

Rowan University

## Rowan Digital Works

---

Stratford Campus Research Day

26th Annual Research Day

---

May 5th, 12:00 AM

# A Preliminary Report: The Hippocampus and Surrounding Temporal Cortex of Patients With Schizophrenia Have Impaired Blood-Brain Barrier

Eric L. Goldwaser

*University of Maryland - Baltimore*

Randel L. Swanson

*Corporal Michael J. Crescenz VA Medical Center*

Edgardo J. Arroyo

*Corporal Michael J. Crescenz VA Medical Center*

Venkat Venkataraman

*Rowan University*

Mary C. Kosciuk

Follow this and additional works at: [https://rdw.rowan.edu/stratford\\_research\\_day](https://rdw.rowan.edu/stratford_research_day)

Rowan University



Part of the [Cardiovascular System Commons](#), [Medical Neurobiology Commons](#), [Neurology Commons](#), [Neuroscience and Neurobiology Commons](#), [Pathological Conditions, Signs and Symptoms Commons](#), [See next page for additional authors](#) and the [Psychiatry Commons](#)

Let us know how access to this document benefits you - share your thoughts on our [feedback form](#).

---

Goldwaser, Eric L.; Swanson, Randel L.; Arroyo, Edgardo J.; Venkataraman, Venkat; Kosciuk, Mary C.; Nagele, Robert G.; Hong, L. Elliot; and Acharya, Nimish K., "A Preliminary Report: The Hippocampus and Surrounding Temporal Cortex of Patients With Schizophrenia Have Impaired Blood-Brain Barrier" (2022). *Stratford Campus Research Day*. 11.

[https://rdw.rowan.edu/stratford\\_research\\_day/2022/May5/11](https://rdw.rowan.edu/stratford_research_day/2022/May5/11)

This Poster is brought to you for free and open access by the Conferences, Events, and Symposia at Rowan Digital Works. It has been accepted for inclusion in Stratford Campus Research Day by an authorized administrator of Rowan Digital Works.

---

**Author(s)**

Eric L. Goldwaser, Randel L. Swanson, Edgardo J. Arroyo, Venkat Venkataraman, Mary C. Kosciuk, Robert G. Nagele, L. Elliot Hong, and Nimish K. Acharya

# A Preliminary Report: The Hippocampus and Surrounding Temporal Cortex of Patients With Schizophrenia Have Impaired Blood-Brain Barrier

Eric L. Goldwaser<sup>1</sup>, Randel L. Swanson<sup>2-3</sup>, Edgardo J. Arroyo<sup>2-3</sup>, Venkat Venkataraman<sup>4</sup>, Mary C. Kosciuk<sup>5</sup>, Robert G. Nagele<sup>5</sup>, L Elliot Hong<sup>1</sup>, and Nimish K. Acharya<sup>2,5,6</sup>

1. Department of Psychiatry, Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD. 2. Center for Neurotrauma, Neurodegeneration, and Restoration, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA. 3. Dept. of PMR, Perlman School of Medicine, University of Pennsylvania, Philadelphia, PA. 4. Dept. of Academic Affairs Rowan University SOM, Stratford, NJ. 5. Dept. of Geriatrics and Gerontology, NJISA, Rowan University SOM, Stratford, NJ. 6. Dept. of Cell Biology and Neuroscience, Rowan University SOM, Stratford, NJ.

