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Appel's New Monthly Bulletin

Content:

-Interview with Dr. Jacqueline Burre

-Burre's Lab news

-New publications in Appel

-Welcoming new lab members

-Creativity in Appel

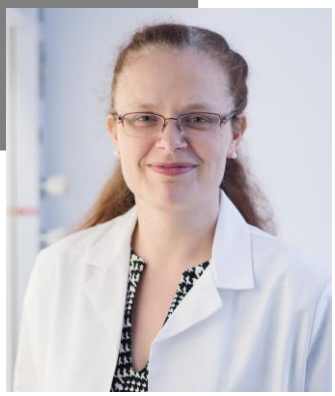
-Celebrations

-Birthdays!

-Puzzle

-Safety recommendations

Interview- Dr. Jacqueline Burre



Dr. Jacqueline Burre
Principal Investigator
Appel Institute
Lab BB-1052

Jacqueline, when did you know you wanted to become a scientist?

Already as a little girl, I was always interested in how things work, and, according to my parents, always made my way to the front in museums and exhibits to not miss a word from the guide. This interest eventually led to me choosing math and biology as majors in high school. My biology teacher inspired me to pursue my interests and I eventually decided to study biochemistry and biophysical chemistry at Goethe University, Frankfurt/Germany. The desire to solve nature's puzzles only grew from there, and my interests shifted more and more towards neuroscience. My undergraduate and Ph.D. thesis was focused on mapping the proteome of purified synaptic vesicles, and excitingly, I discovered two novel synaptic vesicle proteins, which are now ascribed zinc transporter function and which change their association with synaptic vesicles during synaptic activity. During my postdoctoral studies, I wanted to do something more functional and disease-relevant, and I joined Dr. Tom Südhof's lab as a postdoctoral fellow first in Dallas, and then moved with him to Stanford.

Who inspired you in your career to get to where you are today? Can you name that person and tell us how she or he inspired you?

My parents are probably my earliest inspiration. Nobody in my family had gone to university before and the process of applying to a university was a mystery, but they taught me to be resilient and not to give up, especially after I was rejected the first round. This was a very important life lesson and as it turned out, essential to be successful in science. The inspiration for science in particular came from my high school biology teacher Brigitte Cibis, who, unlike all the other biology teachers I had until then, focused on problem solving and experimental science. I knew right then that this is what I wanted to do for a living. I still have a harder time sitting in my office compared to swinging the pipet and testing my hypotheses at the bench which is the most fun part of my job.

Interview

What is your favorite book and why?

I used to read a lot of Jules Verne books before having my son, which combines my interests for science and science fiction. Now, my favorite book is Five Little Dinosaurs ☺

Recently, you were awarded as the Mentor of the Year in the BMRI, can you share with us your satisfaction about this merit?

The award came as a surprise, and I am obviously thrilled about it. I feel honored to work with such great students, and very much appreciate their hard work and dedication. It is quite rewarding to see that my own passion for science is able to ignite curiosity and passion in my students as well, and it is very satisfying to see them mature and move on with their scientific life.

What is your favorite place in Weill Cornell Medicine and why?

The lab and in particular my bench ☺

Your lab has recently been awarded a R01 to study the toxicity of alpha-synuclein, what are the main goals you want to address in this project?

A big focus in the alpha-synuclein field is to get rid of alpha-synuclein and to thereby prevent its toxic activity. However, us and others have found that alpha-synuclein has also a vital function in the brain, to support neuronal communication over the long life of a neuron. Plus, we now know that silencing alpha-synuclein induces nigrostriatal degeneration in mice, rats, and non-human primates, knockout mice have reduced dopamine neurons, and our own studies demonstrate age-dependent neurological impairments and premature death in synuclein null mice. In addition, patients carrying gene polymorphisms that result in lower αSyn levels exhibit earlier disease onset, a faster disease progression, and worse motor and cognitive scores. So instead of clearing alpha-synuclein from the brain, we are trying to stabilize its functional state on synaptic vesicles. We have generated a set of mutants of alpha-synuclein that display increased affinity towards synaptic vesicles, and my student Katie is testing these mutants for their effects on motor behavior and pathology in mice.

