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TITLE: Studying Microglia as Possible Therapeutic Targets for Autism Spectrum Disorder (ASD) in a Mouse Model of Maternal Anti-Caspr2 Antibody-Induced ASD

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14. ABSTRACT

Our studies use a model in which *in utero* exposure to maternal anti-Caspr2 antibody affects microglial maturation program, possibly arresting microglial development in male, but not female mice, leading to of Autism Spectrum Disorder (ASD)-like phenotype. We also study if we can ameliorate the ASD-like phenotype by suppressing microglial activation using an FDA approved drug.

15. SUBJECT TERMS
None listed.

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INTRODUCTION

Maternal brain-reactive antibodies (Abs) are present in one of every 10-20 mothers of a child with ASD. They pose a potential risk to the developing brain because they can gain access to the brain during gestation altering brain development during a critical period of neurodevelopment. We identified Caspr2, a neuronal protein, to be a target of monoclonal Abs (IgG) derived from mothers with anti-brain Abs and an ASD child and found that ~40% of mothers with anti-brain Ab harbor anti-Caspr2 IgG. We showed that exposure in utero to the human monoclonal anti-Caspr2 IgG led to an ASD-like phenotype in male, but not female, mice. Similarly, we showed that male mice born to dams immunized with human Caspr2, hence harboring anti-Caspr2 IgG throughout gestation, exhibit neurodevelopmental phenotypes similar to mice exposed in utero to human monoclonal anti-Caspr2 IgG. Single nucleus (sn) RNA-seq of the adult hippocampus from male mice demonstrates that in utero exposure to maternal anti-Caspr2 IgG leads to differentially regulated genes (DEGs) that overlap with high-risk ASD genes, further validating the relevance of the model. We decided to focus on microglia since we found a high burden of DEGs in these cells. We also found that almost 50% of the microglial DEGs are developmentally regulated, with many of these genes suggesting that the microglia are immature and more activated. We therefore hypothesize that microglial activation contributes to the ASD-like phenotype in male offspring. This isfurther buttressed by our data on adult mice born to dams immunized with Caspr2 or control and fed for two weeks a diet containing colony stimulating factor 1 receptor (CSF1R) inhibitor, PLX 3397, leading to loss of microglia. PLX 3397 normalized repetitive behavior at the time of depletion. These data together support a model in which the microglia are activated due to an early brain insult, and this activation results in ASD-like phenotypes. The objective of this proposal is to determine the contribution of microglia to the persistent ASD-like phenotype, and to assess if suppressing microglial activation can reverse the phenotype. In Aim 1, we test if we can reverse or mitigate the ASD-like phenotype in male mice exposed in utero to anti-Caspr2 antibody using Angiotensin Converting Enzyme (ACE) inhibitors. In Aim 2, we wish to understand the changes in microglia and in other cell types that interact with microglia to understand the pathologic interactions of brain cells in ASD. In Aim 3, we will explore the mechanism by which anti-Caspr2 antibodies lead to microglial alterations.

KEYWORDS

Antibodies, Angiotensin converting enzyme (ACE), Autism spectrum disorder (ASD), Caspr2, Captopril, Cntnap2, Enalapril, IgG, In-utero, Maternal, Microglia, scRNA-seq

ACCOMPLISHMENTS

Major goals of the project:

The goal of this proposal is to determine the contribution of microglia to the persistent ASD-like phenotype, and to assess if suppressing microglial activation can reverse the phenotype.

Aim 1: **The effect of Angiotensin Converting Enzyme (ACE) inhibitors on maternal anti-Caspr2 IgG induced ASD-like phenotype**: We will test whether we can reverse the ASD-like phenotype following in utero exposure to anti-Caspr2 IgG using ACE inhibitors. We chose to use ACE inhibitor to suppress the microglia activation because ACE inhibitors are FDA-approved drugs and are safe in the low dosage used in this study. Male mice born to dams exposed in utero to anti-Caspr2 or Control IgG will be treated with ACE inhibitors captopril (BBB-permeable) or enalapril (BBB-impermeable), or the appropriate vehicle, beginning at 3 weeks of age. We will assess the mice in ASD-relevant behavioral tests while they receive drug treatment, and will also perform histopathology assessment, including microglial activation and neuronal dendrites and spines.
Aim 1 as described in SOW is near completion.