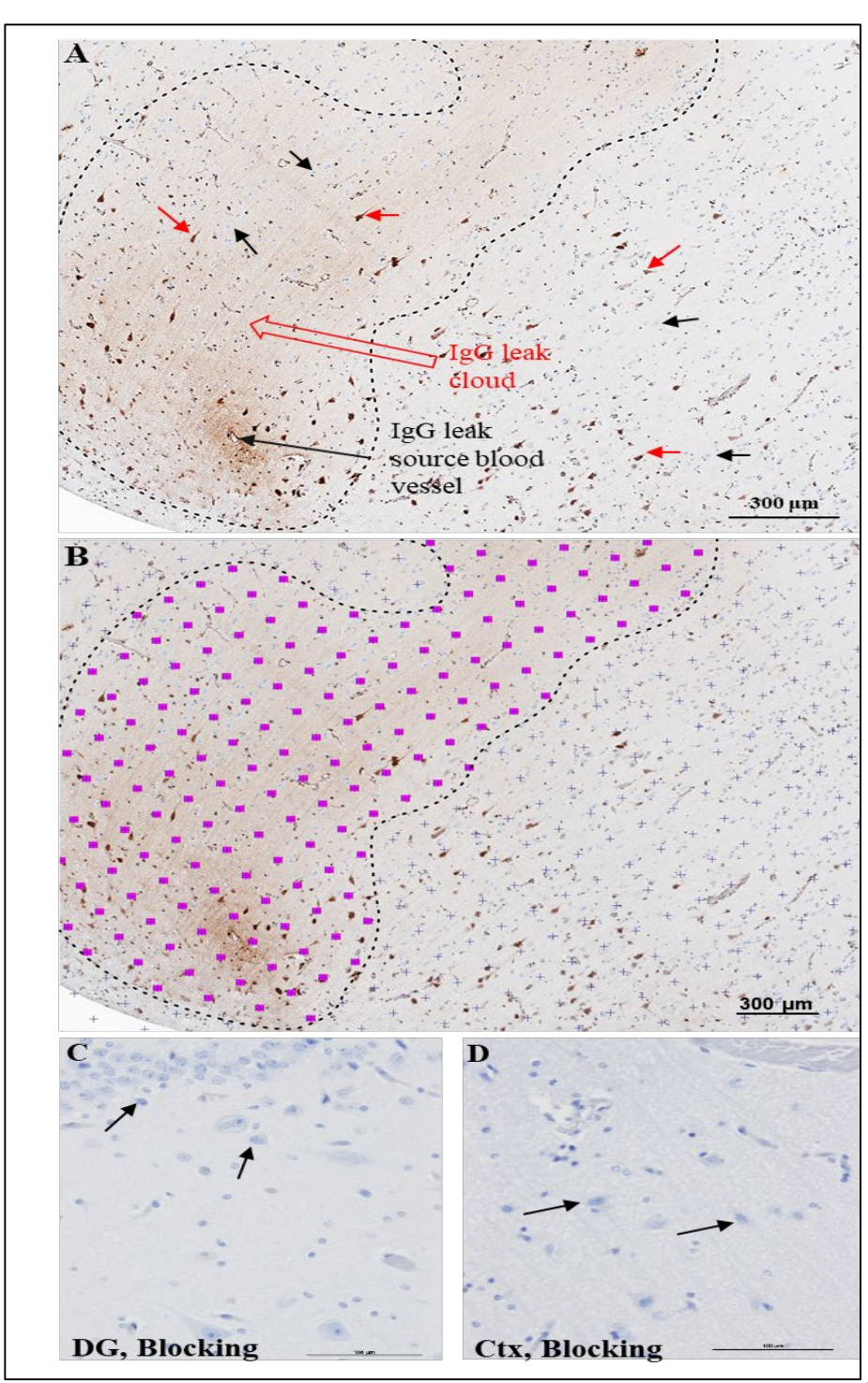
## Introduction

Schizophrenia (SZ) is one of the most severe forms of mental illness, yet mechanisms remain unclear. A widely established brain finding in SZ is hippocampal atrophy, and a coherent explanation similarly is lacking. Epidemiological evidence suggests increased cerebrovascular and cardiovascular complications in SZ independent of lifestyle and medication, pointing to disease-specific pathology. Endothelial cell contributions to blood-brain barrier (BBB) compromise may influence neurovascular unit and peripheral vascular function, and we hypothesize that downstream functional and structural abnormalities may be explained by impaired BBB.

