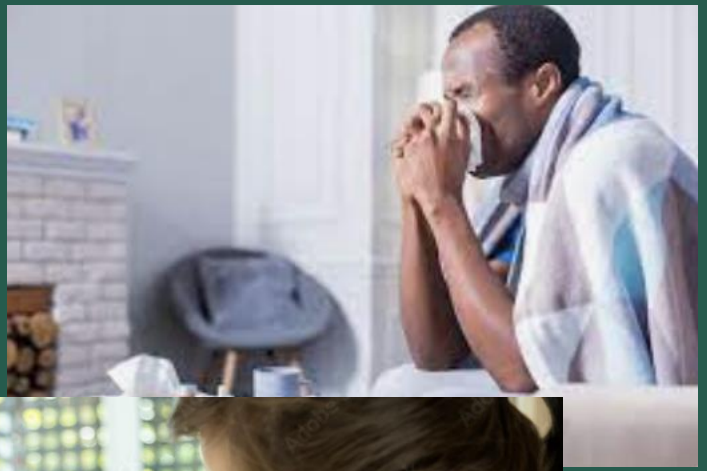
Hurricane Harvey, Texas 2017

California Wildfires, 2020

Intermittent Infection Impacts on Brain

Premise:

- Aging is associated with shifts in neurobiology, cognitive ability and immune function (Bulati et al., 2017; Burke and Barnes, 2006; Franceschi and Campisi, 2014; Riley, 2013)
- Experience with infection is common but not shared equitably across the population (Balls-berry et al., 2022; Feinstein et al., 2016; Deitrich et al., 2021)
- Acute infection affects cognition in humans (i.e., delirium) and laboratory rodents; age potentiates these effects (Chen et al., 2008; Tarr et al., 2011; Van Gool et al., 2010)
- Long-term cognitive consequences of acute infections are not well studied
  - increased infection burden exacerbates age-related cognitive decline, especially in 'dementia'-susceptible organisms (De Chiara et al., 2019; Katan et al., 2013; Strandberg et al., 2004; Sy et al., 2011)

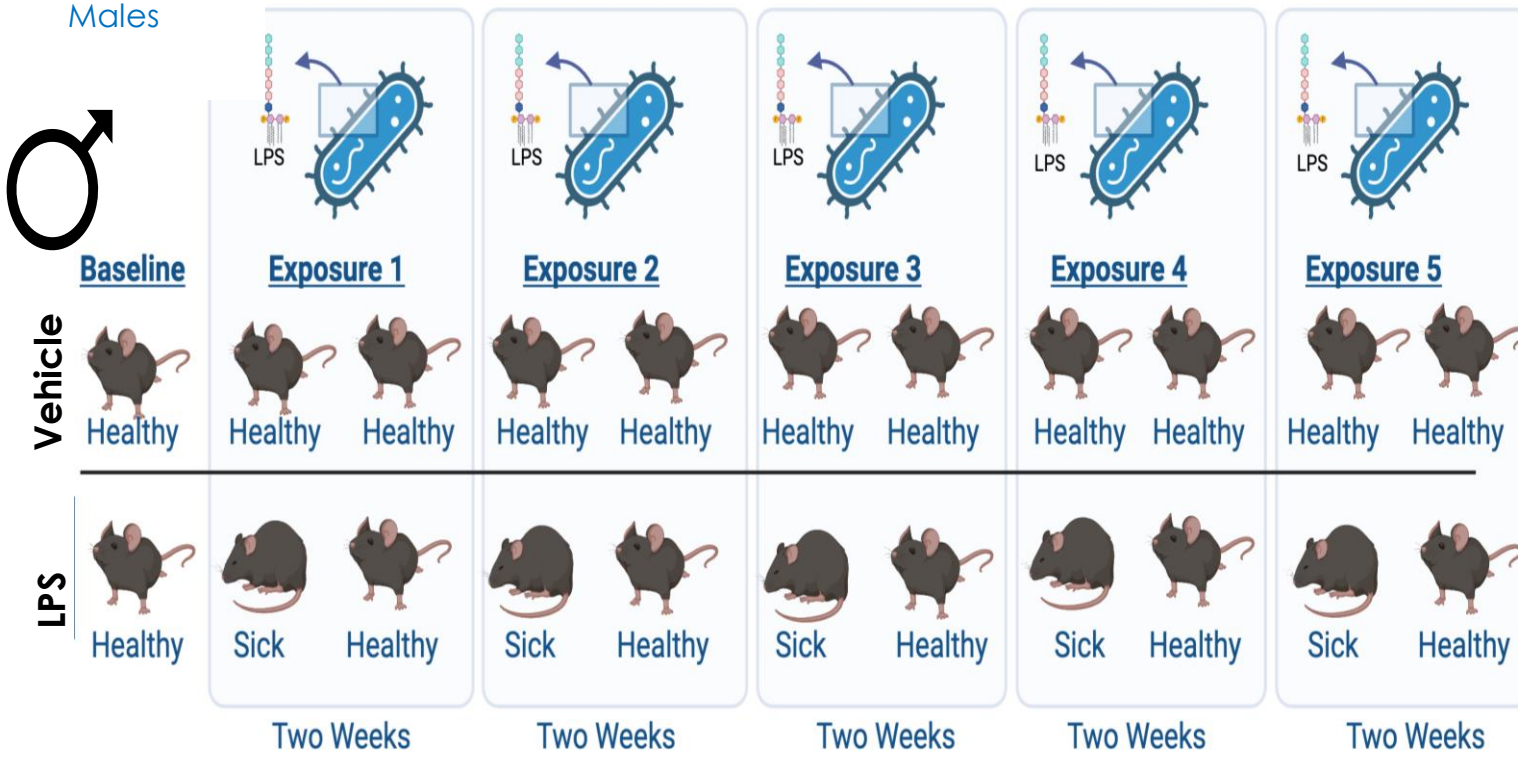


Question:

Does intermittent experience with inflammatory immune activation alter the trajectory of cognitive aging?

Intermittent Infection Impacts on Brain *During Aging*

Healthy Adult Males



10 Months Old

Repeated intermittent LPS 'infection' reliably induces sickness behavior

Health/Sickness Screen

Parameter	Observation	Score
General Appearance	Normal Groomed, healthy appearing fur, pink mucous membranes and ear lobes	0
	Mild Abnormal Mildly rough/scruffy/dull fur, slightly less well-groomed, light pink mucous membranes/ear lobes, minimal porforin staining, slightly squinted eyes	1
	Moderate Abnormal Rough/scruffy fur, piloerection, poor grooming, pale mucous membranes and ear lobes, squinted eyes	2
	Severe Abnormal Very rough fur, no evidence of grooming, white mucous membranes and ear lobes, substantial porforin staining, severely squinted or closed eyes	3
Posture	Normal	0
	Slight Hunch Spine slightly curved	1
	Moderate Hunch Spine curved, paws slightly under body	2
	Severe Hunch Spine dramatically curved, paws tucked under body, head angled downward	3
Body Condition	Normal	0
	Thin Slight segmentation of vertebrae, dorsal pelvic bones are more prominent, slight dehydration (skin pinch test response is slightly delayed)	1
	Emaciated Prominent vertebrae and skeletal bones that are readily palpable, dehydrated (skin pinch test results in skin remaining tented)	2
Respiration	Normal	0
	Altered Increased rate and/or effort	1
	Abnormal/Distressed Very increased rate or gasping/labored breathing, irregular	2
Body Temperature	Normal/No change	0
	1-4 degree C	1
	5-8 degree C	2
	9-12 degree C	3
Body Weight	0-5% change	0
	5.1-10% change	1
	10.1-15% change	2
	15.1-20% change	3
	> 20.1% change	4
Spontaneous Locomotion/Social Interaction	Normal Active and interacting with cage-mate(s)	0
	Mild Abnormal Still spontaneous activity and some peer interaction but reduced	1
	Moderate Abnormal Lethargic (may need probing via tapping on cage or cage tilt) and minimal peer interaction	2
	Severe Abnormal Immobile and no peer interaction	3

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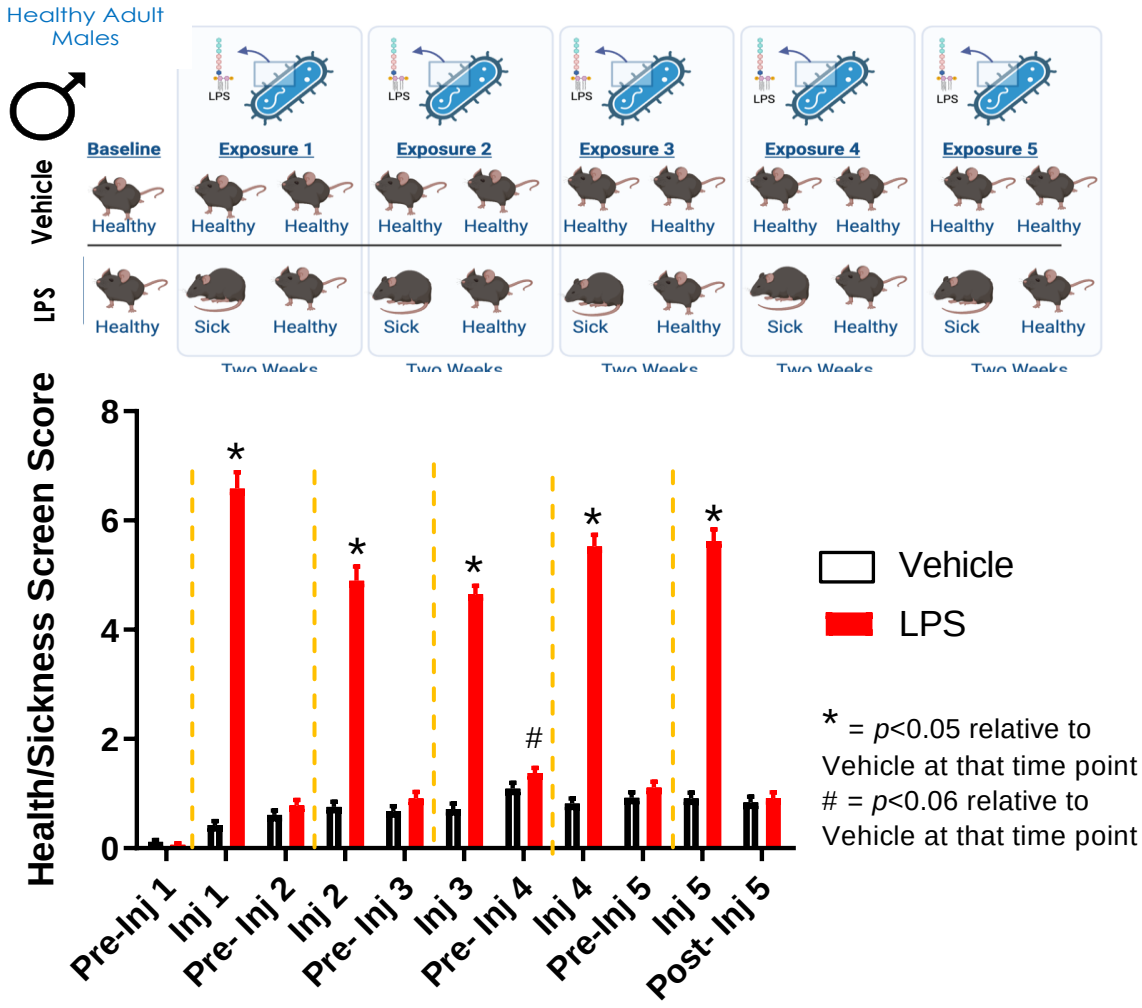
Brain Behavior & Immunity