Interview

How does research in neuroscience impact your everyday life?

Science has had a big impact on my life. I have met my husband in the lab, and we were lucky enough to get lab space next to each other. We discuss science while commuting in the car and at home, we are each other's fiercest grant and paper critics which is fantastic, and our three year-old son has already learned about the concepts of hypotheses and experiments and knows not to give up when something does not work out the first time.

Can you share with us your future projects for your lab in Alzheimer's, Parkinson's and aging research?

The overall goal in my lab is to understand the molecular mechanisms underlying synaptopathies in Parkinson's disease and childhood encephalopathies. We are specifically interested in early pathogenic changes that trigger disease, to be able to eventually intervene at an earlier time point. A clinical trial based on the findings of my students Noah and André on the use of 4-phenylbutyrate in children with mutations in STXBP1 is already on-going, and a pilot clinical study on assessing biochemical changes of alpha-synuclein in the enteric nervous system of Parkinson's disease patients is about to launch, with the hope to identify a novel biomarker that would enable detection of Parkinson's disease at an earlier stage during routine cancer screening colonoscopies.

What is your favorite part of the brain and why?

We are analyzing the substantia nigra and striatum for our Parkinson's disease-related projects, but otherwise, focus on the entire brain.

Finally, can you share any advice to those who would like to pursue a career in Academia?

For me, science is not work but fun, and I feel privileged to enjoy my work every single day. My advice for those who would like to pursue a career in Academia or anywhere else is to: (1) Have fun and be excited about your work - you can chose any field of research!; (2) Be patient and resilient because as scientists, we face rejections every day; and (3) Be open to adventure into new territories, since most of the fun is to explore the uncharted territories.

By Guillermo Coronas
Laboratory Manager
Appel Institute

Burre’s Lab News

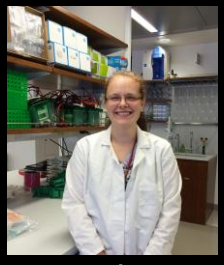
Pilot Study: Biochemical characterization of Parkinson's disease-related proteins in the enteric nervous system

Summary: The goal if this study is to determine whether gut pathology and types of bacteria in the gut can serve as an indicator of Parkinson's disease in subjects aged 45-75, to not only facilitate earlier diagnosis, but to also strengthen our understanding of the link between the gut and brain in Parkinson's disease.

Dr. Virginia Gao

Dr. Carl Crawford

Dr. Andrea Lee



Dr. Jacqueline Burre

Burre lab students published an invited review

Summary: Congratulating Noah Guiberson and Debra Abramov from Burré Lab on their published invited review. Their review is part of the Special issue "Presynaptic Dysfunction and Disease” in the Journal of Neurochemistry. They focus on the current understanding of the phenotypic spectrum of STXBP1-linked disorders, as well as discuss disease mechanisms in the context of the numerous pathways in which STXBP1 functions in the brain. They additionally evaluate the available animal models to study these disorders and highlight potential therapeutic approaches. Here is the link to the revew: https://onlinelibrary.wiley.com/doi/full/10.1111/jnc.15120

