Toward Treatment of Lupus Cognitive Dysfunction

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December 8, 2022

Icahn School of Medicine at Mount Sinai

Financial Disclosures

None.

Objectives

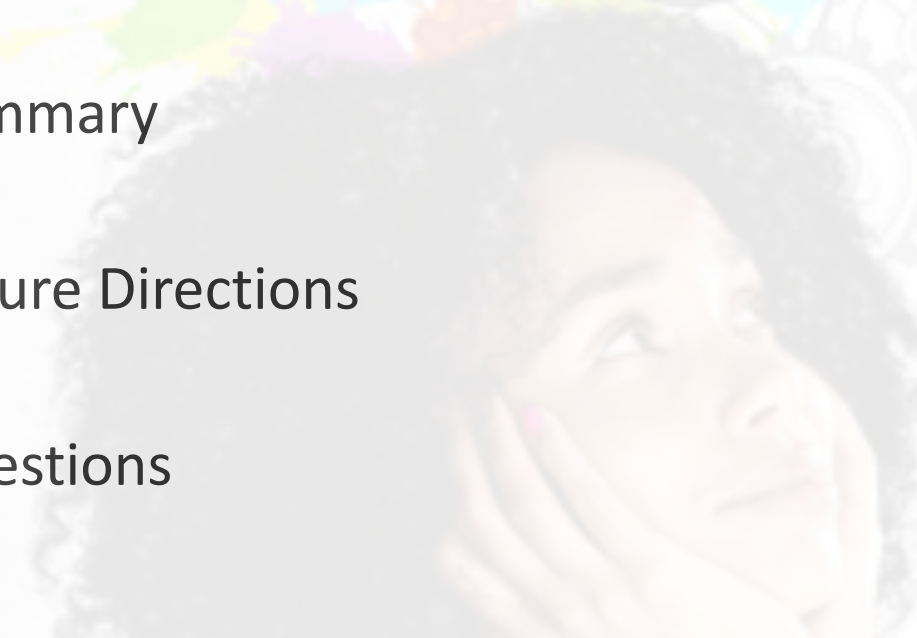
1. To appreciate the impact of SLE-cognitive dysfunction on patients.

2. To understand select promising mechanisms of SLE-associated cognitive dysfunction.

3. To discuss our recent publication highlighting avenues to be further explored for treatment of SLE-cognitive dysfunction.

Outline

1. Background
2. Association of Mycophenolate and Azathioprine Use with Cognitive Function in Systemic Lupus
3. Summary
4. Future Directions
5. Questions



https://dictionaryblog.cambridge.org/2022/09/14/thinking-outside-the-box-talking-about-creativity/

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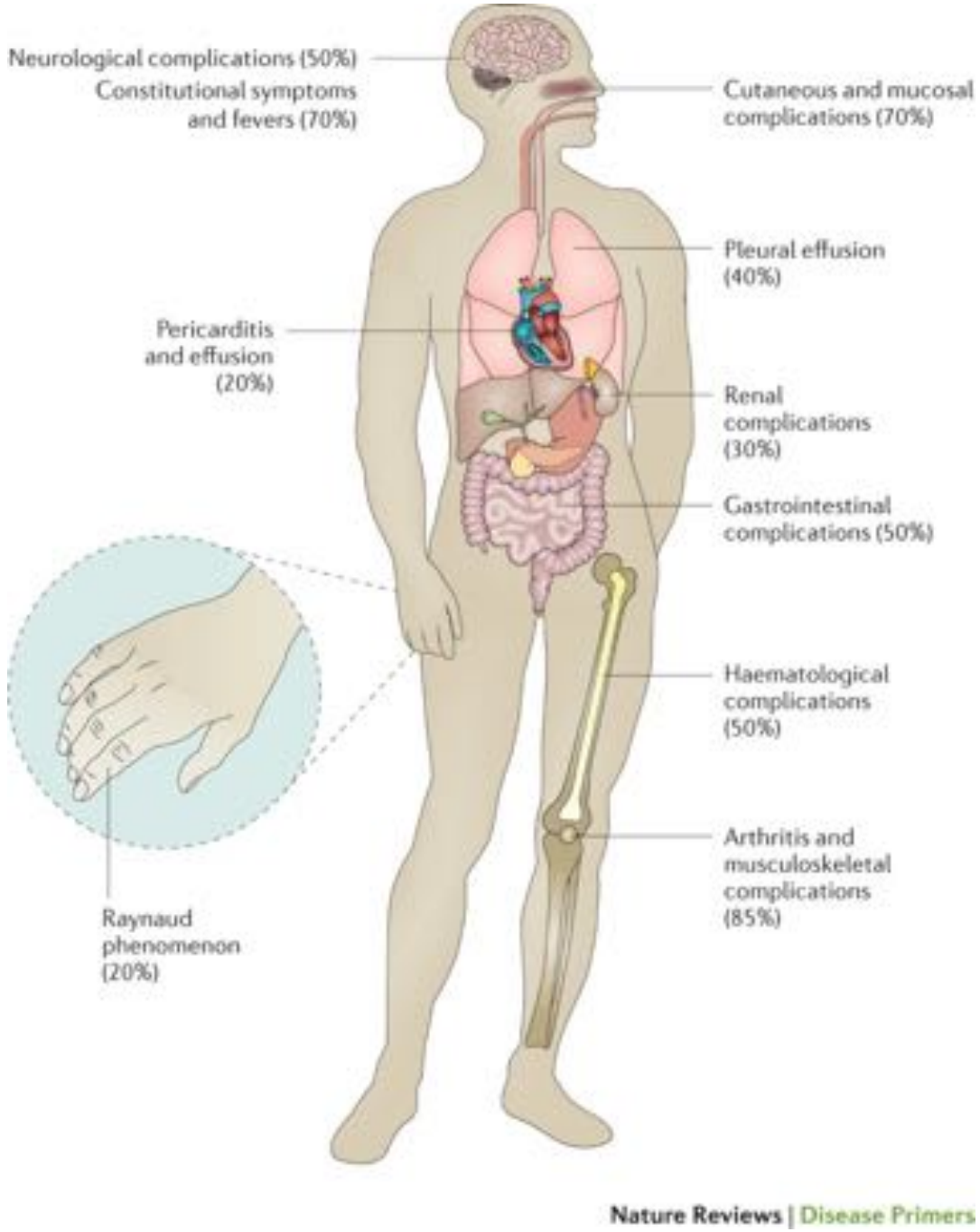
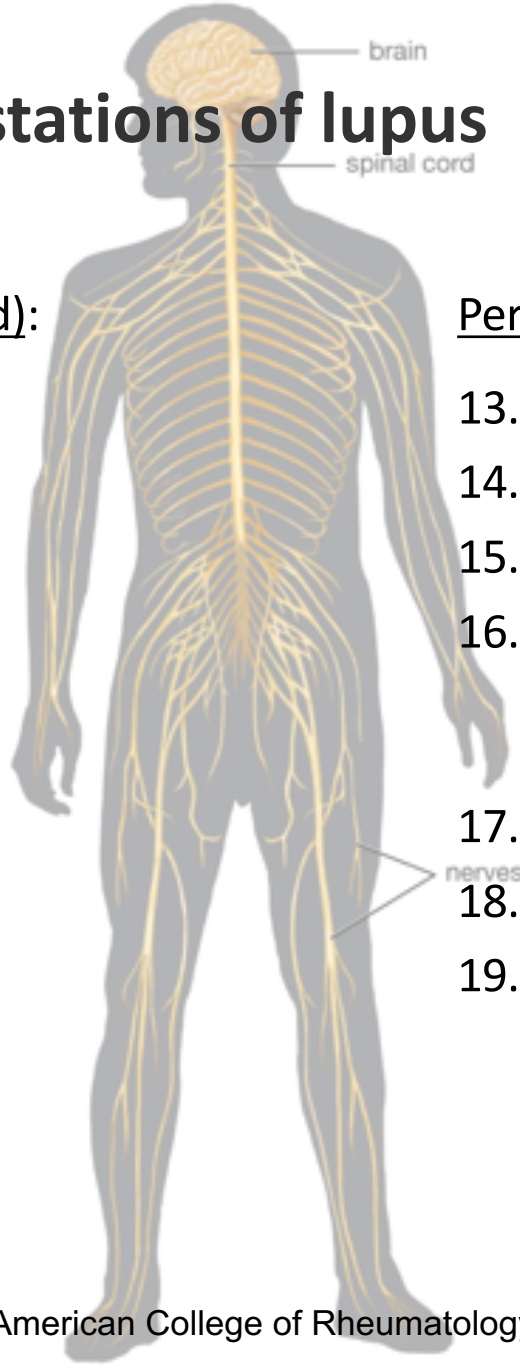
Systemic Lupus (SLE)