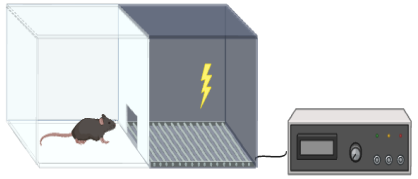


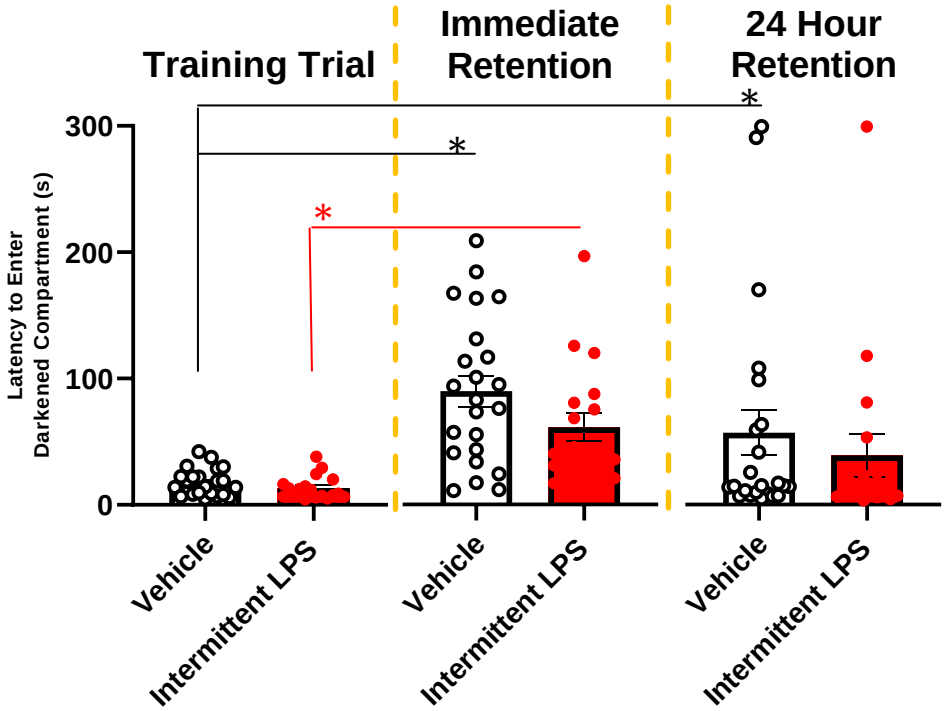
- LPS reliably induced a moderate sickness
- Animals made a full recovery from each exposure*

Intermittent ‘Infections’ Subtly Impair Retention of Learned Information

Passive Avoidance

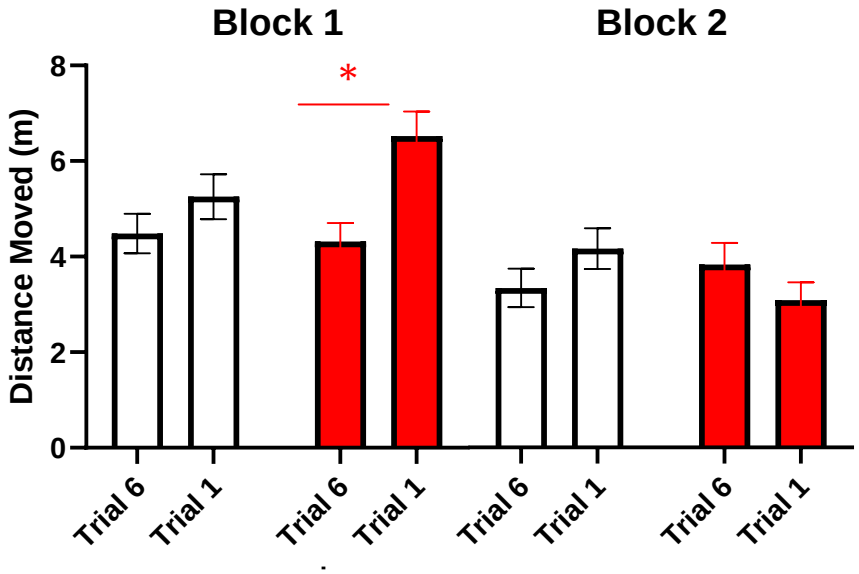
Learning and Retention





Morris Water Maze

(Spatial/hippocampal-dependent) Learning and Retention)



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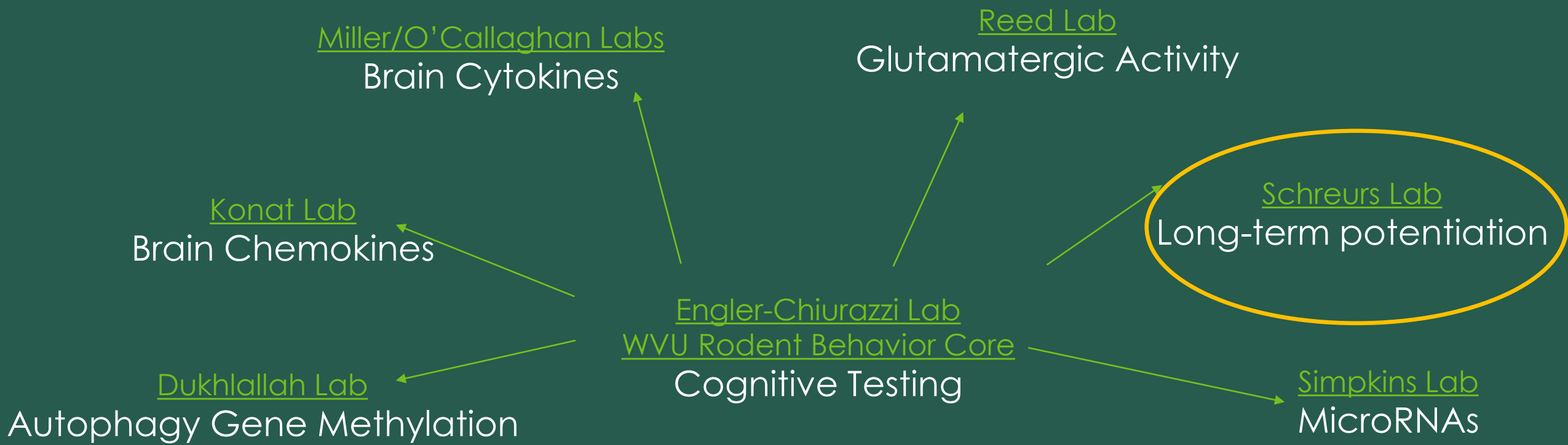
- No differences in learning new information*
- LPS impaired overnight retention between days during the early training period