Aim 2: **The effect of exposure in utero to anti-Caspr2 IgG on microglial activation state:** We will use single cell RNA-seq (scRNA-seq) to assess the transcriptional programming of hippocampal microglia from E15.5, E18.5, P21 and 8 week old male and female mice exposed in utero to anti-Caspr2 or Control IgG. We will also analyze microglia from mice treated with ACE inhibitors if we find that to be an effective therapeutic modality.
Aim 2 as described by SOW is in progress.

Aim 3: **To determine how anti-Caspr2 IgG mediates microglial activation:** Antibodies can cause inflammation through the effector functions of the Fc region of the antibody molecule such as antibody-dependent cell-mediated cytotoxicity (ADCC). We will therefore ask if anti-Caspr2 IgG activates microglia secondary to ADCC using Fc receptor (FcR) ɣ chain deficient mice.
The work on Aim 3 has not started.

Accomplishments under these goals:

Aim 1: The effect of Angiotensin Converting Enzyme (ACE) inhibitors on maternal anti-Caspr2 IgG induced ASD-like phenotype. Since large number of mice is required in this aim, we first tested whether captopril could ameliorate the neurological phenotype in mice exposed in utero to anti-Caspr2 IgG. To this aim, C57BL/6 female mice from Jackson Laboratories (Jax) were immunized with the extracellular region of human Caspr2; Control female mice were immunized with adjuvant only, as described in (1). Immunized mice were mated to unmanipulated male mice. At weaning, mice were marked by ear notch and mice from different litters born to dams exposed in utero to anti-Caspr2 (“Anti-Caspr2”) or Control IgG (“Control”) were grouped, so each cage has up to 5 mice (same sex and same in utero exposure), one from each litter. Each cage was randomly assigned to one of the treatment groups. Mice received daily injections (i.p.) of the ACE inhibitor, 5 mg/kg of captopril (BBB-permeable) or an equivalent volume of the appropriate vehicle (saline), beginning at 3 weeks of age continuing for 2 weeks. At 5 weeks of age, mice were sacrificed, and microglia reactivity was assessed based on colocalization of CD68 with Iba1, cell shape and Sholl analysis of microglial processes using immunohistochemistry and confocal microscopy quantification. We also examined the CA1 neuronal dendritic arborization and dendritic spine density by Golgi staining. We found that captopril suppressed microglial reactivity and ameliorated the reduction of dendrites and spines in the CA1 region of the hippocampus in Anti-Caspr2 males compared to vehicle-treated Anti-Caspr2 males (**Figure 1**). Anti-Caspr2 mice treated with captopril showed no statistically significant differences from Control mice (**Figure 1**). To rule out a possible peripheral effect of captopril, we repeated this experiment as described above, only this time Anti-Caspr2 male mice were treated with 5 mg/kg of captopril (BBB-permeable), 5 mg/kg of enalapril (BBB-impermeable), or an equivalent volume of the appropriate vehicle (saline), beginning at 3 weeks of age and continuing for 2 weeks. We found that Anti-Caspr2 male mice treated with enalapril, a BBB-impermeable ACE inhibitor, show microglial activation and reduced dendritic arborization and dendritic spine density in the hippocampus, similar to Anti-Caspr2 mice treated with saline (**Figure 2**) suggesting that captopril is acting on the brain rather than on the periphery to suppress microglia reactivity**.** Last, we immunized an additional cohort of mice and treated them with captopril or saline as described above. Treatment with captopril or saline initiated at 3 weeks of age and was sustained during behavioral assessment. Male Control and Anti-Caspr2 mice treated with captopril or saline were subjected to behavioral assessments, starting at 5 weeks of age. Handling (three 15-min sessions), aimed to familiarize

mice with the experimenters, was followed by an observational screen (2), an open field assay, and a reciprocal social interaction assay (3). We decided to focus on these tests as they are relevant to ASD-like phenotype in mice during juvenile/young adult age. We observed an increase in reciprocal social interaction time in Anti-Caspr2 mice treated with captopril. They exhibited more time socializing than did Anti-Caspr2 mice treated with saline, and similar time socializing to Control mice (**Figure 3**). Anti-Caspr2 mice were not different from Control in the open field test, suggesting that anxiety (time spent in the center of the arena) or alterations in mobility or exploration (total distance moved, moving velocity) cannot explain this phenotype.

Milestone achieved: Our data show unequivocally that captopril treatment can ameliorate ASD-like phenotype in male mice exposed in utero to anti-Caspr2 IgG. We are finishing up few additional analyses and believe that this will conclude the activity of this Aim as specified in SOW (Major task 1 subtasks 1-5).
Milestone achieved: I (LB) will present this data at the Synchrony Symposium 2023 (Brain Foundation) and at the annual Society for Neuroscience meeting this fall in a symposia entitled: "The Good, the Bad, and the Microglia: How Microglia Shape Brain Circuitry Across the Lifespan" on November 14th.