- Frequently affects the central nervous system (CNS).

- No guidelines for screening and no approved treatments.



19 nervous system manifestations of lupus



<u>Central nervous system (brain / spinal cord)</u>:

1. Headache
2. Mood disorder
3. Anxiety disorder
4. **Cognitive dysfunction**
5. Psychosis
6. Acute confusional state
7. Aseptic meningitis
8. Movement disorder
9. Seizure disorders
10. Cerebrovascular disease
11. Demyelinating syndrome
12. Myelopathy

<u>Peripheral nervous system</u>:

13. Mononeuropathy
14. Polyneuropathy
15. Cranial neuropathy
16. Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)
17. Plexopathy
18. Autonomic disorder
19. Myasthenia gravis

Ainiala H, Hietaharju A, Loukkola J, et al. Validity of the new American College of Rheumatology criteria for neuropsychiatric lupus syndromes: a population-based evaluation. *Arthritis Rheum* 2001; 45: 419-423.

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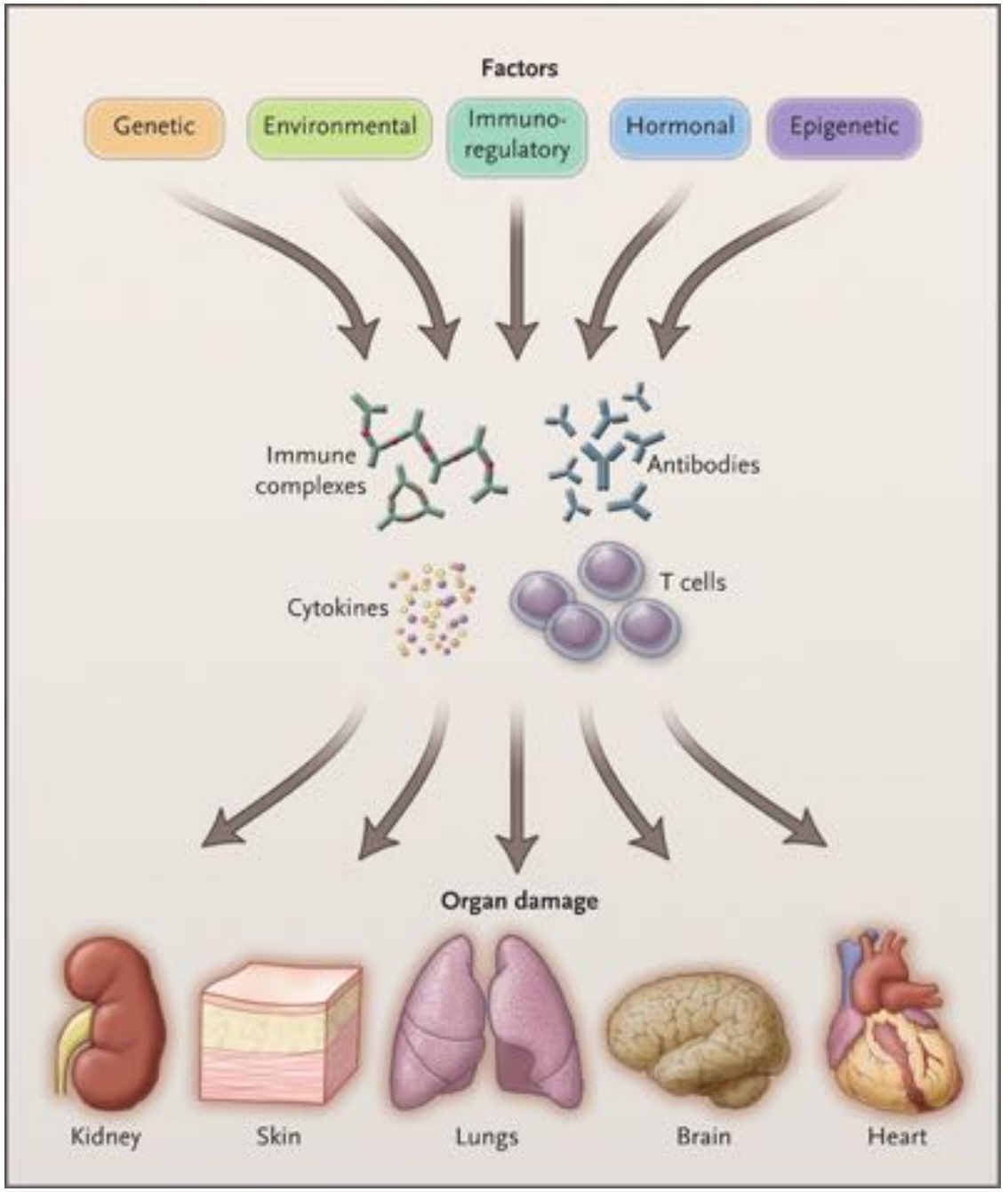
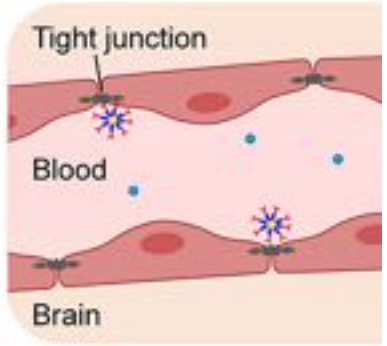
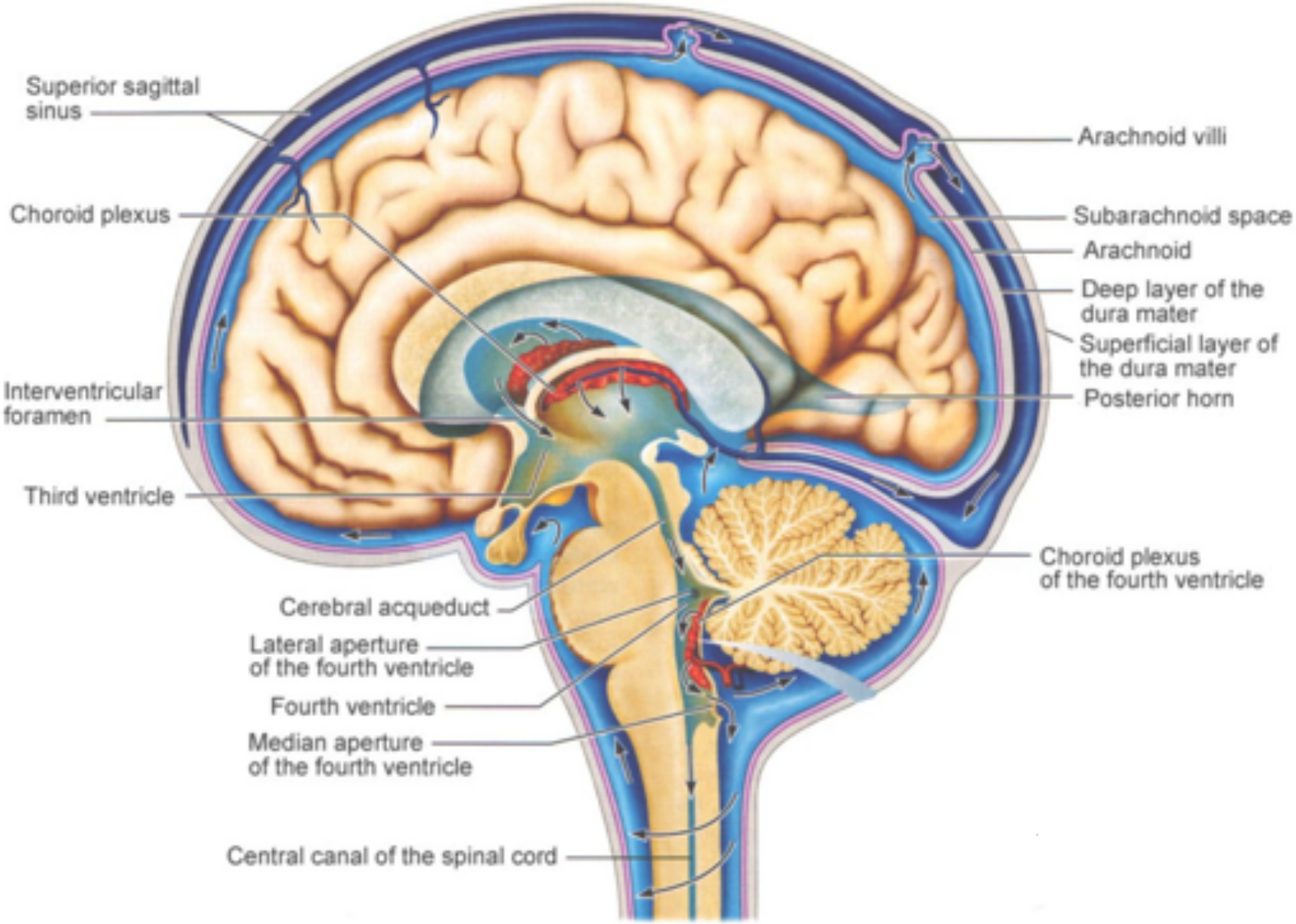
Etiology of SLE is Complex



George C. Tsokos. Systemic Lupus Erythematosus. N Engl J Med 2011; 365:2110-2121

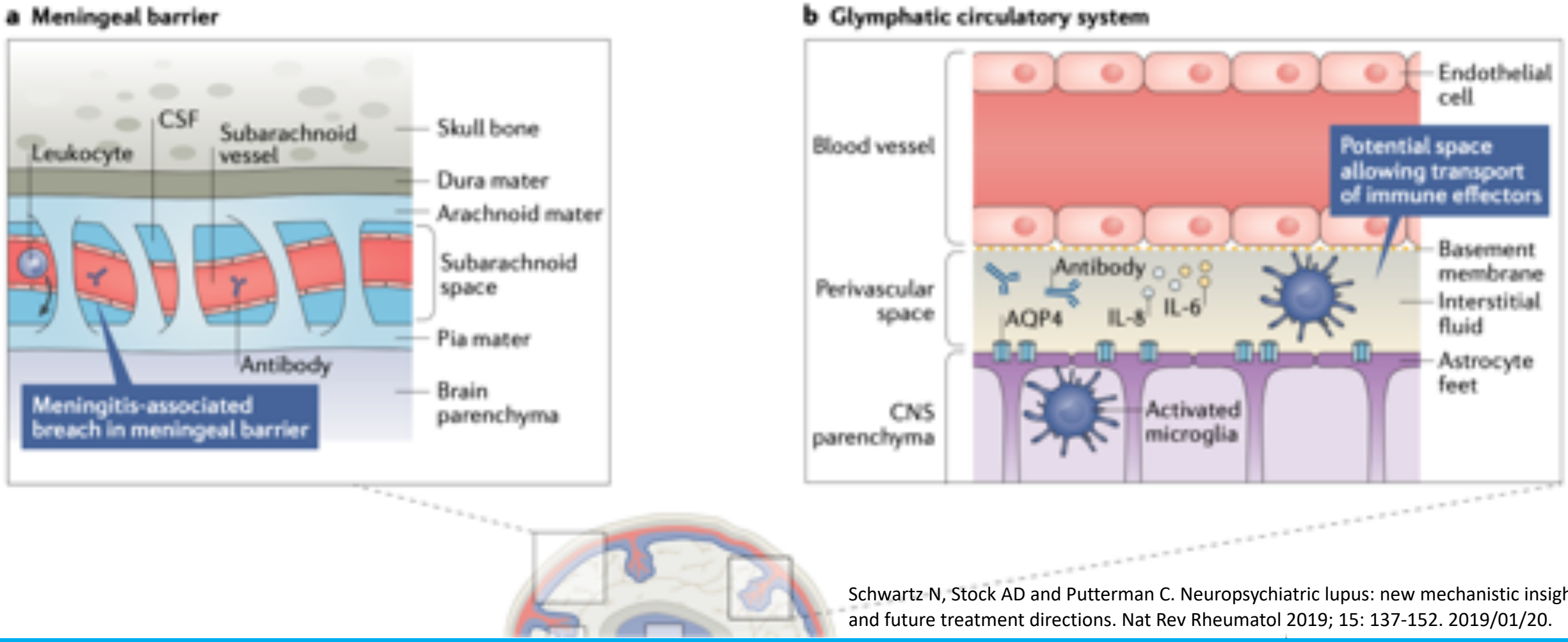
CNS previously considered **immune privileged** (protected) due to the blood-brain-barrier (BBB).