Noah Guiberson

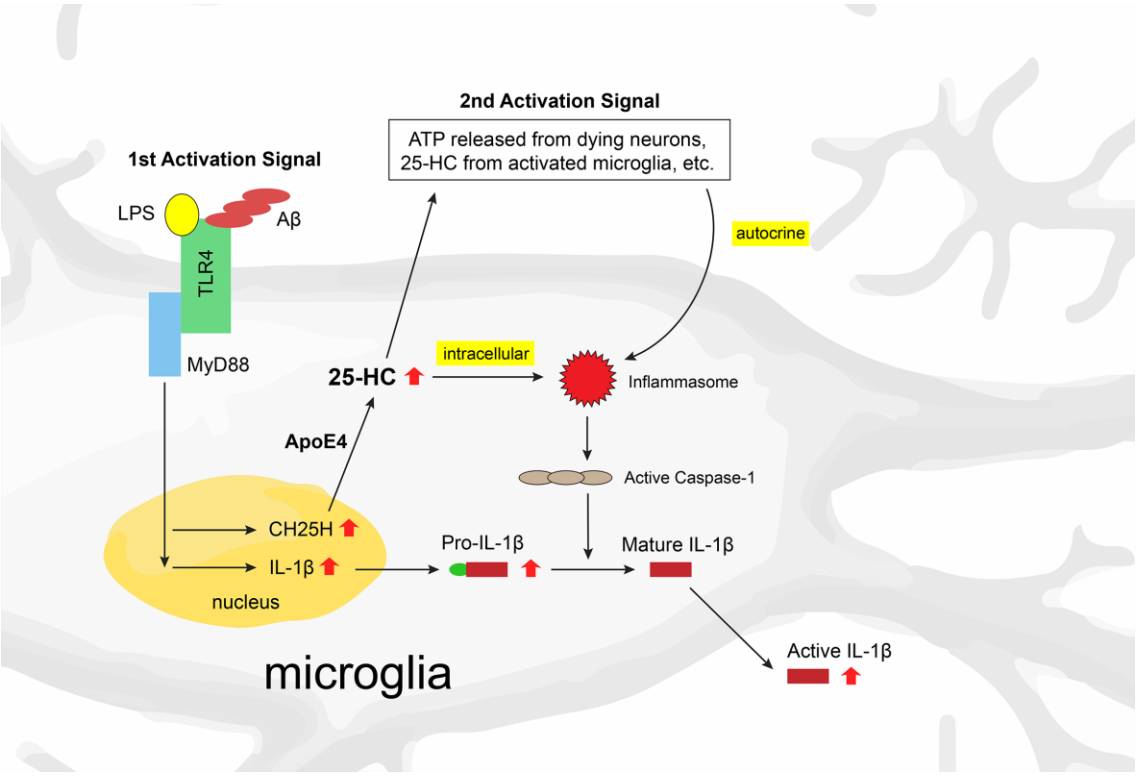
Debra Abramov

New publications in Appel

25-Hydroxycholesterol amplifies microglial IL-1β production in an apoE isoform-dependent manner

Man Ying Wong, Michael Lewis, James J. Doherty, Yang Shi, Anil G. Cashikar, Anna Amelianchik, Svitlana Tymchuk, Patrick M. Sullivan, Mingxing Qian, Douglas F. Covey, Gregory A. Petsko, David M. Holtzman, Steven M. Paul & Wenjie Luo

Alzheimer's disease (AD) is a fatal neurodegenerative disorder that is characterized by progressive cognitive and functional impairment and memory loss. The lack of an effective cure or even treatments that slow progression of this disease drives a strong urge for our biomedical research to gain new insights into the mechanisms of the disease. Genome-wide association studies of Alzheimer's disease (AD) have implicated pathways related to lipid homeostasis and innate immunity in AD pathophysiology. However, the exact cellular and chemical mediators of neuroinflammation in AD remain poorly understood. The oxysterol 25-hydroxycholesterol (25-HC) is an important immunomodulator with wide-ranging effects on cell signaling and innate immunity. Cholesterol 25-hydroxylase (CH25H), the enzyme responsible for 25-HC production, has also been identified to be one of the disease-associated microglial (DAM) genes that are upregulated in the brain of AD and AD transgenic mouse models. Our recent study found that CH25H expression is upregulated in human AD brain tissue and in transgenic mouse brain tissue bearing amyloid-b plaques or tau pathology. Using primary microglia in vitro, we observed that LPS-induced microglial production of the pro-inflammatory cytokine IL-1b is markedly potentiated by 25-HC and attenuated by deletion of CH25H. Interestingly, we also found that apolipoprotein E4 (apoE4), a genetic risk factor for AD, regulates this 25-HC-induced immune response. Moreover, caspase-1 inflammasome is likely activated by 25-HC and mediates its specific stimulation of IL-1β production. Therefore, our results suggest that 25-HC may function as a microglial secreted inflammatory mediator in brain, promoting IL-1b-mediated neuroinflammation in an apoE isoform-dependent manner (E4>>E2/E3) and thus may be an important mediator of neuroinflammation in AD. Its interplay with apoE4 may illuminate a potential disease mechanism underlying the most important genetic risk factor for LOAD. Our work will begin to establish if suppressing 25-HC-dependent inflammation is a viable therapeutic target in AD.