Aim 2: **The effect of exposure in utero to anti-Caspr2 IgG on microglial activation state.**
Since we found that captopril is an effective therapeutic modality, we assessed the microglial transcriptional profile from the hippocampus of male Control and Anti-Caspr2 mice treated with saline or captopril (SOW, Major task 2, subtask 9) which underwent the behavioral assessment in Aim 1 (n=3 per group, each mouse represents a unique litter). scRNA seq was run on the 10 X genomic platform at our Institute followed by library sequencing at the CSHL facility. Sequenced samples were processed using Cell ranger pipeline and aligned to the mouse reference genome. Quality control, selection of highly variable genes and PCA was performed using the Seurat R package. We filtered out cells that express below 1000 and exceed 3500 genes as well as cells that contain more than 5% mitochondrial reads. UMAP was created using significant PCs (n=30) and were subjected to batch correction using Harmony (theta = 0, sigma = 0.1). We selected cluster resolution of 1.25 based on mapping similarity to (4). Mapping our data to (4) and (5) allowed us to eliminate non-microglial cells (**Figure 4**) and to focus on microglial population. We next analyzed differentially expressed genes (DEGs) between Control and Anti-Caspr2 treated with saline and between Anti-Caspr2 treated with saline and Anti-Caspr2 treated with captopril using the General Linearized Model. We computed the number of DEGs that were downregulated by Anti-Caspr2 saline compared to Control saline and then upregulated by captopril treatment, and vice versa i.e. number of DEGs that were upregulated in Anti-Caspr2 saline mice and were downregulated by captopril treatment, significance of which is determined using p-values computed through hypergeometric testing (**Figure 4**). Since we wish to understand the changes in microglia and cells that interact with microglia, we are currently analyzing possible neuronal-microglial interactions using CellTalkDB database.
We have extracted hippocampus from E18.5 Anti-Caspr2 and Control and this is pending analysis SOW, (Major task 2, subtask 4).

Milestone achieved: This Major task is still undergoing**.** We will complete subtask 9 in the next few months and if successful we could suggest pathways that mediates the microglial state in Anti-Caspr2 mice treated with saline and captopril.

Aim 3: **To determine how anti-Caspr2 IgG mediates microglia activation.** Work is pending.

Training and professional development

1. Lab members were trained to use the IMARIS software and we recently implemented a new assessment tool to perform Sholl analysis on microglia in a more time efficient way.
2. Lab members and PI deepen their understanding in scRNA seq through one on one sessions with Dr. Arnon Arazi (an Assistant professor at the Feinstein Institute)
3. Lab members attended Society for Neuroscience annual meeting in November 2022.

Disseminated results to communities:

1. The PI (LB) gave a visitor professor seminar at University of Oklahoma Health Science Center on 02/28/2023. LB shared the data with faculty and trainees during the seminar and in further one on one discussions.

2. The PI (LB) gave a seminar in progress on 06/01/2023 to faculty and trainees of the Institute of Molecular Medicine at the Feinstein Institutes for molecular Medicine.
3. The PI (LB) communicated the data during STEM night for 4th-5th grade school students in Bayside, NYC on 03/10/2023.
4. The PI will present the data at the Synchrony Symposium 2023 (Brain Foundation) to be held on 21/10/23.
5. The PI will present the data at the annual Society for Neuroscience meeting to be held on 11/14/23 as part of symposia entitled: “The Good, the Bad, and the Microglia: How Microglia Shape Brain Circuitry Across the Lifespan”

During the Next reporting Period, I plan to:

1. Finalize Aim 1.
2. Continue the work on Aim 2 (SOW, major task 2).
3. Compile a manuscript which will include data from Aim 1 (SOW, major task 1) and the data described in Aim 2, scRNA seq analysis from mice treated with captopril (SOW major task 2, subtask 9).
4. Present the data as described above.
5. Initiate the studies described in Aim 3.