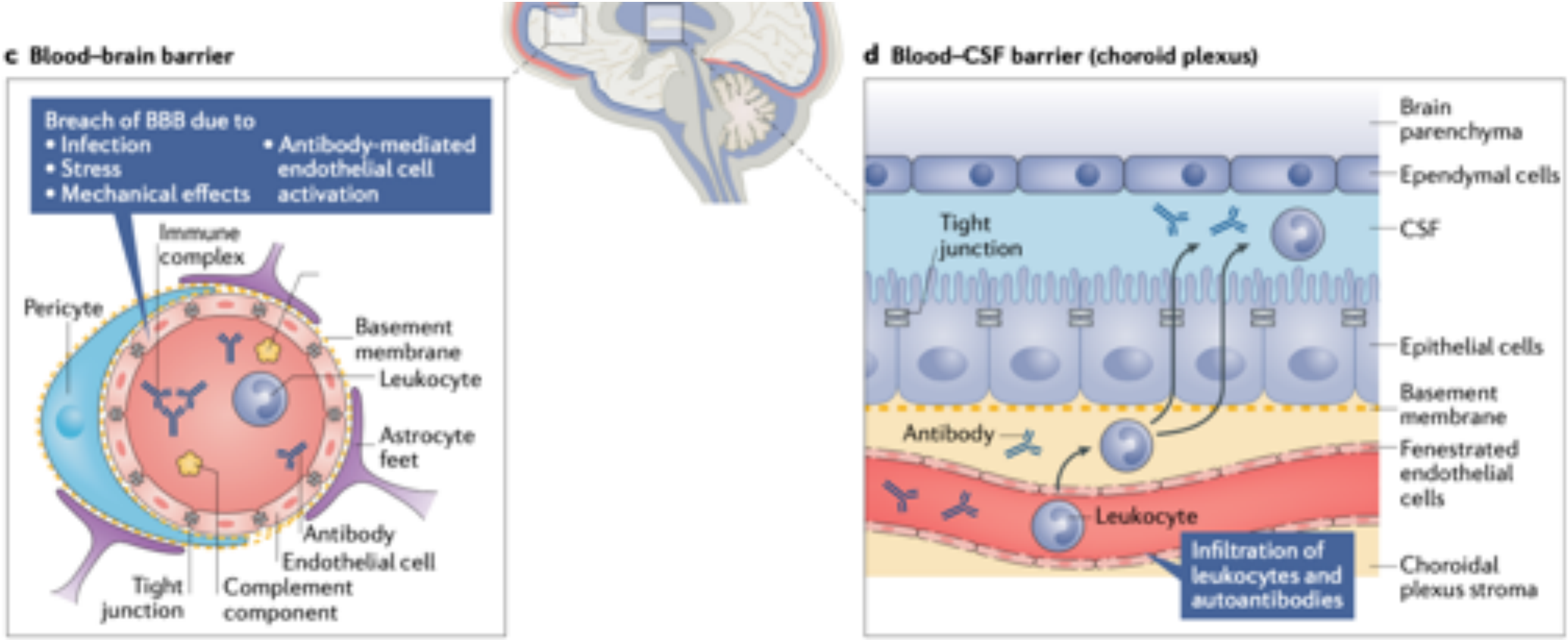


https://www.biorxiv.org/content/10.1101/573345v1.full

However, we now know that '**neuroimmune interfaces**' can break through the BBB.