Intermittent Infections Alter Neuronal Function



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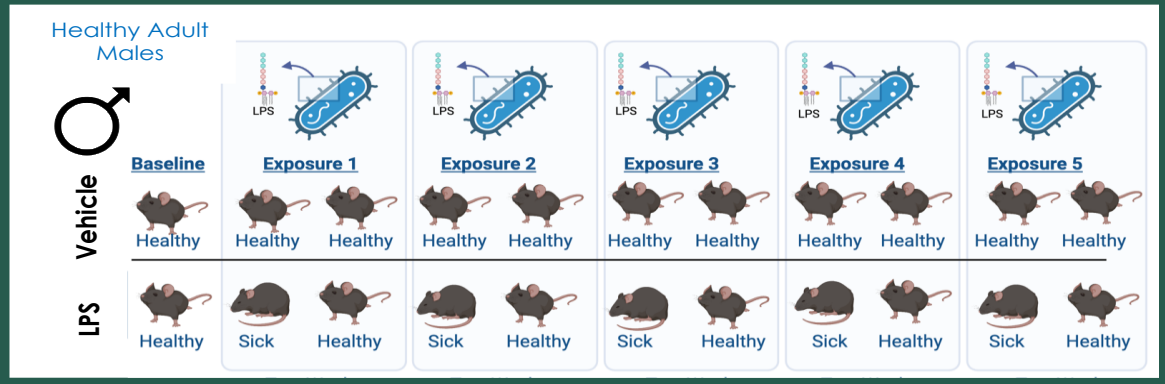
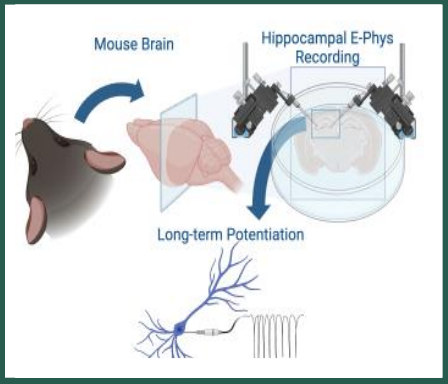
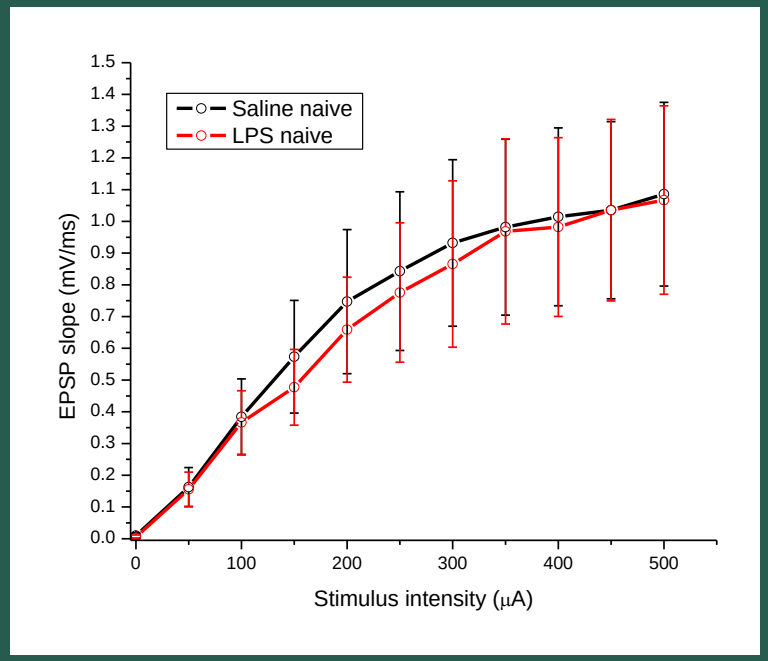
Supported by the West Virginia Clinical and Translational Sciences Institute

Intermittent Infections Alter Neuronal Function

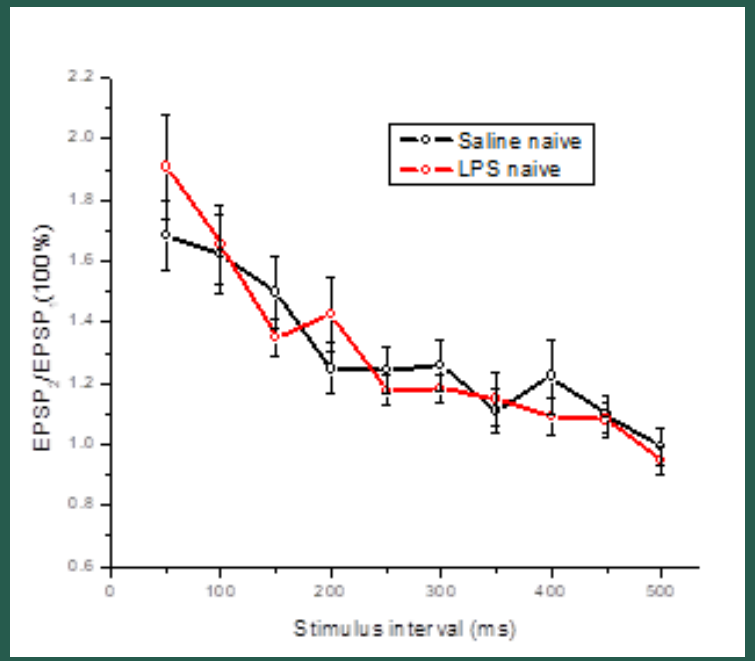




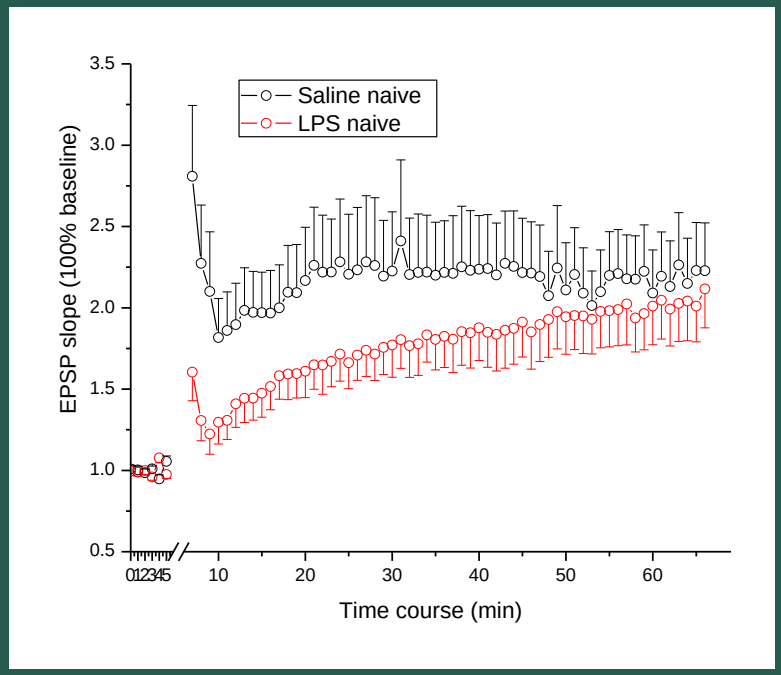
Basal Synaptic Transmission



Pre-synaptic Function



Long-term Potentiation



Single or Intermittent Mild Infection Worsens Stroke

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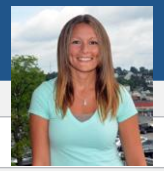

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Behav Brain Funct. 2015 Oct 13;11(1):32. doi: 10.1186/s12993-015-0077-5.

Lipopolysaccharide exacerbates infarct size and results in worsened post-stroke behavioral outcomes

Danielle N Doll [1], Elizabeth B Engler-Chiurazzi [2], Sara E Lewis [3], Heng Hu [4], Ashley E Kerr [5], Xuefang Ren [6], James W Simpkins [7]

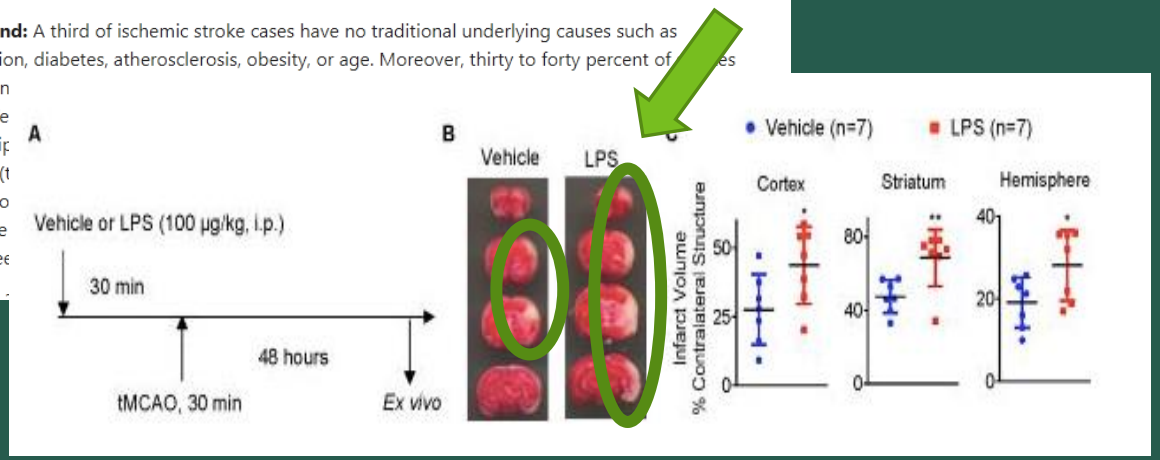
Affiliations + expand

PMID: 26463864 PMCID: PMC4604642 DOI: 10.1186/s12993-015-0077-5

Free PMC article

Abstract

Background: A third of ischemic stroke cases have no traditional underlying causes such as hypertension, diabetes, atherosclerosis, obesity, or age. Moreover, thirty to forty percent of [illegible] occur durin season. We µg/kg of lip occlusion (t epidemiolo occurrence has not bee



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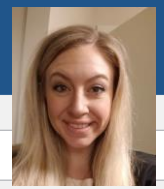

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Simpkins JW

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ASN Neuro. Jan-Dec 2021;13:1759091421991769. doi: 10.1177/1759091421991769.

Intermittent Lipopolysaccharide Exposure Significantly Increases Cortical Infarct Size and Impairs Autophagy

Ashley E Russell [1 2 3], John Z Cavendish [1 2], Ali Rai [4], Mya Vannoy [5], Ahmad H Dakhlallah [6], Heng Hu [2 7], Xuefang Ren [1 2], Amal Amer [8], Candice M Brown [1 2], Clay B Marsh [9], James W Simpkins [1 2], Duaa Dakhlallah [5 10]

Affiliations + expand

PMID: 33626880 PMCID: PMC8020222 DOI: 10.1177/1759091421991769

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Abstract

Globally, stroke is a le
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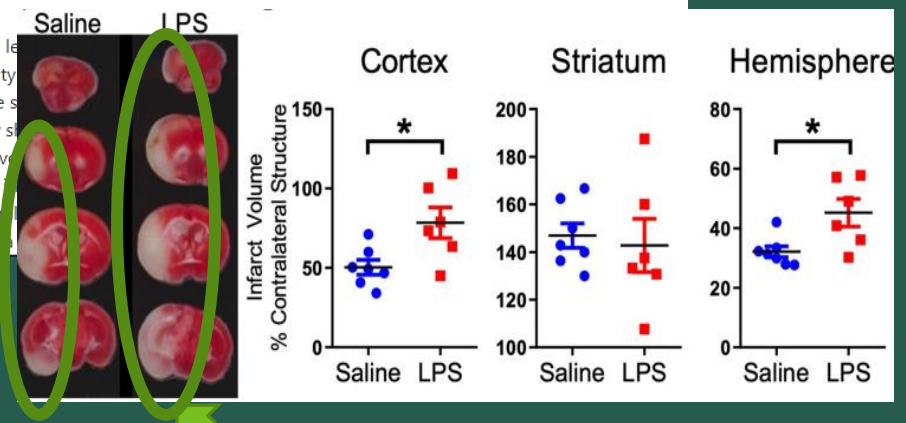

Review > Cytokine Growth Factor Rev. 2021 Apr;58:1-15. doi: 10.1016/j.cytogfr.2021.02.002. Epub 2021 Feb 19.