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Figure 1

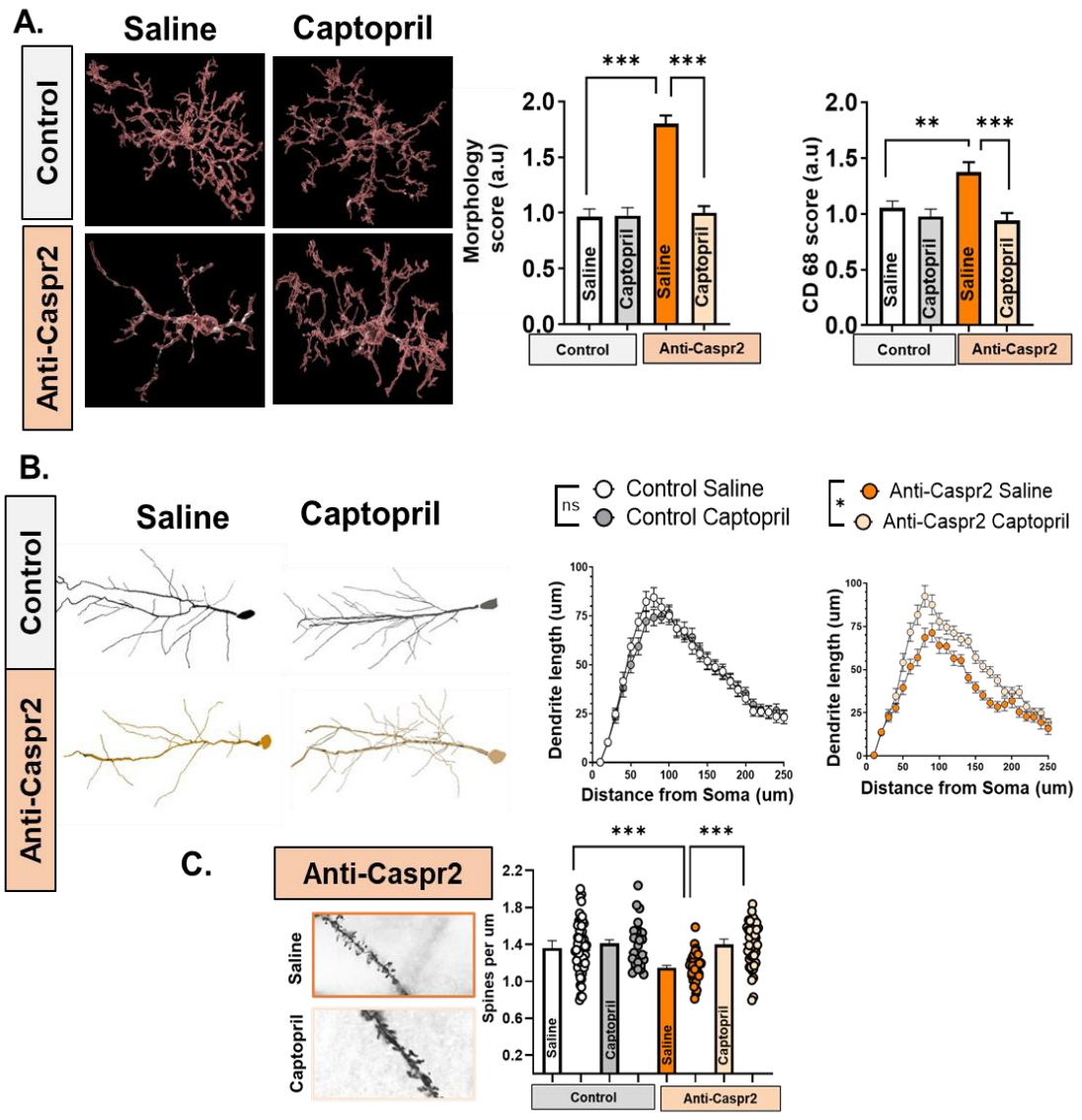

Figure 1: Anti-Caspr2 male mice treated with captopril show decreased microglial activation and increased dendritic complexity and dendritic spine density in the hippocampus. (A) Left panel, Imaris surface reconstructions of microglia from the stratum radiatum of Anti-Caspr2 and Control male mice treated with captopril or saline. Red-Iba1, White-CD68. Right panel, reduced number of processes (higher score) and increased CD68 signal (higher score) in Anti-Caspr2 mice treated with saline compared to captopril. Anti-Caspr2 treated with captopril were not different from Control mice. Control; saline or captopril, n = 9 in each group, representing 7 litters per group. Anti-Caspr2 ; saline, n= 6, captopril, n=7 representing 6 or 7 litters per group. 60-80 cells in each group). Mann-Whitney with multiple comparison correction. **(B)** Left panel, tracings of CA1 pyramidal neurons (Neurolucida, following Golgi staining) from 5 week old Control or Anti-Caspr2 mice treated with saline or captopril. Right panel, Quantification of dendritic trees (Sholl analysis) in Control or Anti-Caspr2 mice treated with captopril or saline, shows that captopril prevented the decrease in dendritic arborization in Anti-Caspr2 mice. No difference was seen between Anti-Caspr2 treated with captopril and Control mice. Number of neurons Control; Saline=60, Captopril =60 Anti-Caspr2; Saline=63, Captopril= 50. Mixed model analysis, * P < 0.05, ICC=8%. **(C)** Left panel, representative images of dendritic spines from Anti-Caspr2 mice treated with saline or captopril. Right panel analysis of the average number of spines per dendritic length in each mouse. Student t test, with multiple comparison correction. Dots represent individual dendrites from which spines were counted. **(B-C)** 5-6 mice in each group, each representing a unique litter. *P<0.5, **P<0.005, ***P<0.0005.