## Methods

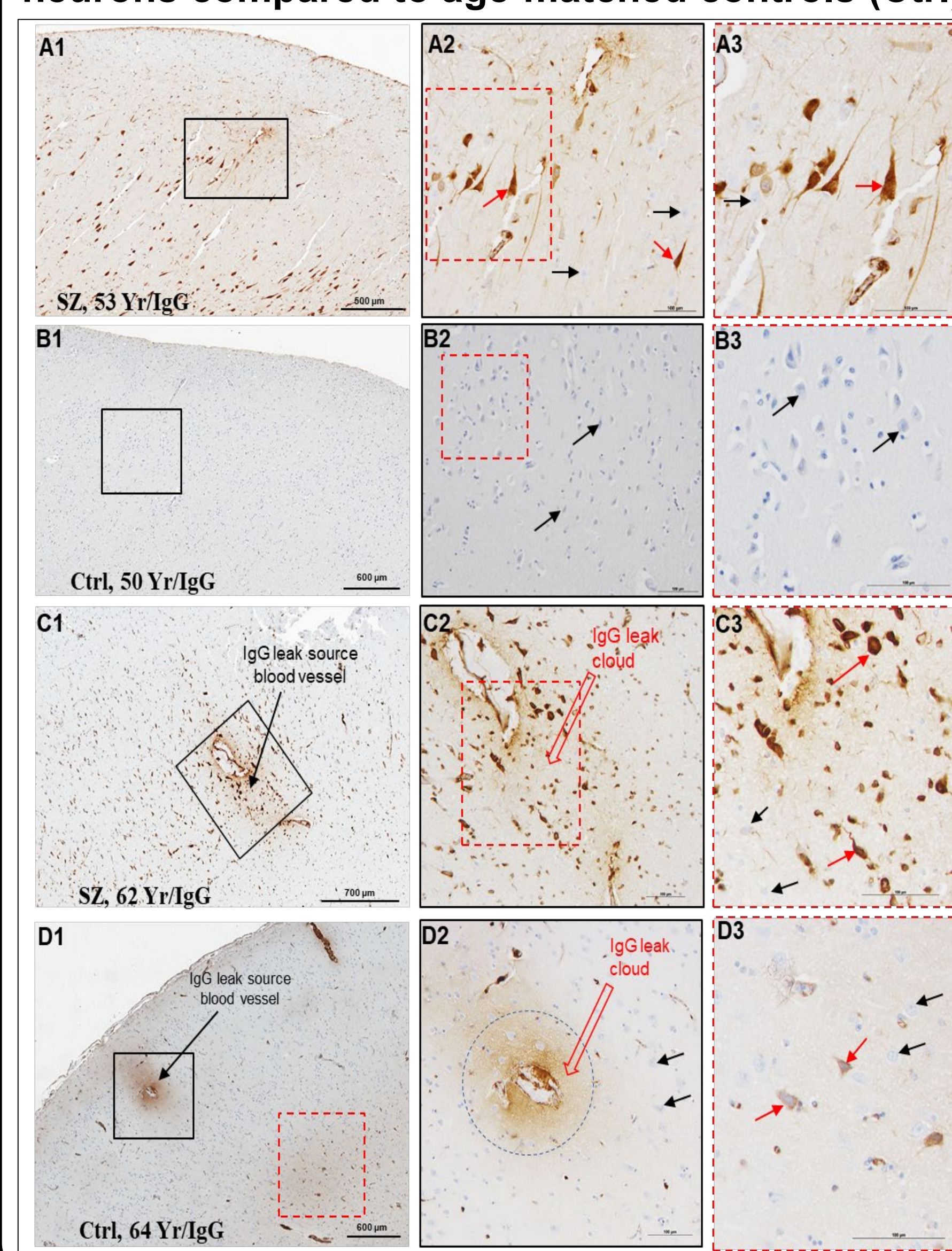
### Fig 1. Semi-quantitative approach to quantify BBB breach extent.

Postmortem samples of human hippocampus sections (n=27 controls, n=25 SZ) were obtained from the NIH NeuroBioBank and Maryland Brain Collection, that were age, gender, race, and postmortem interval frequency-matched. Leakage phenomena was observed using a secondary IgG-only (Vector Laboratories, 1:250) staining technique, to demonstrate endogenous IgG extravasation, a marker of BBB compromise. IgG leak was quantified using unbiased stereology (MBF Bioscience, VT). Analyses was corrected for multiple comparisons using false discovery rate with  $q < 0.05$  where applicable.