SARS-CoV-2 mediated neuroinflammation and the impact of COVID-19 in neurological disorders

Narayanappa Amruta [1], Wesley H Chastain [1], Meshi Paz [1], Rebecca J Solch [2], Isabel C Murray-Brown [1], Jaime B Befeler [1], Timothy E Gressett [1], Michele T Longo [3], Elizabeth B Engler-Chiurazzi [4], Gregory Bix [5]

Affiliations + expand

PMID: 33674185 PMCID: PMC7894219 DOI: 10.1016/j.cytogfr.2021.02.002

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Abstract

SARS-CoV-2 is a novel coronavirus that severely affects the respiratory system, is the cause of the COVID-19 pandemic, and is projected to result in the deaths of 2 million people worldwide. Recent reports suggest that SARS-CoV-2 also affects the central nervous system along with other organs. COVID-19-associated complications are observed in older people with underlying neurological conditions like stroke, Alzheimer's disease, and Parkinson's disease. Hence, we discuss SARS-CoV-2 viral replication and its inflammation-mediated infection. This review also focuses on COVID-19 associated neurological complications in individuals with those complications as well as other groups of people. Finally, we also briefly discuss the current therapies available to treat patients, as well as

that neurological symptoms of COVID-19 are common and potentially profound. This is particularly problematic given that previous coronavirus infections, including MERS and SARS, did not report significant CNS-targeted complications [105].

7.1. COVID-19 and stroke

Stroke is emerging as a common and potentially devastating complication following SARS-CoV-2 infection. Indeed, 2–6 % of hospitalized patients with COVID 19 have suffered an acute cerebrovascular event [106]. Like those who experience stroke in the general population, COVID-19 relatedstroke is commonly ischemic in nature, although there have been a few hemorrhagic cases [107]. Further, strokes were more likely in COVID-19 patients who were older, hypertensive, had higher D-dimer and C-reactive protein levels, and a more severe clinical course of COVID 19 infection [107]. The mechanisms by which SARS-CoV-2 can cause strokes are varied and include coagulopathy, myocardial damage with cerebral embolism, or destabilization of pre-existing atheroma plaque [108]. Viruses lead to thrombosis by triggering immune system responses involving endothelium, platelets, and coagulation. In addition, the "cytokine storm" produced in response to SARS-CoV-2 can increase D-dimers and affect coagulation, prompting stroke. The virus may also damage the heart, causing viral myocarditis, leading to cardioembolic stroke. Inflammation may additionally destabilize the fibrous capsule around the atheroma plaque, which could expose the thrombogenic clotting material, thus prompting clogging of the arteries, which in turn would also cause stroke [108].

One study found that COVID-19 patients with a history of stroke have a worse prognosis and are three times more likely to die than individuals without stroke history [108]. Even among non-infected patients, indirect consequences of the COVID-19 pandemic could be increasing stroke morbidity and mortality. Fear of going to hospitals, along with hospital resources being focused on COVID-19 patients could indirectly lead to increases in stroke incidence [108]. Management of stroke in the setting of concurrent COVID-19 should follow the standard of care for non-COVID stroke. Hemorrhagic strokes may be caused by the cytokine storm or by SARS-COV-2 binding to ACE2 receptors in endothelial and arterial smooth muscle cells of the brain, which damages intracranial arteries to the point of rupture [107].

7.2. Headache and COVID-19

Tulane Intermittent CMV + Aging Working Group

Prasad Katakam
Microvessel Energetics

Ricardo Mostany
Brain Aging & Hippocampal Long-term Potentiation

Liz Engler-Chiurazzi
Cognitive Aging

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Engler-Chiurazzi EB

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> Brain Behav Immun. 2024 Mar:117:36-50. doi: 10.1016/j.bbi.2023.12.033. Epub 2024 Jan 3.

Intermittent cytomegalovirus infection alters neurobiological metabolism and induces cognitive deficits in mice

Mark A A Harrison [1], Sara L Morris [2], Grace A Rudman [3], Daniel J Rittenhouse [4], Chandler H Monk [5], Siva S V P Sakamuri [6], Md Mehedi Hasan [7], Mst Shamima Khatun [8], Hanyun Wang [9], Lucas P Garfinkel [9], Elizabeth B Norton [10], Sangku Kim [7], Jay K Kolls [11], S Michal Jazwinski [12], Ricardo Mostany [13], Prasad V G Katakam [14], Elizabeth B Engler-Chiurazzi [15], Kevin J Zwezdaryk [16]

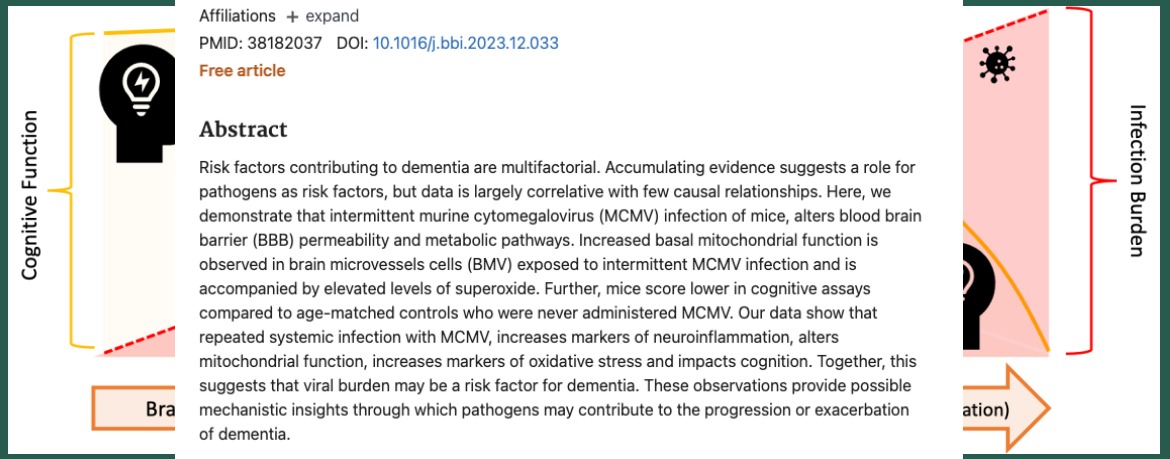
Affiliations + expand

PMID: 38182037 DOI: 10.1016/j.bbi.2023.12.033

Free article

Abstract

Risk factors contributing to dementia are multifactorial. Accumulating evidence suggests a role for pathogens as risk factors, but data is largely correlative with few causal relationships. Here, we demonstrate that intermittent murine cytomegalovirus (MCMV) infection of mice, alters blood brain barrier (BBB) permeability and metabolic pathways. Increased basal mitochondrial function is observed in brain microvessels cells (BMV) exposed to intermittent MCMV infection and is accompanied by elevated levels of superoxide. Further, mice score lower in cognitive assays compared to age-matched controls who were never administered MCMV. Our data show that repeated systemic infection with MCMV, increases markers of neuroinflammation, alters mitochondrial function, increases markers of oxidative stress and impacts cognition. Together, this suggests that viral burden may be a risk factor for dementia. These observations provide possible mechanistic insights through which pathogens may contribute to the progression or exacerbation of dementia.



Kevin Zwezdaryk
Viral/Immune Cascades

Supported by Tulane Brain Institute Research Fund Award & Infectious Disease Society of America

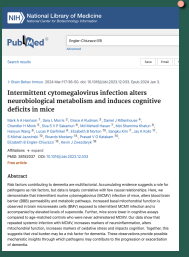
Intermittent CMV + Aging Working Group

Premise:

- 'Microbial origins of Alzheimer's disease/dementia' and 'Anti-microbial role of amyloid-beta' theories (Harris and Harris, 2015; Moir et al., 2018)
  - Herpes simplex 1 (De Chiara et al., 2021; Itzhaki, 2021; Laval and Enquist, 2021)
- Cytomegalovirus (CMV)
  - High (60-80%) seropositivity levels (Fowler et al., 2022)
  - Neurological consequences are poorly studied and conflicting (Barnes et al., 2015; Lurain et al., 2013; Loren-Gash et al., 2019)

Design:

- Vehicle
- Repeat Cytomegalovirus (MCMV)
  - Smith strain, 1x10^5 PFU
- Single Early-in-life CMV (LT CMV)
  - Smith strain, 1x10^5 PFU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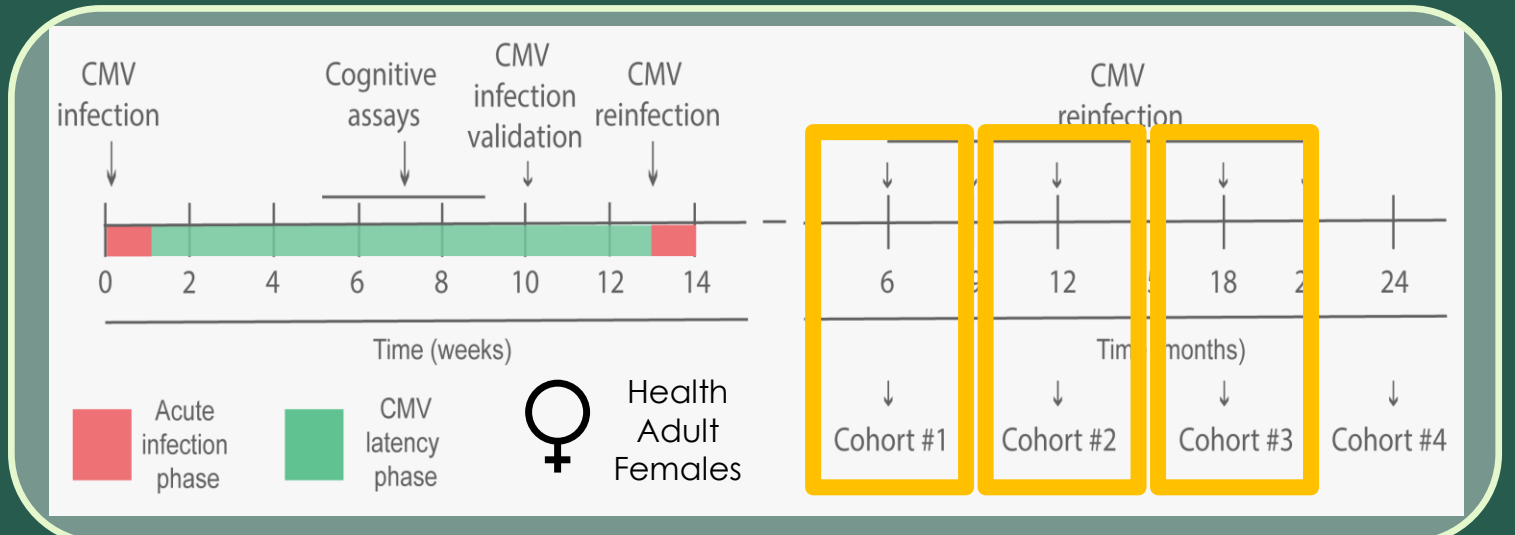
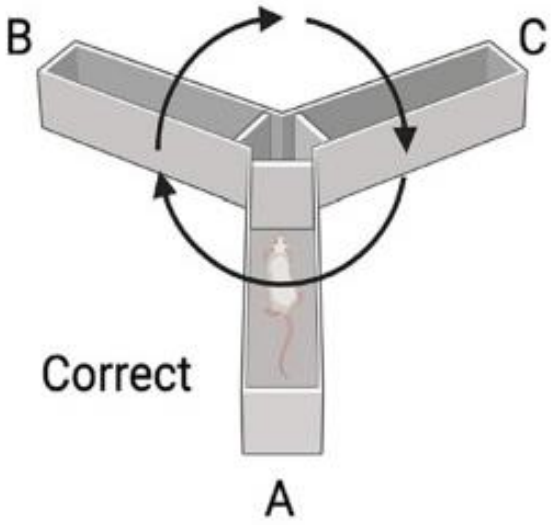
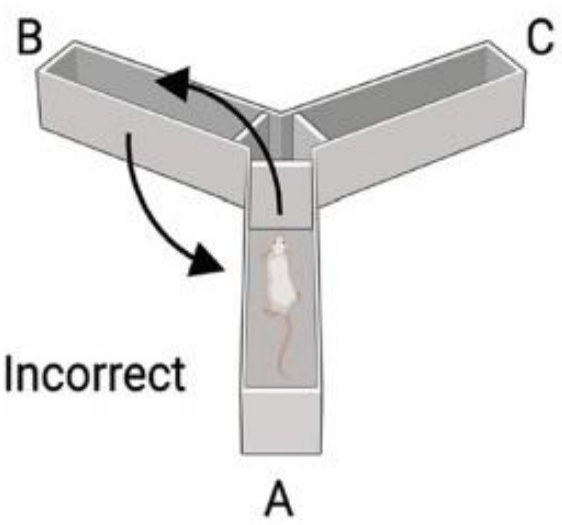
Intermittent cytomegalovirus infection alters neurobiological metabolism and induces cognitive deficits in mice

Harrison et al., 2024
Brain Behavior & Immunity

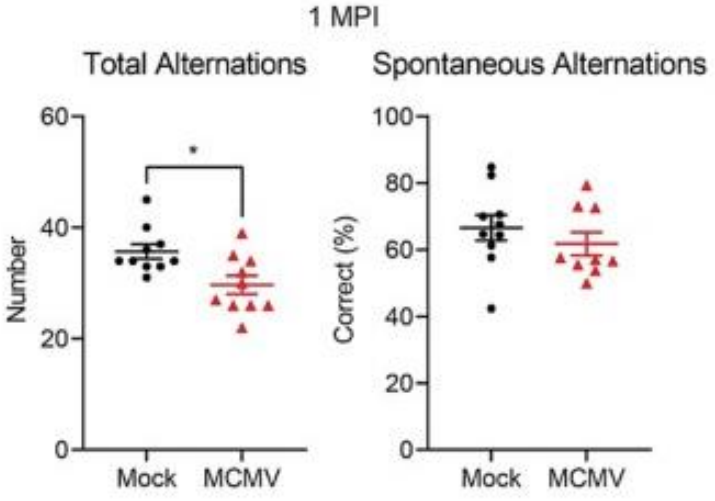


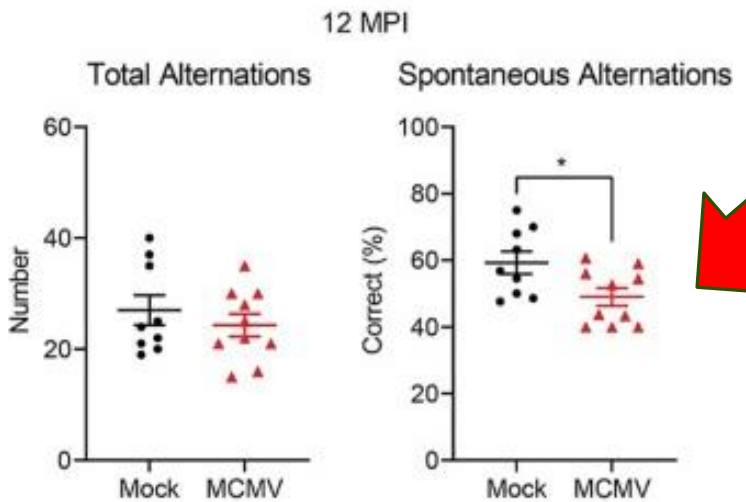
CMV Induces Cognitive Impairment



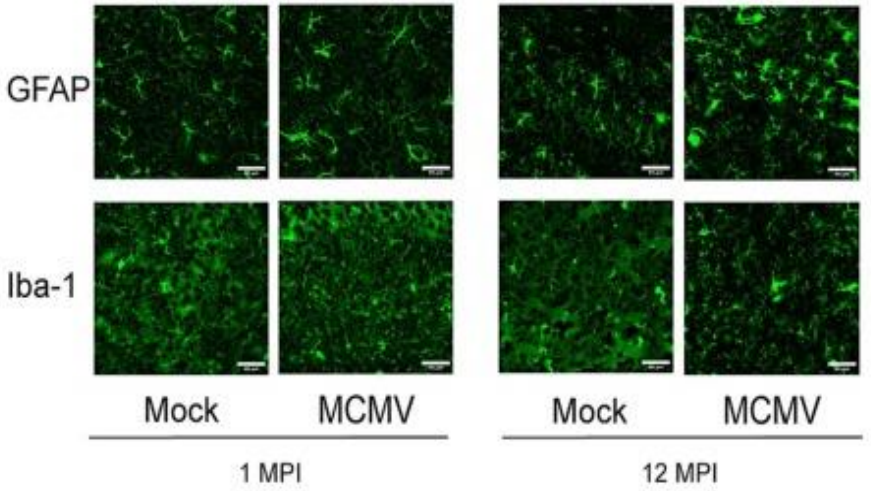


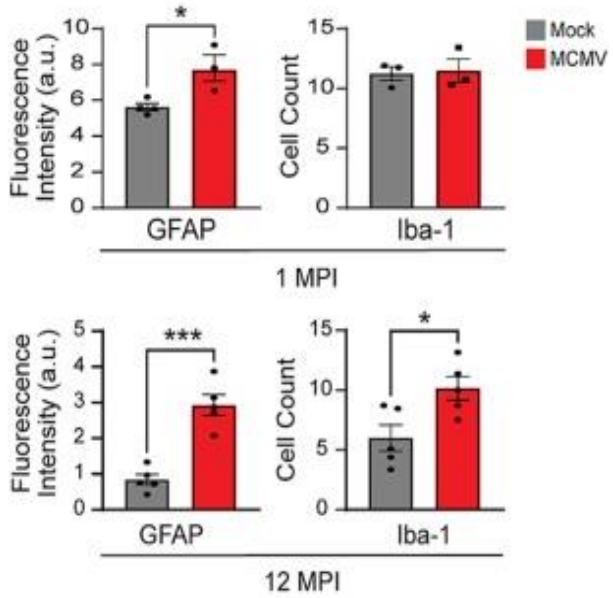
- One CMV exposure (~2 months old):
  - reduces movement
  - does not affect short-term recognition memory
- Four CMV exposures by 14 months of age:
  - does not impact movement ability
  - impairs short-term recognition memory