New publications in Appel

Discovery of small molecules that normalize the transcriptome and enhance cysteine cathepsin activity in progranulin-deficient microglia

Maria A. Telpoukhovskaia[1,2], Kai Liu[3], Faten A. Sayed[1,2,4], Jon Iker Etchegaray[1], Min Xie[1,3], Lihong Zhan[1,2], Yaqiao Li[1], Yungui Zhou[1], David Le[1], Ben A. Bahr[5], Matthew Bogyo[6], Sheng Ding[3] & Li Gan[1,2,7]✉

Patients with frontotemporal dementia (FTD) resulting from granulin (GRN) haploinsufciency have reduced levels of progranulin and exhibit dysregulation in infammatory and lysosomal networks. Microglia produce high levels of progranulin, and reduction of progranulin in microglia alone is sufcient to recapitulate infammation, lysosomal dysfunction, and hyperproliferation in a cellautonomous manner. Therefore, targeting microglial dysfunction caused by progranulin insufciency represents a potential therapeutic strategy to manage neurodegeneration in FTD. Limitations of current progranulin-enhancing strategies necessitate the discovery of new targets. To identify compounds that can reverse microglial defects in Grn-defcient mouse microglia, we performed a compound screen coupled with high throughput sequencing to assess key transcriptional changes in infammatory and lysosomal pathways. Positive hits from this initial screen were then further narrowed down based on their ability to rescue cathepsin activity, a critical biochemical readout of lysosomal capacity. The screen identifed nor-binaltorphimine dihydrochloride (nor-BNI) and dibutyrylcAMP, sodium salt (DB-cAMP) as two phenotypic modulators of progranulin defciency. In addition, nor-BNI and DB-cAMP also rescued cell cycle abnormalities in progranulin-defcient cells. These data highlight the potential of a transcription-based platform for drug screening, and advance two novel lead compounds for FTD.

Welcome to Appel

Daniel Barnett
Graduate Student
rotation
Orr's Lab

I graduated with a B.S. in Neuroscience from the University of Rochester. During my undergraduate career, I worked in the laboratory of Dr. Houhui Xia studying the role of protein phosphatase-1 in synaptic transmission and plasticity. For this research, I was awarded Rochester's de Kiewiet Research Fellowship. I am fascinated by the cellular and molecular study of learning and memory. In particular, I am interested in glial signaling pathways and glial-neuronal interactions as it pertains to Alzheimer's Disease and Frontotemporal Dementia. I am very excited to pursue these interests in the Orr Lab, where I will be studying astrocyte signaling and mitochondrial reactive oxygen species in the context of neurodegeneration and cognitive dysfunction. I look forward to joining the Appel Institute community, where I hope to learn from, and contribute to, the excellent science being practiced. A fun fact about me is that I danced in a Bollywood performance group at the University of Rochester. I am also passionate about pursuing scientific outreach with younger students.

Welcome to Appel

Celeste Parra Bravo
Graduate Student
rotation
Gan's Lab

My name is Celeste Parra Bravo and I graduated from UC Santa Barbara in 2020 with a B.S. in Biochemistry and Molecular Biology. During my undergraduate career, I was in the lab of Dr. Ken Kosik at UC Santa Barbara where I studied a translocation of delta-catenin, a key protein in the regulation of synapse density and plasticity. I also spent a summer in the lab of Dr. Martin Kampmann at UCSF where I conducted CRISPR screens to uncover the cellular factors involved in tau oligomerization. In the Gan lab, I'm interested in understanding the role of microglia in neurodegenerative diseases in order to identify potential therapeutic targets. Outside of the lab, I like hiking, trying new foods, exploring the city, and playing with my hamster.