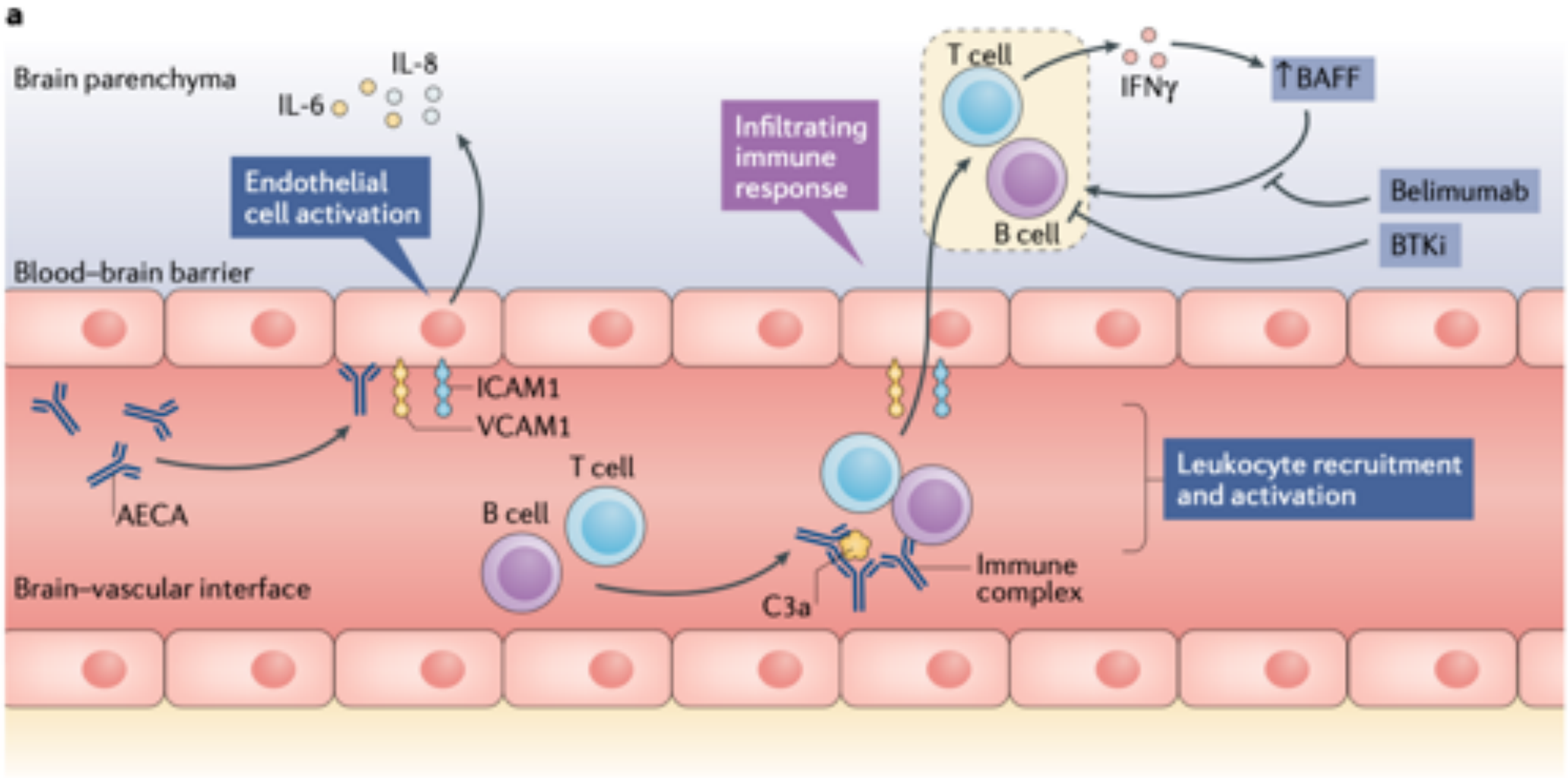


Schwartz N, Stock AD and Putterman C. Neuropsychiatric lupus: new mechanistic insights and future treatment directions. Nat Rev Rheumatol 2019; 15: 137-152. 2019/01/20.



Schwartz N, Stock AD and Putterman C. Neuropsychiatric lupus: new mechanistic insights and future treatment directions. Nat Rev Rheumatol 2019; 15: 137-152. 2019/01/20.

With this access, SLE mechanisms can exert strong pro-inflammatory effects on the CNS.



Schwartz N, Stock AD and Putterman C. Neuropsychiatric lupus: new mechanistic insights and future treatment directions. Nat Rev Rheumatol 2019; 15: 137-152. 2019/01/20.

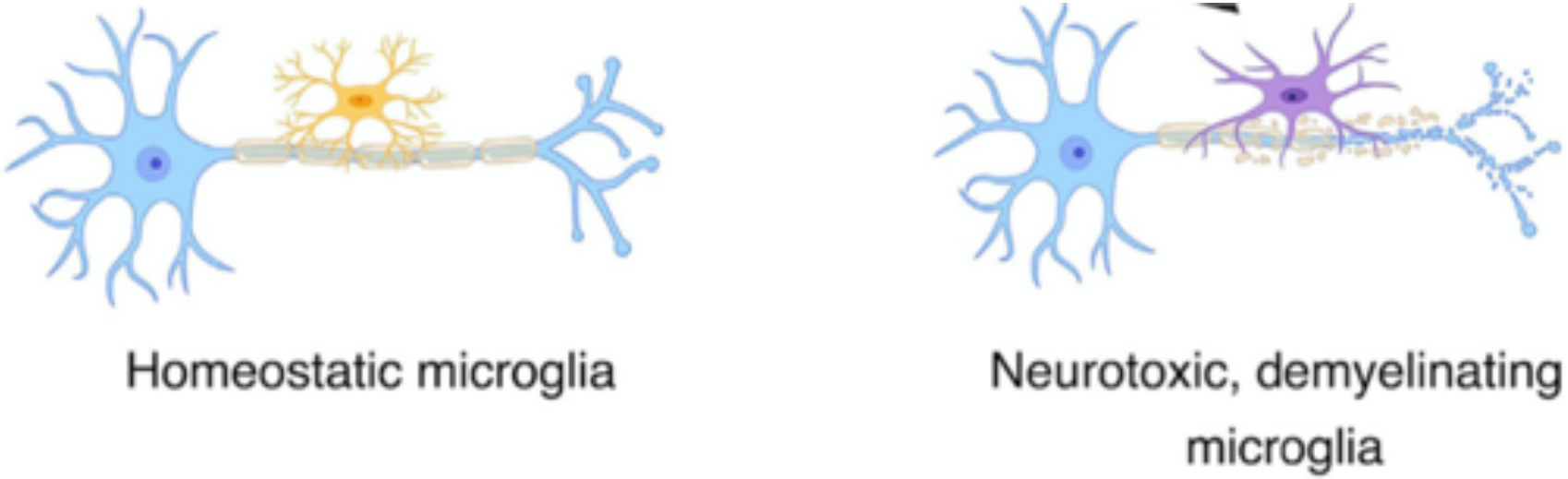
However, there is more to the story than lupus-specific CNS inflammation.

- Many patients who have antibodies thought to lead to CNS lupus (Ribosomal P, NMDA), do not have CNS lupus.
- Lupus disease activity does not correlate well with cognitive impairment in lupus patients.
- Likely additional, non-lupus factors involved.

Schwartz N, Stock AD and Putterman C. Neuropsychiatric lupus: new mechanistic insights and future treatment directions. Nat Rev Rheumatol 2019; 15: 137-152. 2019/01/20.

Enter Microglia.

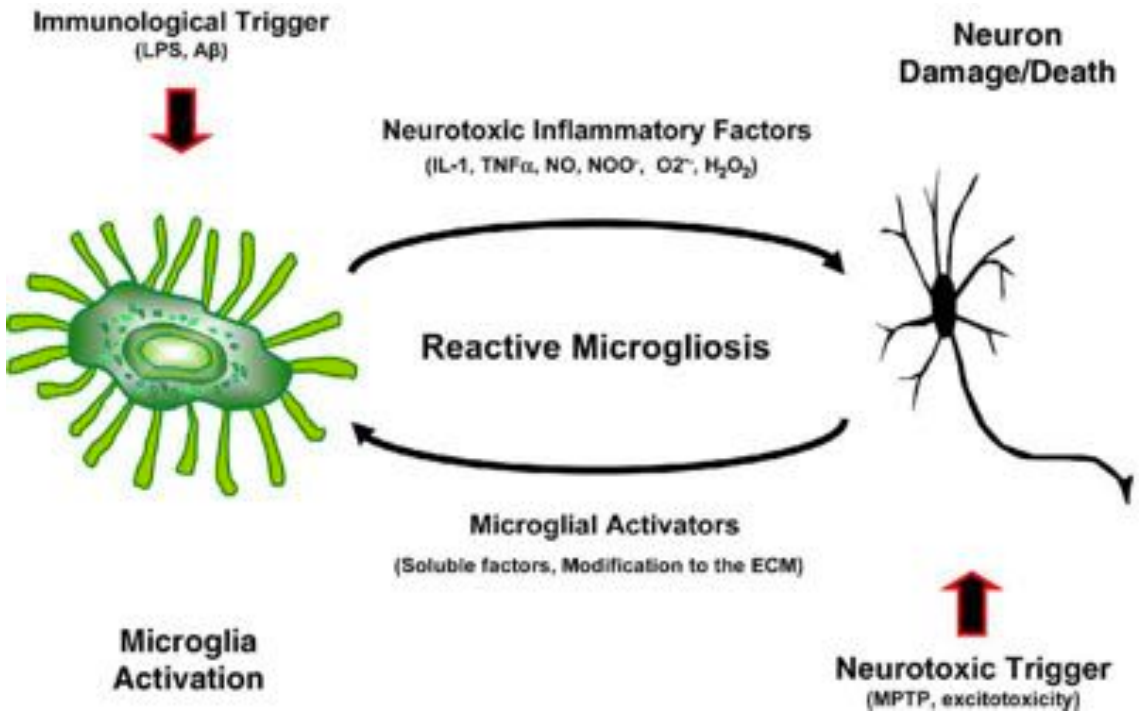
- Immune cells of the CNS.
- Various ‘pro-inflammatory’ & ‘neuroprotective’ phenotypes.
- Shown to be potential key players in CNS lupus & many other types of brain dysfunction.