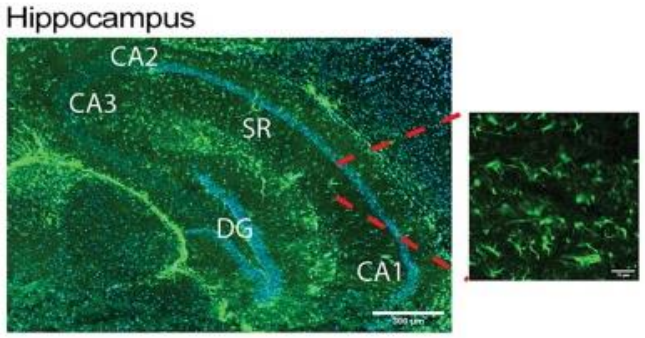




CMV Increases Hippocampal Barrier Permeability







Harrison et al., 2024
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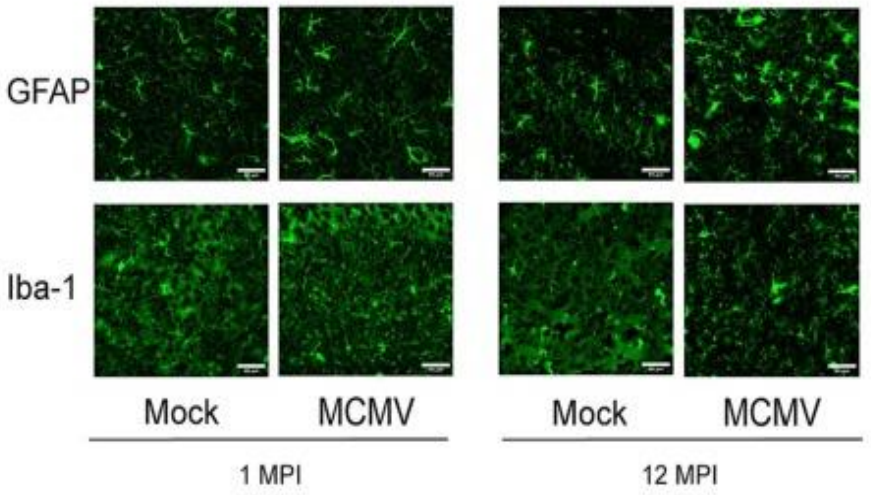
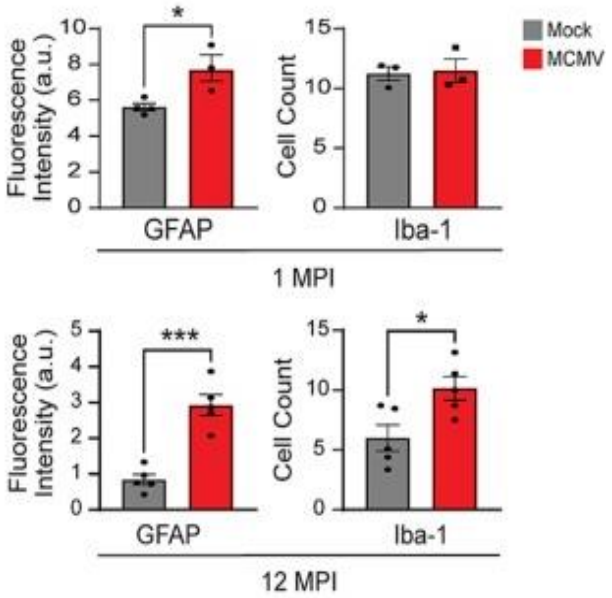
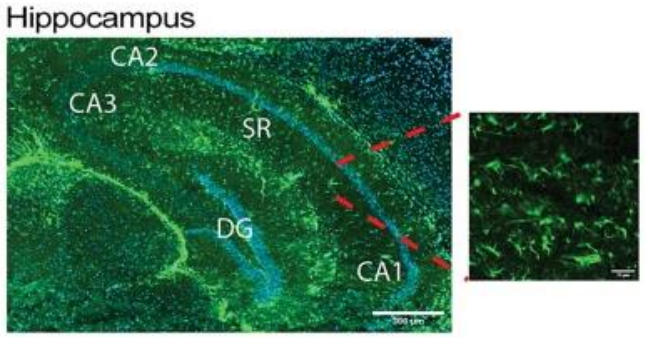
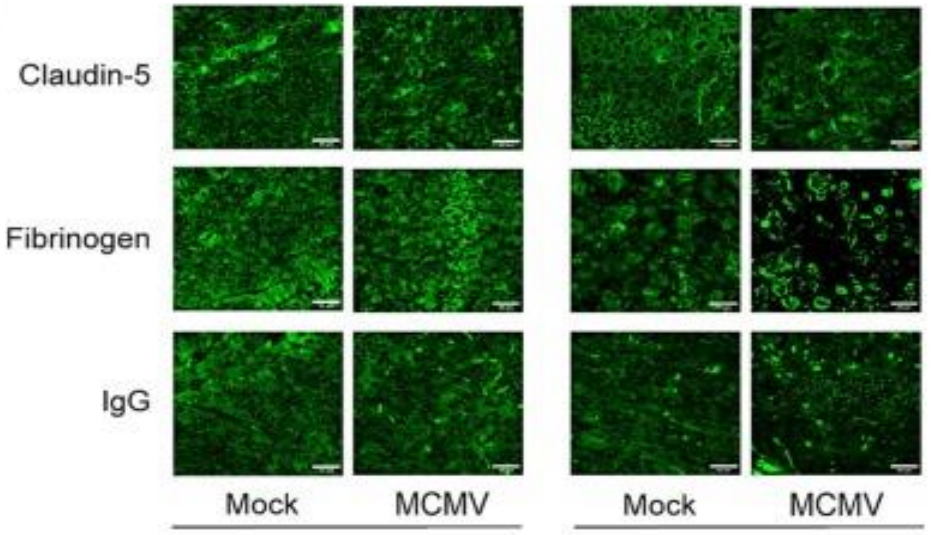
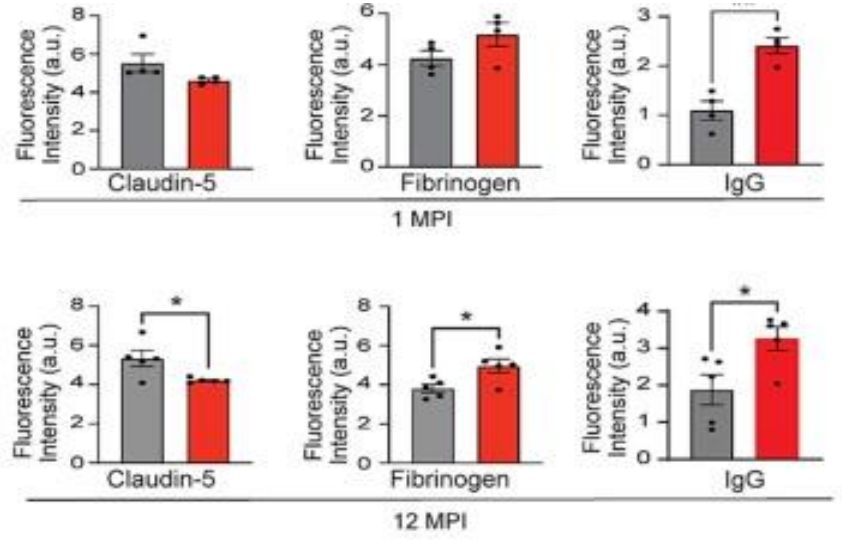
CMV Increases Hippocampal Barrier Permeability











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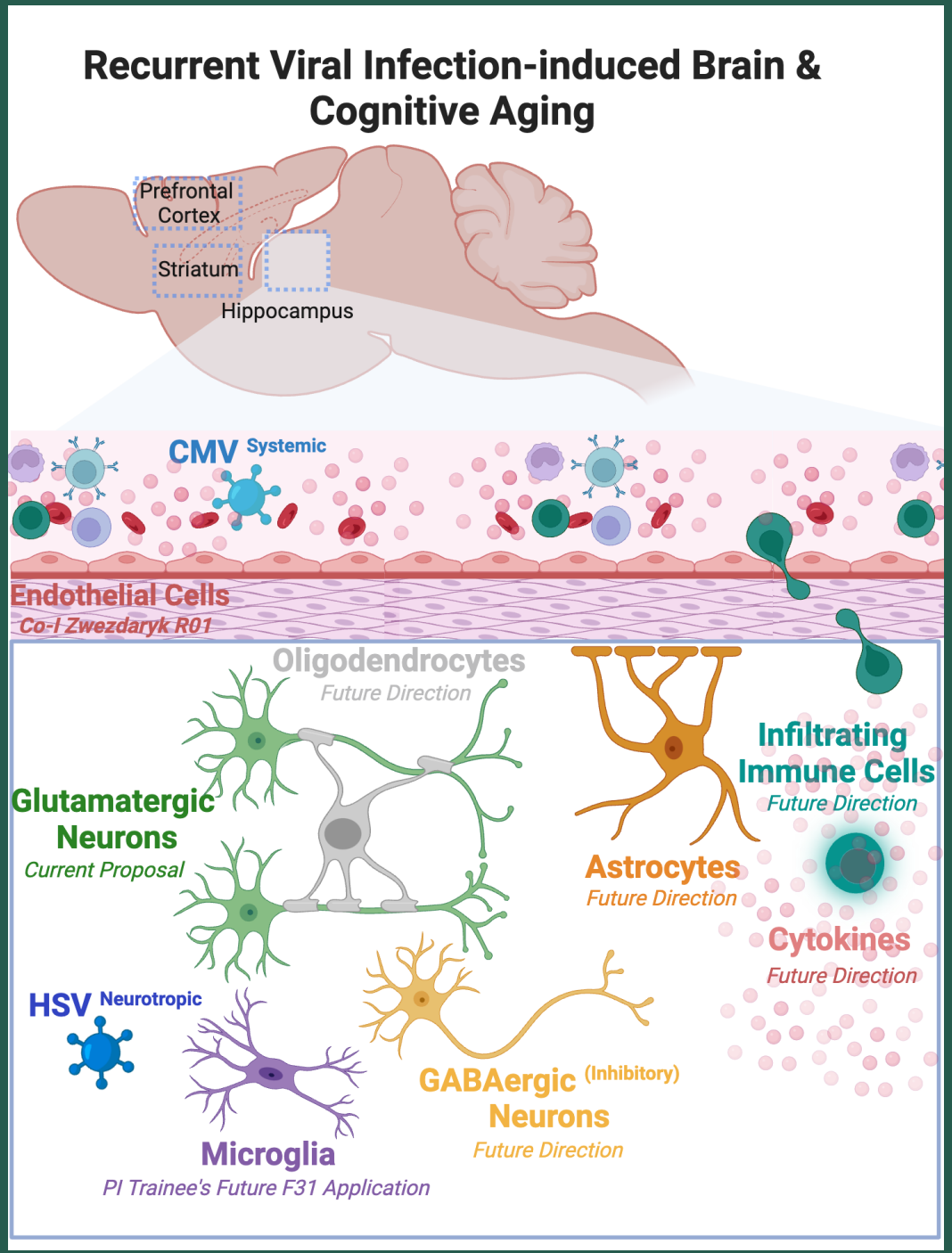
Harrison et al., 2024
Brain Behavior & Immunity



Future Directions

Why is cognition negatively impacted by intermittent systemic viral infection?