Welcome to Appel

Berkiye Sonustun
Graduate Student
rotation
Sharma's Lab

I am a clinical biomedical scientist by training, and completed my bachelor's degree at the Queen Mary University, London School of Medicine in 2017. After graduating, I was accepted into a specialized Masters of Research (M.Res) degree in Translational Neurology, at University College London, Institute of Neurology. There, I worked on a thesis lab project at the Queen Square Brain Bank on Parkinson's disease and Multiple System Atrophy pathogenesis using primarily human post-mortem brains. I was then recruited to the Mayo Clinic as a research assistant to work on how different *APOE* isoforms contribute to AD and DLB pathogenesis. I have been playing the piano since the age of four, and am trilingual. I am also from an island not many people have heard of.

Welcome to Appel

Eileen received her B.S. in Neuroscience at UCLA and her Ph.D. in Behavioral Neuroscience at Oregon Health & Science University working with Dr. Jacob Raber. She's fascinated by apolipoprotein E and wants to understand the molecular mechanisms that result in isoform-specific differences in risk associated with Alzheimer's disease. Eileen is dedicated to building a more equitable environment for underrepresented minorities in science education. When she's not in lab, she loves to try new recipes, tackle craft projects, and explore the city.

Eileen Ruth Torres, PhD.
Postdoc
Gan's Lab

Creativity in Appel

Poem

by Silvie Ḥannah Lundgren
Research Technician
Sinha's Lab

How? 05-10 June 2020

How can any life come from me,
From this body, this mind, this soul?
How can any life come from me
If I am holding all this death?
How can any life come from me
If inside is all this rot?
How can I shed light around
If my heart seems set on shedding blood?
How can any life come from me …
If I am choking myself?

I am so scared,
I am so, so scared
Of what is in me—
Not just the world.
I am scared of who I am
And who I might be.
I am afraid of being loved,
Because I might kill that love.

Love is light,
And I do not want for the lights to go out,
Put out by the whirling, hurtling mess within me.
So I hold back because I am not safe—
Not safe for you,
Not safe for me.
But the angry winds just scream more,
And my pain becomes a weapon
I can barely control,
And, really, really, I do not want to hurt you.
So stay away, away …
I do not want to keep burning you.

How can I bring life
When I am this?
I did not want- …
This is not the way I want to be.
How can I bring life
When there are certain things
I cannot seem to
Get off my mind?

I can be so selfish,
So hurtful,
And sometimes I
Just want
To dissolve.
But that would be more selfishness—

Change is no easy thing;
Change is hard.

Comment: I wrote this while going through a hard time coping with things in my life and feeling very stuck. Sometimes when we feel bad in some way about ourselves it feels conflicting for someone to love us or for someone to see wonderful things in us, but those good things are still there within and are worth recognition, encouragement and nurturing. Personal growth is an often treacherous and intense process, and a little grace goes a long way. SHL

Creativity in Appel Neuro Fashion

by Rose Horowitz
Research Technician
Gan's Lab

Hi Appel! My name is Rose and I'm a Research Technician in the Gan Laboratory. I graduated from Wellesley College in 2020 with honors in Neuroscience. While at Wellesley I completed my undergraduate thesis in Dr. Margaret Keane's laboratory where I studied human memory, and in the future I plan to pursue my PhD in Neuroscience. When not at the lab bench, I can be found building elaborate historically inspired costumes—from Elizabethan ballgowns to Tang Dynasty qixiong ruqun.