1. Schwartz, N., Stock, A.D. & Putterman, C. Neuropsychiatric lupus: new mechanistic insights and future treatment directions. *Nat Rev Rheumatol* **15**, 137-152 (2019).
2. Wang X, L.Y., Wang Y, Feng Q, Yang P, Qin L. Intracerebroventricular administration of lupus serum induces microglia activation and leukocyte adhesion in the cerebromicrovasculature of mice. *Journal of Neuroimmunology* **334**(2019). 12: 205. 2015/11/08.
3. Stock AD, Wen J, Doerner J, et al. Neuropsychiatric systemic lupus erythematosus persists despite attenuation of systemic disease in MRL/lpr mice. *J Neuroinflammation* 2015
4. Wendeln, A. C. et al. Innate immune memory in the brain shapes neurological disease hallmarks. *Nature* **556**, 332–338 (2018).
5. Duarte-Garcia A, Romero-Diaz J, Juarez S, et al. Disease activity, autoantibodies, and inflammatory molecules in serum and cerebrospinal fluid of patients with Systemic Lupus Erythematosus and Cognitive Dysfunction. *PLoS One* 2018; 13
6. Chitu et al., 2020, Cell Reports 30, 3004–3019.

Microglia can stay **activated for months** beyond an insult.

- Ongoing secretion of pro-inflammatory cytokines, additional microglial proliferation and activation.
  - Possible explanation for the disconnect between lupus disease activity and cognitive dysfunction?



Rajagopal Shanmuga Sundaram et al. The Role Of Reactive Microglia In Neurodegenerative Disease: Multiple Triggers With A Common Mechanism •February 2012.

Background: Mechanisms

What if we inhibit microglial activation?

- Mycophenolate (MMF)
  - ↓ microglial secretion of TNF-α and IL-1β; ↓ microglial activation, proliferation.
  - May reduce neuron damage post excitotoxic injury.
  - Associated with complete or partial resolution of various CNS manifestations of SLE in observational studies.
- Azathioprine (AZA)
  - ↓ microglial secretion of TNF-α.
  - Associated with complete or partial resolution of various CNS manifestations of SLE in observational studies.

1. Wadhwa, M.*, et al.* Inhibiting the microglia activation improves the spatial memory and adult neurogenesis in rat hippocampus during 48 h of sleep deprivation. *J Neuroinflammation* **14**, 222 (2017).
2. Acharya, M.M.*, et al.* Elimination of microglia improves cognitive function following cranial irradiation. *Sci Rep* **6**, 31545 (2016)
3. DiSabato, D.J., Quan, N. & Godbout, J.P. Neuroinflammation: the devil is in the details. *J Neurochem* **139 Suppl 2**, 136-153 (2016).
4. Dehghani, F.*, et al.* Inhibition of microglial and astrocytic inflammatory responses by the immunosuppressant mycophenolate mofetil. *Neuropathol Appl Neurobiol* **36**, 598-611 (2010).
5. Liao, L.X.*, et al.* Highly selective inhibition of IMPDH2 provides the basis of antineuroinflammation therapy. *Proc Natl Acad Sci U S A* **114**, E5986-E5994 (2017)
6. Dehghani, F.*, et al.* The immunosuppressant mycophenolate mofetil attenuates neuronal damage after excitotoxic injury in hippocampal slice cultures. *Eur J Neurosci* **18**, 1061-1072 (2003).

Cognition

Processes by which information is transformed, reduced, elaborated, stored, recovered and used (Neisser, 1967).

Six domains of cognition (thinking):

1. Visual-Spatial function
2. Motor Speed and Dexterity
3. Attention & Concentration
4. Learning & Memory
5. Language
6. Executive function

Zucchella C, Federico A, Martini A, *et al*. *Pract Neurol* 2018;18:227– 237

Cognitive **dysfunction** has many causes

Temporary:

Infection, intoxication, depression, anxiety, SLE, others.

Or Permanent:

Stroke, dementia, traumatic brain injury, developmental delay, SLE, others.

Cognitive Dysfunction has a **profound impact** on patients

- Memory loss.
- **Trouble exercising judgment.**
    - E.g. not following recommended treatments.
- **Difficulty planning and carrying out tasks.**
    - E.g. following a recipe or keeping track of monthly bills.
    - Difficulty keeping up at work.
- **Changes in mood or behavior**
    - Interpersonal difficulties at home & work.
- Many others.

Cognitive impairment: a call for action, Now! is available at www.cdc.gov/aging/healthybrain/index.htm

Cognitive dysfunction occurs in **40% of patients with SLE**

Not life- or limb- threatening: ‘Invisible’ manifestation.

- Symptoms of cognitive dysfunction often overlooked.
- No universal screening. No approved treatments.

However, significant impact on patient quality of life & employment.

1. Dobrowolski C et al. Cognitive Impairment and Health-Related Quality of Life in a Lupus Cohort [abstract]. *American College of Rheumatology Annual Meeting*. Chicago: American College of Rheumatology, 2018.
2. Tam, L. S., et al. (2008). "The relationship between neuropsychiatric, clinical, and laboratory variables and quality of life of Chinese patients with systemic lupus erythematosus." J Rheumatol 35(6): 1038-1045.
3. Panopalis P, Julian L, Yazdany J, et al. Impact of memory impairment on employment status in persons with systemic lupus erythematosus. *Arthritis Rheum* 2007; 57: 1453-1460. DOI: 10.1002/art.23090.13.
4. Appenzeller S, Cendes F and Costallat LT. Cognitive impairment and employment status in systemic lupus erythematosus: a prospective longitudinal study. *Arthritis Rheum* 2009; 61: 680-687. DOI: 10.1002/art.24346.