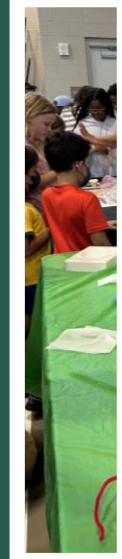
1. Determine how viral infection perturbs metabolic function of cells at the brain-immune interface
2. Discern impacts of intermittent systemic viral infection to neuronal function
3. Evaluate how intermittent viral infection affects the interplay of neurons and other supporting neural cell types
4. Identify how systemic and/or central immune responses to intermittent viral infection contribute and therapeutically target these cascades

Tulane

Prevention and Protection

Social Embeddedness & Community Engagement

Feed Our Brains-Lockdown



New Orleans Book Fest

WVU Football Game

Brico

~2500 NOLA children, te

~12,500 co

impacted (2020-today)

since 2006

Let's Connect & Collaborate!

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Email: eenglerchiurazzi@tulane.edu

lizsbrainlab@gmail.com

Instagram: @scientistlizec

Reddit: u/ScientistLiz

Twitter: @ScientistLizEC @brainsbruises

@LizsBrainLab

Website: www.lizslab.com www.brainsandbruises.com

Thanks AAAS for my statue at the Smithsonian Museum!

In this lab,
WE BELIEVE

SCIENCE is real

LOVE is love

BLACK LIVES matter

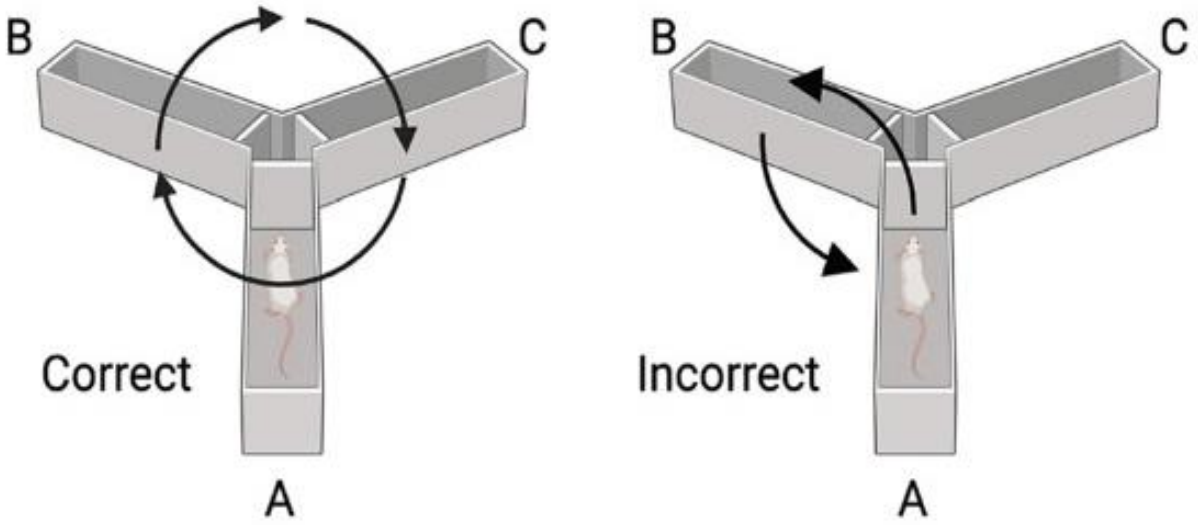
FEMINISM is for everyone

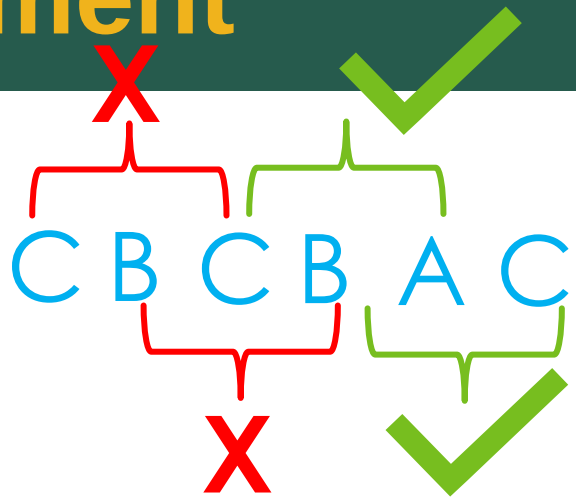
MICE are cool

IMMIGRANTS are welcome

Liz's Lab

CMV Induces Cognitive Impairment





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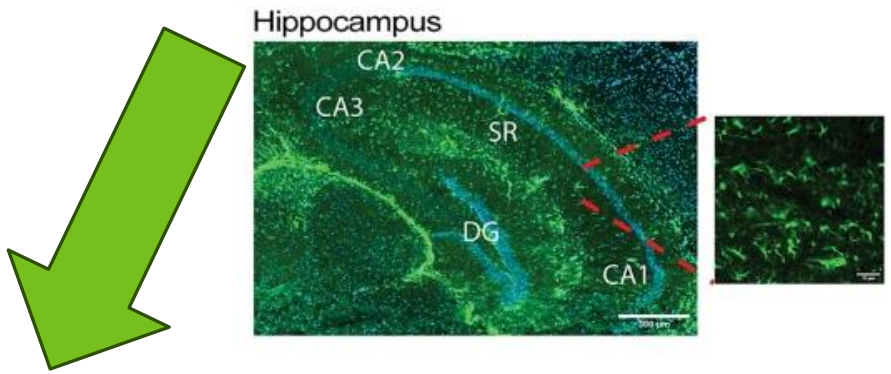
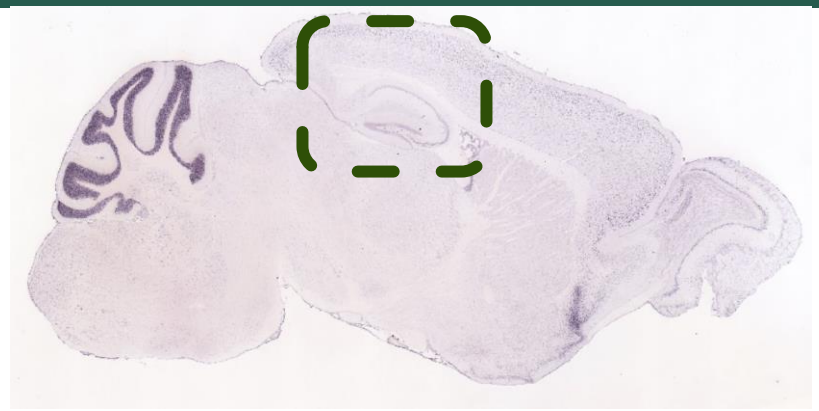
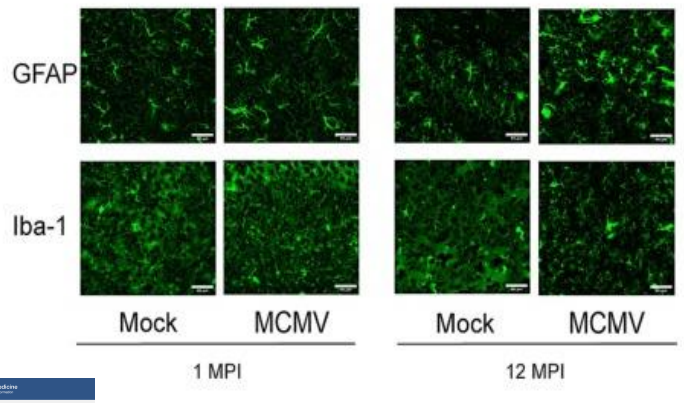
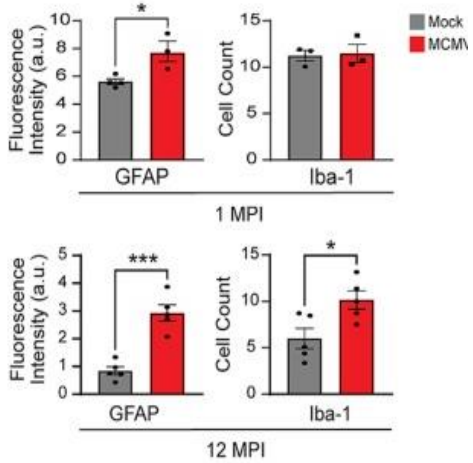
CMV Increases Hippocampal Neuroinflammation





Hippocampus






Intermittent cytomegalovirus infection alters neurobiological metabolism and induces cognitive deficits in mice

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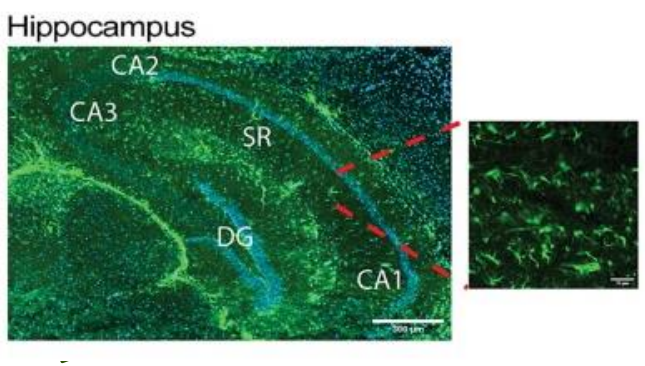
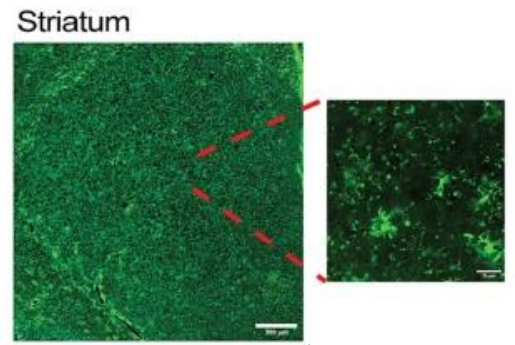
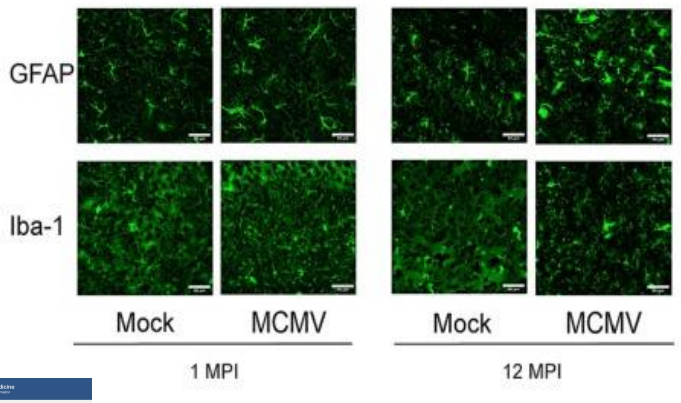
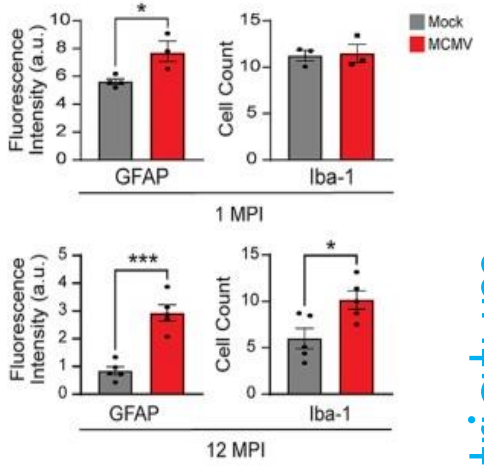