Figure 2

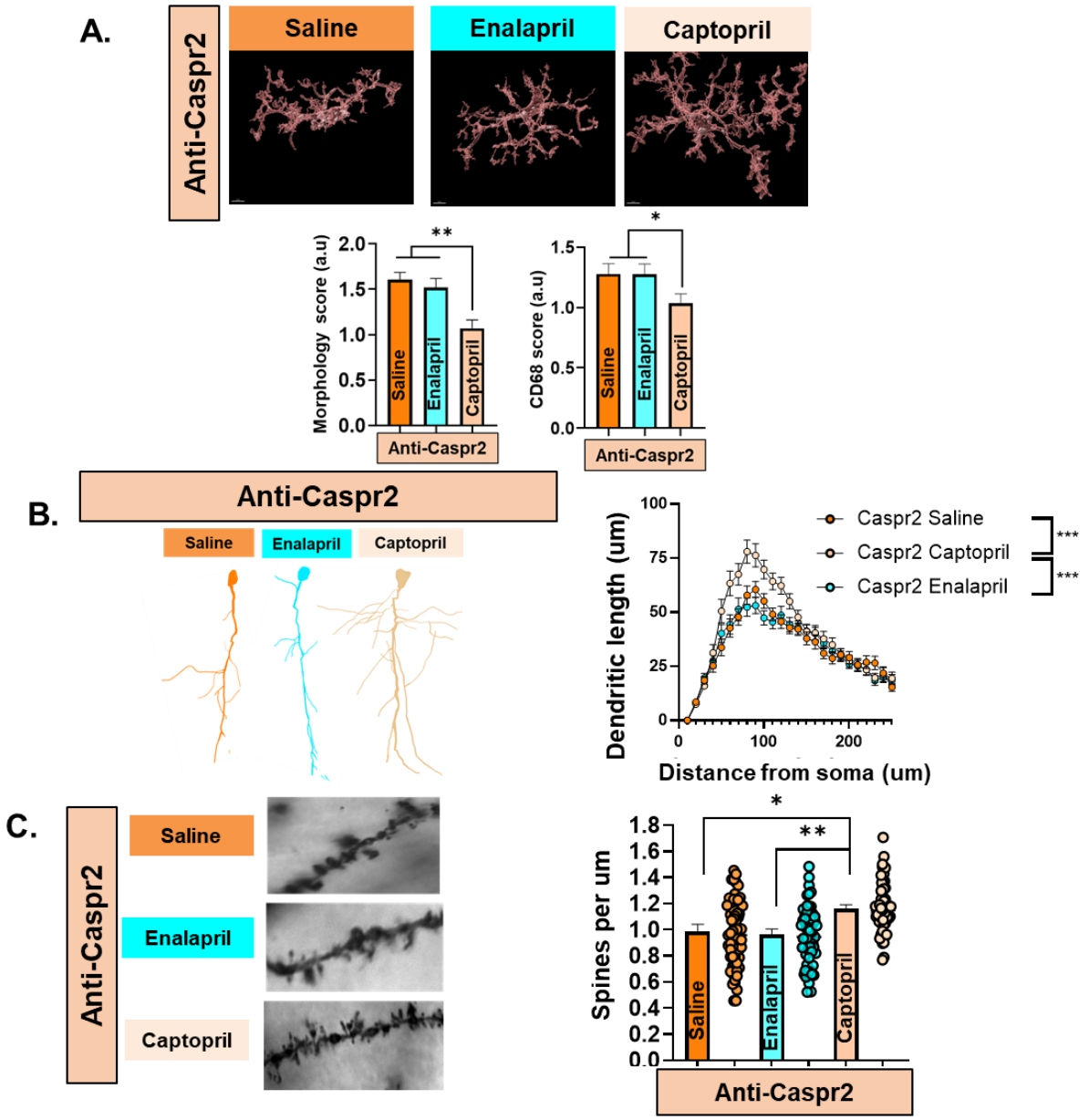

Figure 2: Anti-Caspr2 male mice treated with enalapril, a BBB-impermeable ACE inhibitor, show microglial activation and reduced dendritic complexity and dendritic spine density in the hippocampus, suggesting that captopril is acting on the brain rather on the periphery to suppress microglia reactivity. (A) Top panel, Imaris surface reconstructions of microglia from stratum radiatum from Anti-Caspr2 male mice treated with saline, enalapril or captopril. Red-Iba1, White-CD68. Bottom panel, reduced number of processes (higher score) and increased CD68 signal in Anti-Caspr2 mice treated with saline or enalapril compared to Anti-Caspr2 mice treated with captopril. n = 4 in each group, representing 4 litters per group. 40 cells in each group). Mann-Whitney with multiple comparison correction. **(B)** Left panel, tracings of CA1 pyramidal neurons (Neurolucida, following Golgi staining) from 5 week old Anti-Caspr2 mice treated with saline, enalapril or captopril. Right panel, quantification of dendritic trees (Sholl analysis) in Anti-Caspr2 mice treated with saline, enalapril or captopril shows that captopril prevented the decrease in dendritic arborization in Anti-Caspr2 mice. No difference was seen between Anti-Caspr2 treated with saline and enalapril. 