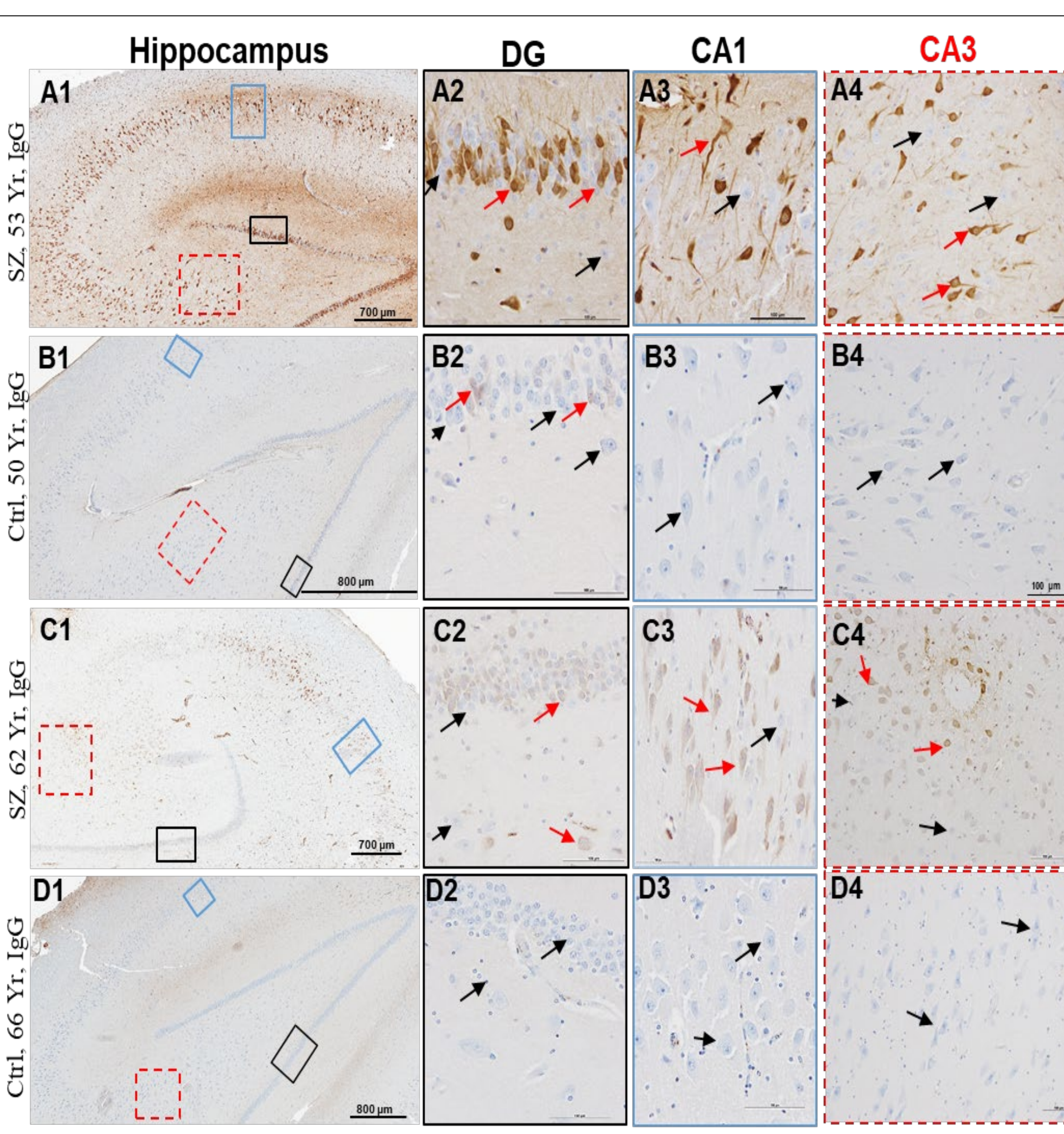


## Results

### Fig 2. Temporal cortex near hippocampus of SZ patients demonstrated increased BBB permeability and selective interaction between IgGs and pyramidal neurons compared to age-matched controls (Ctrl).