Cognitive dysfunction & quality of life in SLE

- 171 participants from the Toronto Lupus Cohort:
  - Comprehensive neuropsychological battery.
  - Medical Outcomes Study Short Form 36 (SF-36) & Lupus Quality of Life (LupusQoL).

- Linear regression models revealed that SLE patients with CD showed statistically significantly lower scores in:
  - SF-36 Physical Component Summary score.
  - SF-36 Mental Health.
  - SF-36 Physical Functioning.
  - SF-36 Social Functioning.
  - LupusQoL Planning.

Dobrowolski C et al. Cognitive Impairment and Health-Related Quality of Life in a Lupus Cohort [abstract]. *American College of Rheumatology Annual Meeting*. Chicago: American College of Rheumatology, 2018:

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Rheumatology, 2022, **00**, 1–10
https://doi.org/10.1093/rheumatology/keac540
Advance access publication 22 September 2022
Original article

British Society for Rheumatology
RHEUMATOLOGY
OXFORD

Clinical science

Association of mycophenolate and azathioprine use with cognitive function in systemic lupus

Chrisanna Dobrowolski[1], John McGinley[2], Melissa Fazzari[3], Jiandong Su[4], Kathleen S. Bingham[5], Nicole Anderson[4], Lesley Ruttan[6], Dorcas E. Beaton[7], Joan E. Wither[4], Maria Carmela Tartaglia[8], Mahta Kakvan[4], Dennisse Bonilla[4], May Y. Choi[9], Marvin J. Fritzler[9], Juan Pablo Diaz Martinez[4], Patricia Katz[10], Robin Green[6], Chaim Putterman[11,12,13,14], Zahi Touma[4,*]

Study Design

Single-center, retrospective study using data from the Toronto Lupus Cohort.

Longitudinal design:

- Measurements completed at baseline, 6 months and 12 months.

Participants

All consenting adult SLE patients attending the University of Toronto Lupus Clinic between July 2016 and April 2020 were considered.

Inclusion criteria:

- Fulfillment of the revised American College of Rheumatology SLE classification criterion.
- English language proficiency (due nature of cognitive tests).
- Age 18 to 65 years.
- Ability to provide informed consent.

Exclusion criteria:

- History of irreversible CNS damage, developmental delay or dementia.
- Other physical or mental disability preventing full participation in the study.

Participants

Project was approved by the University Health Network Research Ethics Board & the Albert Einstein College Of Medicine Institutional Review Board.

A Neuropsychometrist administered a comprehensive neuropsychological battery (NB) to all participants. Overseen by Neuropsychologist.

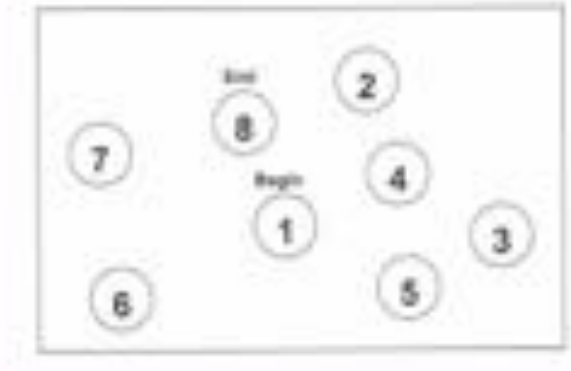
- Equivocal to the American College of Rheumatology cognitive battery developed for lupus, except the Hopkins Verbal Learning Test replaced the California Verbal Learning Test.
- Scores were compared to sex- and age- matched control to obtain normalized values.

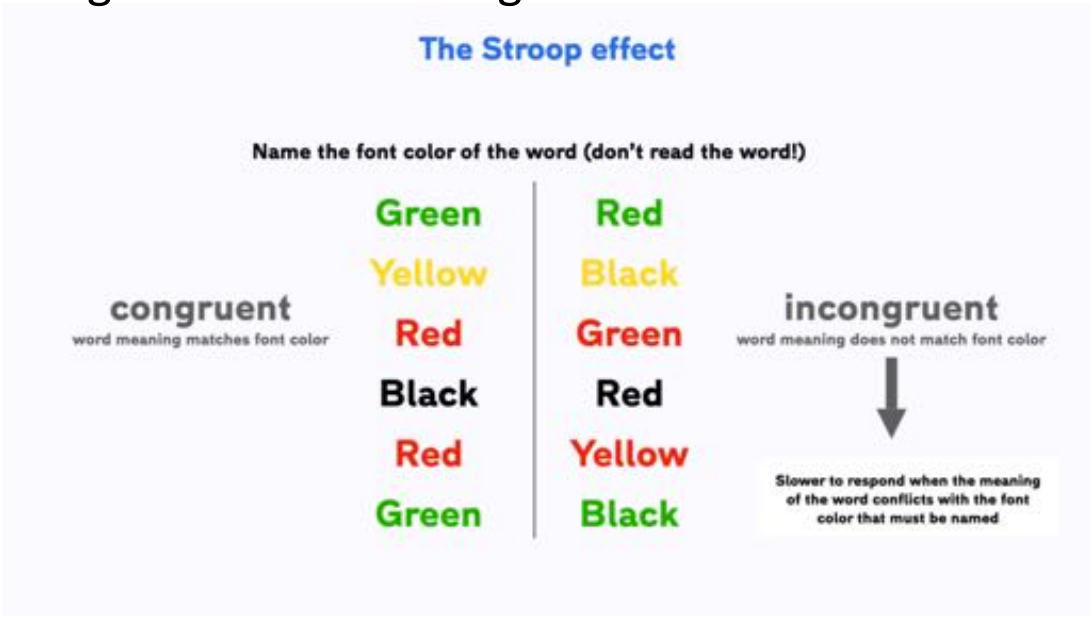
Clinical and demographic information were gathered same day as the NB.

Neuropsychological battery of tests

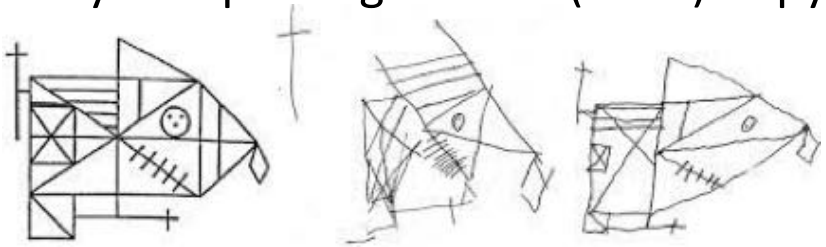
1. Motor speed and Dexterity:
   Dominant and non-dominant hand tapping tests.