Creativity in Appel Neuro Fashion

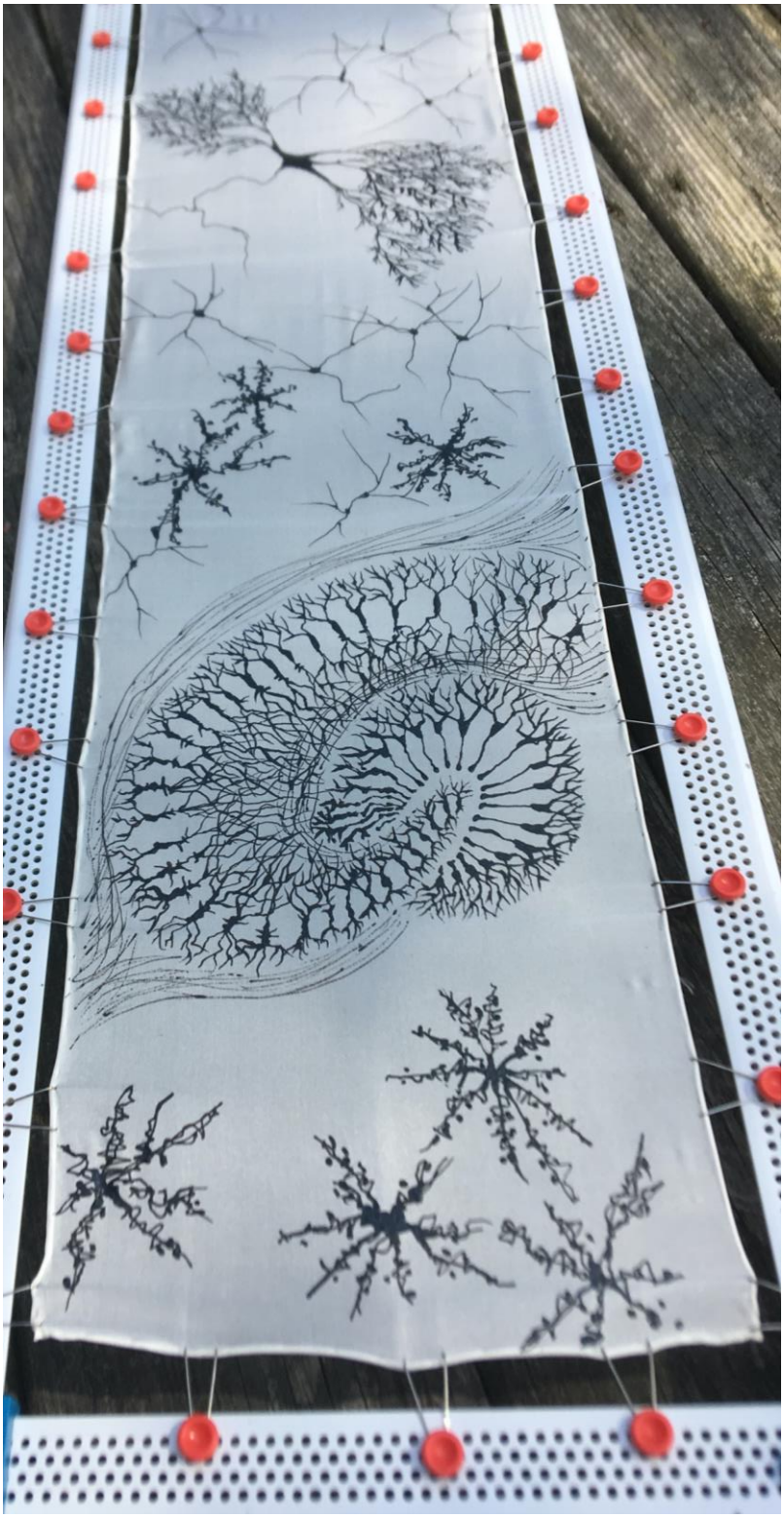
I built my first costume in 2013, and in 2016 I apprenticed at the Maine State Music Theatre Costume Shop. In 2017 I studied bespoke tailoring at the London College of Fashion with the goal of learning to make menswear-cut suits for the LGBTQIA+ community. Although I ultimately decided to pursue Neuroscience as a career and costuming/tailoring as a hobby, I try to integrate my two passions whenever possible. I recently built my neuron jacket to wear to graduation and conferences. The entire build took about a year, from hand-embroidering all of the neurons to patterning, canvassing, and assembling.

Creativity in Appel Neuro Fashion

Impulse. Materials: AV wires, telephone wires, recycled aluminum foil, trash bag.