### Fig 3. Hippocampus proper of SZ patients demonstrated increased BBB permeability and selective interaction between IgGs and neurons compared to age-matched controls (Ctrl).



### Fig 4. Comparison of the extent of BBB breakdown in the hippocampus and surrounding temporal cortex of the SZ and Ctrl subjects with respect to diagnosis, age, and sex.

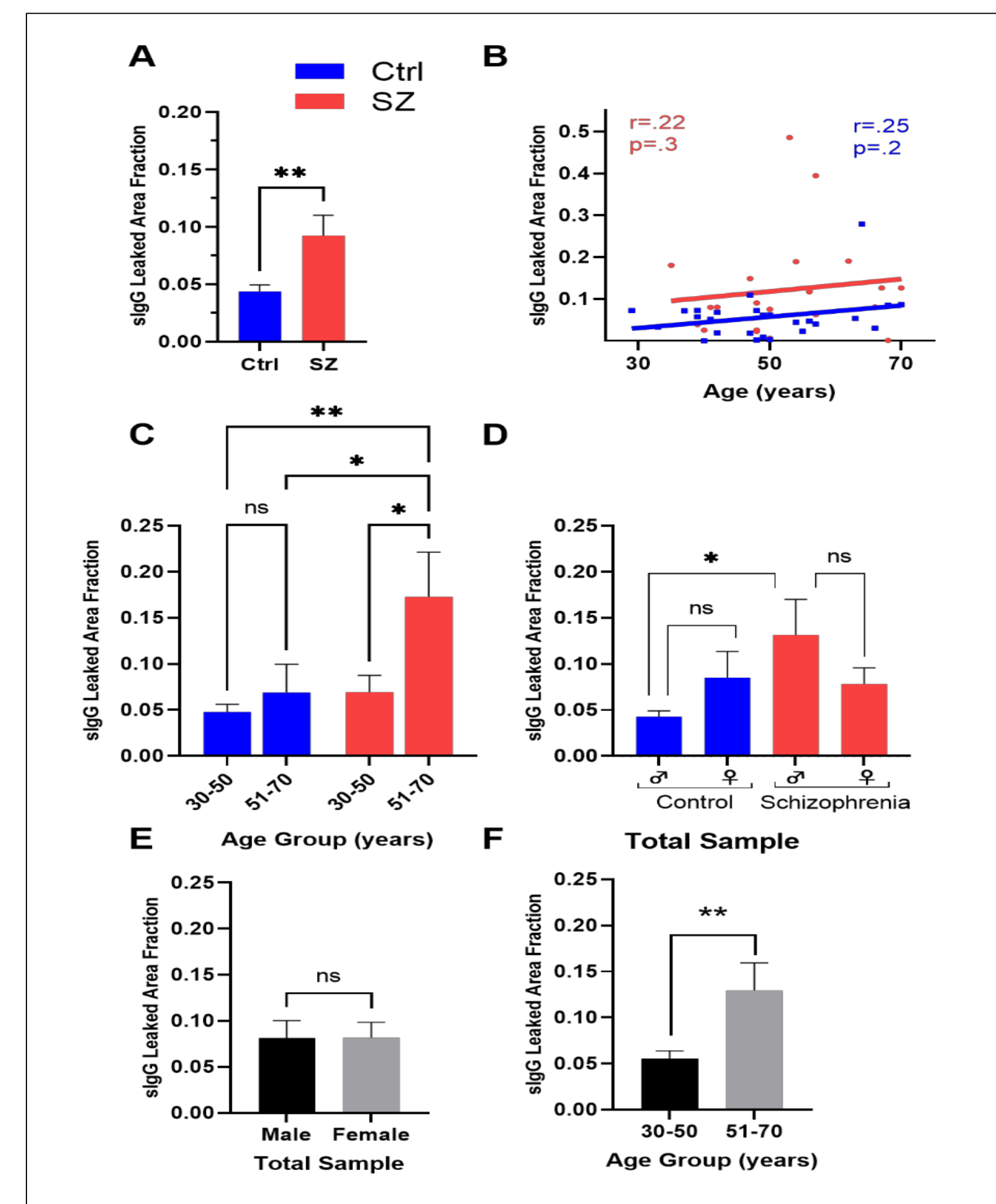
Postmortem samples demonstrated 11% BBB leakage in SZ compared to 5% in controls ( $t_{50} = -2.3, p = 0.02$ ).