50 neurons per group, 5 mice in each group, each represents a unique litter. Mixed model analysis, saline versus captopril ICC=1.8%, enalapril versus captopril ICC=1.6% **(C)** Left panel, representative images of dendritic spines from Anti-Caspr2 mice treated with saline, enalapril or captopril. Right panel analysis of the average number of spines per dendritic length in each mouse. Student t test, with multiple comparison correction. Dots represent individual dendrites from which spines were counted. 5-6 mice in each group, each represents a unique litter. *P<0.05, **P<0.005, ***P<0.0005.

Figure 3

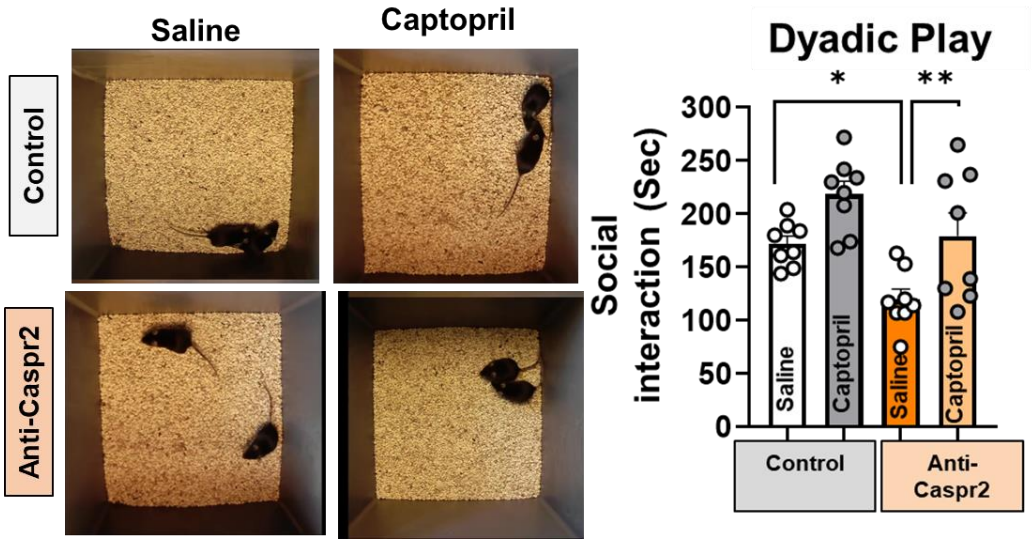

Figure 3: Captopril treatment improves social interaction in Anti-Caspr2 male mice. Left panel, Representative snapshot images from the dyadic play. **Right panel**, Bar plot of total time of reciprocal social interaction. Each dot represents the interaction time of a pair of mice from the same exposure and the same treatment. (In each group: 8 pairs, each mouse represents a unique litter). One way ANOVA followed by post hoc analysis, *<0.05, **<0.005.