In 2019 I competed in the MIT Trashion show where students are challenged to design and build outfits from trash to promote waste-reduction and sustainability in fashion. My entry "Impulse" was inspired by an experience I had first year of college in NEURO 100. While working with capacitors I mildly electrocuted myself trying to understand the electrical impulses produced by neurons, hence my material choice of AV cords and telephone wires. I placed 2nd overall and won the Materials Award.

Creativity in Appel Neuro Fashion



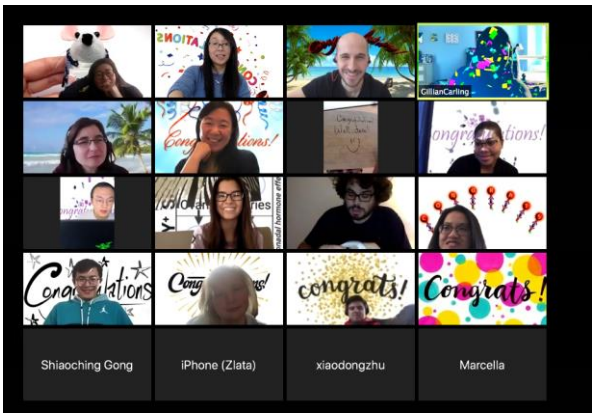
Progress shot of a silk-painted scarf I made for my undergraduate major/thesis advisor.

Recently, I have been working on a wool jacket for the Fall and silk painting before losing the last of the Summer sun. I look forward to sharing more neuroscience-inspired pieces with you in the future!

Celebrations

Congratulations to Anna and Avital on the arrival of the newborns

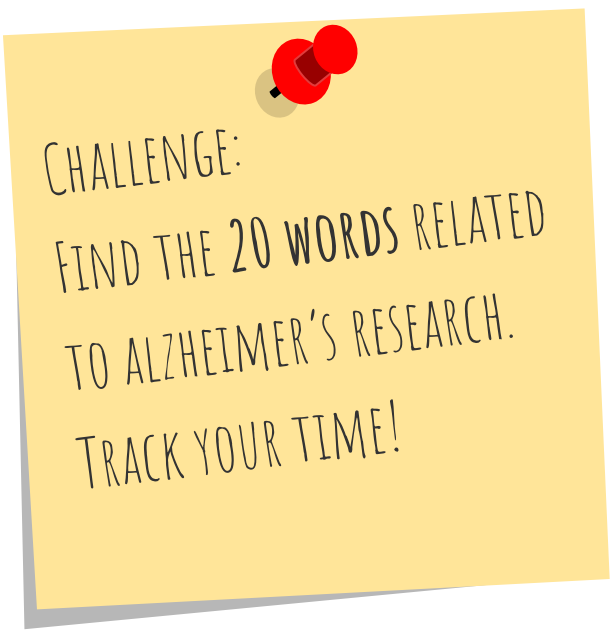
Chloe and Bang passed their ACE exams in April and May



Happy Birthday

Puzzle

F I C O Z M K J O F H M Q R E
C S U R Y U W R J M I A O E O
N D E M E N T I A T Q V W M P
D O S U P M A C O P P I H I A
I X I K P S S C N F C S U E D
O M I S T R H E A I N N R H S
L F A Q S O O M L O A E P Z P
Y B S G N E I T R G K R E L O
M A W D I L R U E R N N B A R
A Z R Y I N E P A I E A N F A
R I T A U N G M E G N W T W D
A X L Q D D O I C D X S L O I
B K C L G I K A T R O P H Y C
Q T S Y B Y R O M E M N S G Q
X M K V N K R F S E U Q A L P



Safety recommendations

Clean your hands often

Put distance between yourself and other people (at least 6 feet)

Cover your mouth and nose with a mask when around others

Clean and disinfect frequently touched objects and surfaces daily

Collaborations

Would you like to recommend a book, a movie, an inspiring quote?

You can participate! This bulletin is for you.

Please contact: guc9014@med.cornell.edu