Linear regression was performed to determine age, sex, and PMI in addition to diagnosis as predictors of BBB leak, and the model remained significant ( $F_{4,47} = 3.0, p = 0.03$ ) with a significant diagnosis ( $t = 3.3, p = 0.002$ ) but no significant age ( $p = 0.5$ ), sex ( $p = 0.2$ ), or PMI ( $p = 0.5$ ) effects.

We further explored the impact of age on BBB permeability by splitting our sample population in two age-groups, **30-50** or **50-70** years-old, based on mean and medians.

BBB leak fraction was also significantly increased in older aged schizophrenics vs controls ( $t_{39} = 2.5, p = 0.02$ ).

We found no significant sex difference in BBB permeability in the combined sample ( $p = 0.99$ ), however, there was a significant increase in BBB permeability only in male schizophrenia subjects compared to male control subjects ( $t_{57} = 2.7, p = 0.009$ ) on post-hoc analysis, while females did not ( $p = 0.9$ ), with a diagnosis x sex interaction ( $p = 0.03$ ).



## Conclusions

- 1) A significantly higher incidence of IgG leak was shown in schizophrenia patients compared to controls. This suggests that the hippocampus and surrounding temporal cortex of the patients with Schizophrenia have impaired blood-brain barrier (BBB).
- 2) Extravasated IgGs selectively interacted with the neurons and neuropil in the regions of BBB breakdown irrespective of pathological state.
- 3) Area fraction of IgG may be a useful tool to gauge BBB deficits.
- 4) BBB permeability progressively increases with age.

## Propose that

1. BBB dysfunction and IgG autoantibodies could be the two key missing pathoetiological links underwriting schizophrenia hippocampal damage.
2. Future research should target peripheral endothelial vascular systems using live imaging and BBB neuroimaging in patients with schizophrenia to conclusively evaluate the observations from this preliminary report.

## Research Support & Acknowledgements

1. ELG is supported by the University of Maryland / Sheppard Pratt Physician-Scientist Training Program with protected time and funding to engage in research.
2. Osteopathic Heritage Foundation Endowment for Primary Care Research. 2020. Rowan University School of Osteopathic Medicine, New Jersey.
3. NJISA, Startup Funds Provided to the PI (NKA).

Manuscript published in Frontiers in Human Neuroscience, March 2022. PMID: 35431844.

## Clinical Demographics and Tissue Characteristics.

	Control (n=27)	SZ (n=25)	Test statistic	p-value	
Demographics	Age [years] (SD)	51.8 (13.4)	56.9 (14.6)	$t = -1.3$	0.2
	Sex (% male)	58%	56%	$\chi^2 = 0.2$	0.9
	Race % (C/AA)	20 / 7	17 / 8	$\chi^2 = 0.2$	0.6
Section Characteristics	PMI [hours] (SEM)	14.5 (1.0)	11.9 (1.3)	$t_{50} = 1.6$	0.12
	Average section surface area ( $\mu\text{m}^2$ ) (SEM)	$1.8 \cdot 10^8$ ( $1 \cdot 10^7$ )	$1.6 \cdot 10^8$ ( $1 \cdot 10^7$ )	$t_{50} = 1.4$	0.17
	sIgG Leaked Area Fraction ( $\mu\text{m}^2$ ) (SEM)	$8.9 \cdot 10^6$ ( $2 \cdot 10^6$ )	$1.5 \cdot 10^7$ ( $3 \cdot 10^6$ )	$t_{50} = -1.9$	0.06
	Fraction of sIgG Leaked Area	0.05 (.01)	0.11 (.02)	$t_{50} = -2.3$	0.02
	Fraction (SEM)	0.047 (.02) <sup>a</sup>	0.12 (0.2) <sup>a</sup>	$F_{1,48} = 7.3^a$	0.009

SD – Standard deviation; C – Caucasian; AA – African American; PMI-Postmortem Interval; SEM-Standard Error of Mean