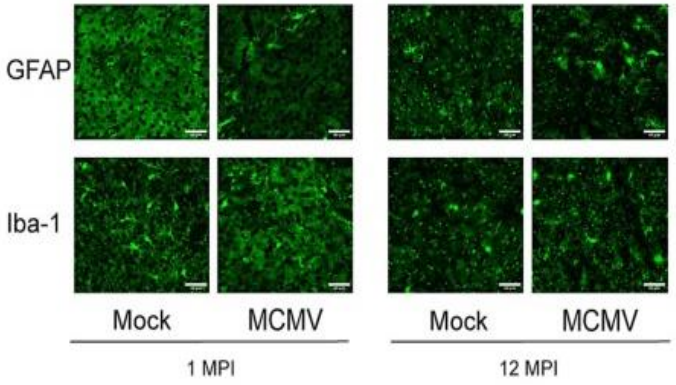


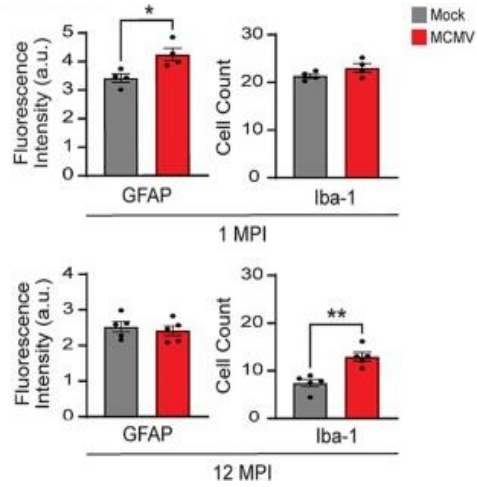
Hippocampus

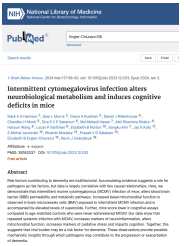




Striatum







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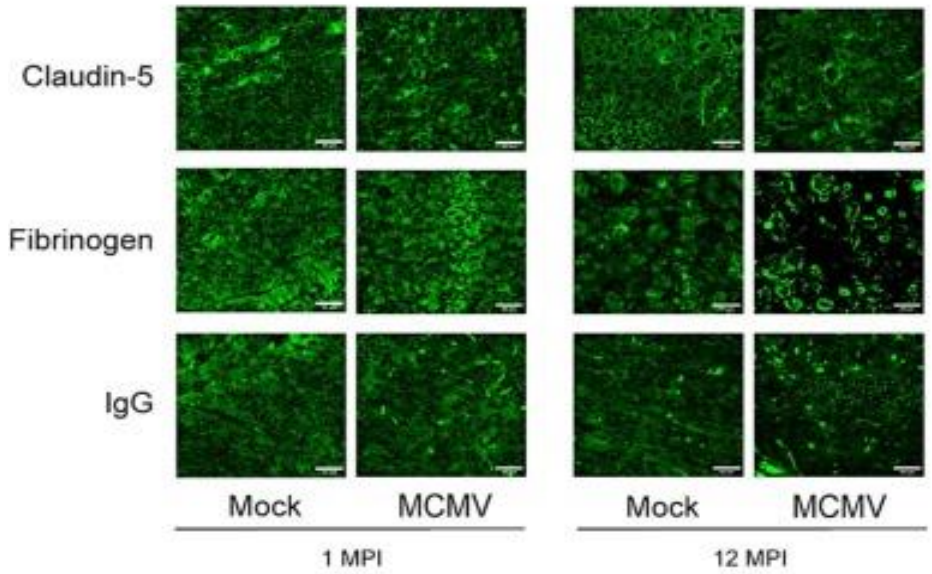
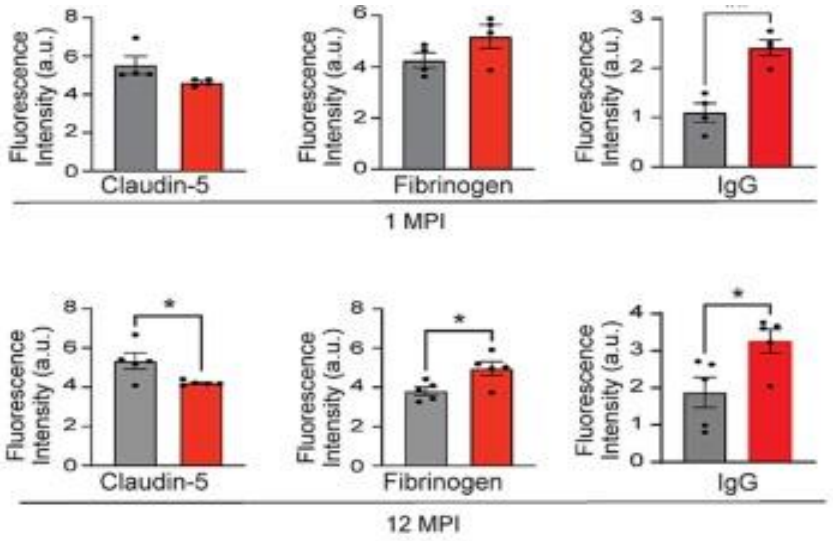
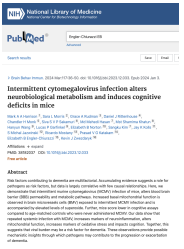
CMV Increases Hippocampal Barrier Permeability

Hippocampus






National Library of Medicine
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Abstract

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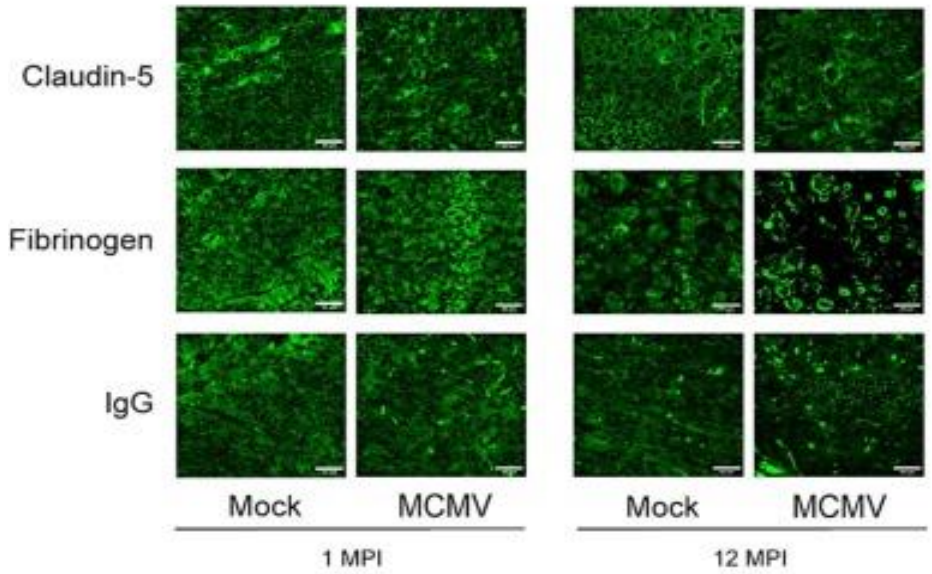
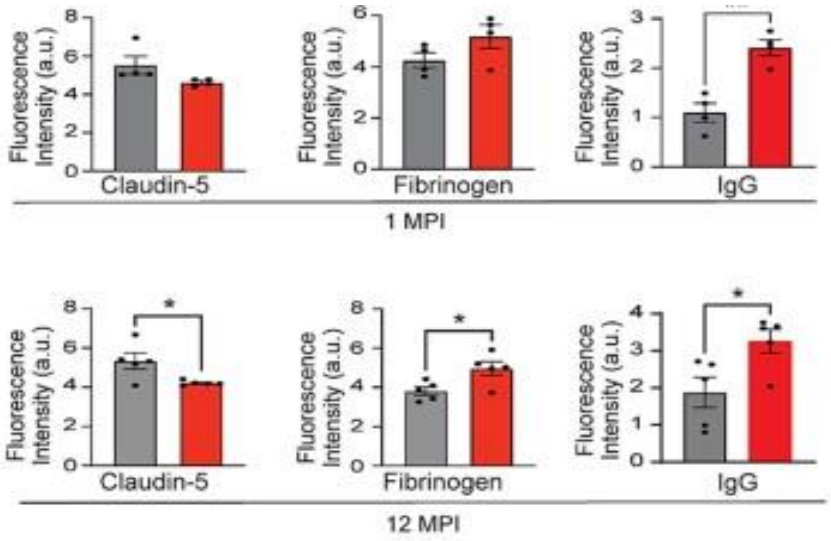
Hippocampus





Striatum