Figure 4

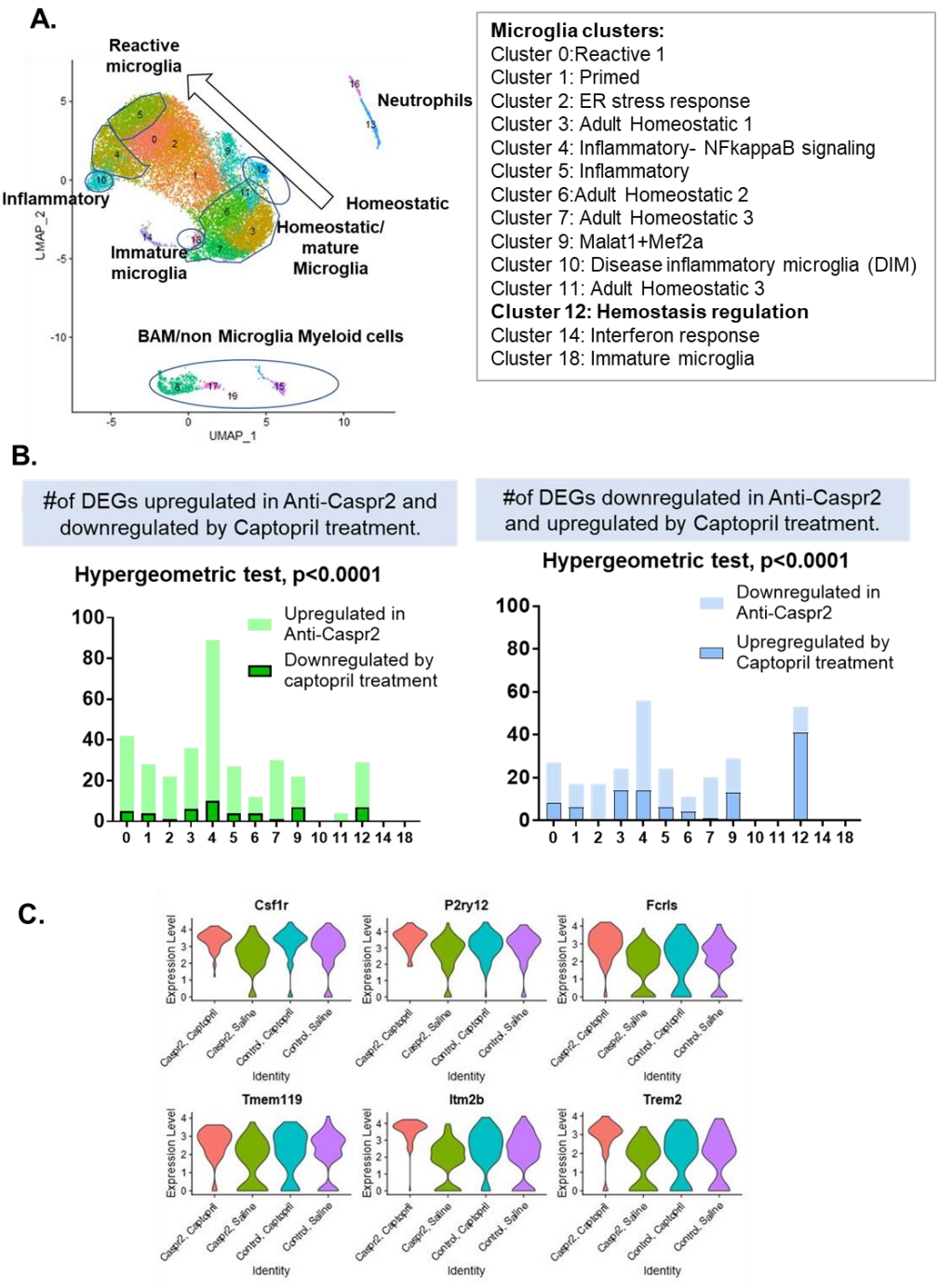

Figure 4: Single cell RNA sequencing of adult hippocampus shows that treatment with captopril reverse some of the transcriptional changes of microglia in Anti-Caspr2 male mice. (A) UMAP of all cells sequenced from Anti-Caspr2 treated with captopril, Anti-Caspr2 treated with saline, Control treated with captopril and Control treated with saline. 3 mice in each group, each represents unique litter (n=20,055 cells). Cells were mapped according to Silvin et al. and Hammond et al. **(B)** Bar plots representing the total number of differentially expressed genes (DEGs) (FDR<0.05) by cluster between Anti-Caspr2 and Control mice treated with saline (light color), and out of these DEGs, the number of genes in which captopril treatment reversed the effect in Anti-Caspr2 mice. **Left panel,** number of DEGs upregulated in Anti-Caspr2 saline compared to Control saline that were downregulated by Captopril treatment in Anti-Caspr2 mice. **Right panel,** number of DEGs downregulated in Anti-Caspr2 saline compared to Control saline that were upregulated by Captopril treatment in Anti-Caspr2 mice. Significance of overlapping DEGs was computed using hypergeometric testing. Note that in cluster 12 most DEGs that were downregulated in Anti-Caspr2 treated with saline compared to Control saline, were reversed upon treatment with captopril. **(C)** Violin plots of normalized log-expression values for representative homeostatic genes significantly downregulated in Anti Caspr2 mice treated with saline
and upregulated in AntiCaspr2 treated with captopril from cluster 12.

IMPACT

Impact on the development of the principal discipline(s) of the project:

1. Understanding the role of maternal anti-brain reactive antibodies: The proposal is built upon previous findings that suggest up to 20% of ASD cases may be attributable to maternal anti-brain Abs. By elucidating the impact of these antibodies on fetal brain development and ASD-like phenotypes, the proposal is aimed to shed light on a previously overlooked aspect of ASD etiology. This research has the potential to influence diagnostic and screening protocols for ASD and improve our understanding of the interplay between genetic and environmental factors in its development.

2. Potential Therapeutic Strategies: The proposal is aimed to explore microglia as targets for potential therapeutic strategies in ASD by studying whether ACE inhibitors can suppress microglial reactivity. If successful, this research could pave the way for future clinical trials and the development of new treatments that target microglial activation in ASD.

3. Translational Impact: The findings from this proposal have the potential to translate into clinical applications. Understanding how in utero exposure to anti-brain antibodies leads to persistent neurological abnormalities and identifying strategies to prevent this outcome could have significant implications for prenatal care and interventions aimed at reducing the risk of ASD. Additionally, the study's focus on microglia as a therapeutic target opens up the possibility of repurposing existing FDA-approved drugs for ASD treatment. This translational impact could lead to the development of more accessible and effective therapeutic options for individuals with ASD.

Impact on other disciplines:

This proposal is aimed to understand whether the ACE inhibitor captopril suppresses the harmful effects of microglia. Understanding of how captopril ameliorates the ASD phenotypes could have important implications for treating as a range of neurological and psychiatric disorders that are associated with alterations in microglia.

Impact on technology transfer

At this point there in nothing to report.

Impact on society beyond science and technology

At this point there in nothing to report.

CHANGES/PROBLEMS

Nothing to report.

PRODUCTS

Expert review:
Bagnall-Moreau, C, Spielman, B and Brimberg, L (2023): Maternal brain reactive antibodies profile in autism spectrum disorder: an update. Translational Psychiatry 13(1):37. PMID: 36737600 PMCID: PMC9898547.

Poster presentation:

Ben Spielman, Ciara Bagnall-Moreau, Christian Cruz & Lior Brimberg: The ACE Inhibitor Captopril May Lead to Reduced Microglial Activation in a Mouse Model of ASD Induced by In Utero Exposure to Maternal Anti-Caspr2 IgG. Society For Neuroscience, San Diego, November 2022.

Oral presentation:

Lior Brimberg: Can Maternal Autoantibodies Play an Etiological Role in Neurodevelopmental Disorders?. A visitor professor seminar at University of Oklahoma Health Science Center, February 2023.

Lior Brimberg: The Role of Maternal Autoantibodies in Neurodevelopmental Disorders. Seminar in progress, Institute of Molecular Medicine, Feinstein Institutes for molecular Medicine, June 2023.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATION

Name:	Lior Brimberg
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	3
Contribution to Project:	Direct the research, help conducting experiments, supervising lab members
Funding Support:	DOD W81XWH-22-1-0880

Name:	Jane Cerise
Project Role:	Biostatistician
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	1
Contribution to Project:	Helping with statistical analysis
Funding Support:	DOD W81XWH-22-1-0880

Name:	Ben Spielman
Project Role:	MD/PhD candidate
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	8
Contribution to Project:	Ben led the study described in Aim 1.
Funding Support:	NIH T32 5T32AI155392

Name:	Cristian Cruz
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	
Nearest person month worked:	6
Contribution to Project:	Cristian is assisting with all mice work. Cell culture, histology, and lab maintenance.
Funding Support:	DOD W81XWH-22-1-0880

Change in the active other support of the PD/PI(s) or senior/key personnel

Nothing to report

APPENDICES

N/A