2. Attention and Processing Speed:
   Trails Making Test Part A, Stroop Color Naming and Word Reading test.





3. Visual-spatial Construction:
   Rey Complex Figure Test (RCFT) Copy



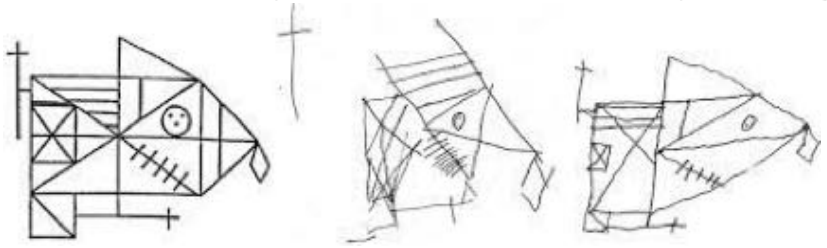
Neuropsychological battery of tests

4. Verbal fluency:

   Controlled Oral Word Association Test (COWAT) and Animal Naming test.

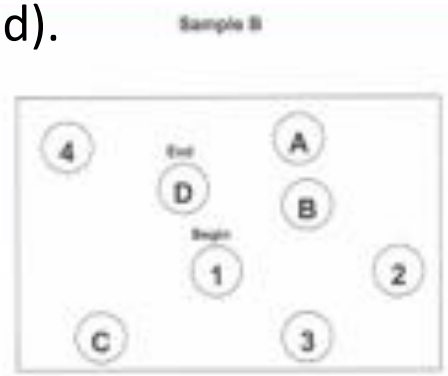
5. Learning and Memory:

   Rey Complex Figure Test (RCFT) Delay Recall, RCTF Delay Recognition and Hopkins Verbal Learning Test-Revised (HVLT-R).



6. Executive Function:

   Stroop Interference score, WAIS-III Letter-Number, WAIS-III Digit Symbol, Trails Making Test Part B and Consonant Trigrams (lower value from 18-second or 36-second).



Outcome Measures

Primary Outcome:

- Cognitive dysfunction, defined as binary variable with z-score of ≤ -1.5 in 2+ cognitive domains.

Secondary Outcome:

- Normal cognition, defined as a binary variable with no z-score of ≤ -1.5.

Predictors

Primary Predictors:

1. Cumulative MMF dose (g/kg).
2. Cumulative AZA dose (g/kg).

Secondary Predictors:

1. Active use of MMF for ≥6 months.
2. Active use of AZA for ≥6 months.

3. Duration of MMF use (months).
4. Duration of AZA use (months).

Missing Values

Data inspected to identify any non-plausible values and inconsistencies.

Multiple imputation used for values assumed to be missing at random:

- Education level.
- Beck Anxiety & Depression Index scores.
- SDI scores.
- Weight & height.
- Cognitive scores (only if multiple other values within the same visit).

Statistical Analysis

Power calculation:

- Minimum sample size of 47 (94 total) for 80% power to detect 20% difference between groups.

Descriptive statistics recorded:

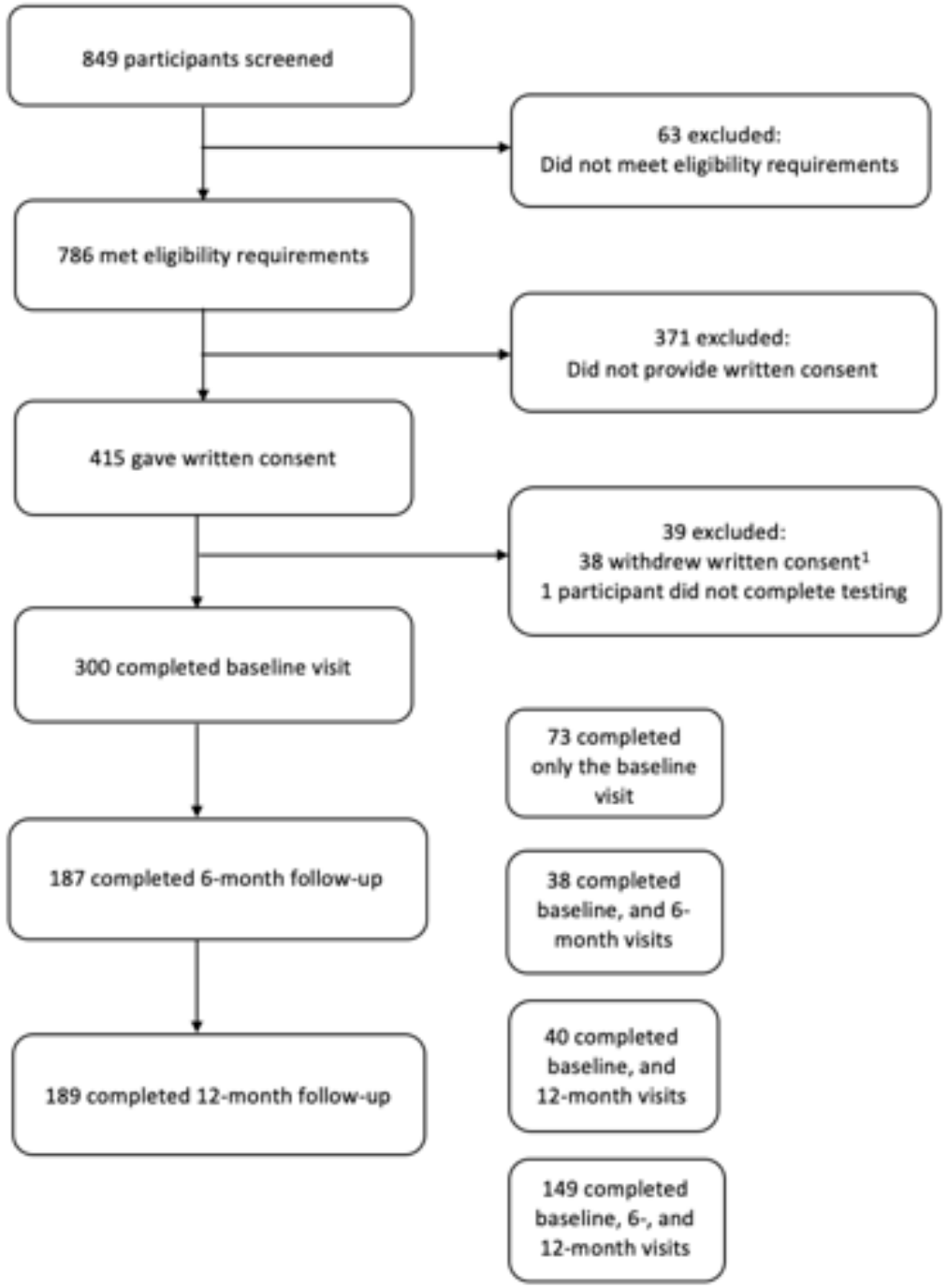
- Baseline characteristics by MMF & AZA use.

Relationship of medication use and cognitive dysfunction was determined through ‘Mixed effects logistic regression modelling’ over the 3 follow-up points.

Covariate selection

Systemic Lupus Erythematosus Disease Activity Index-2000 Glucocorticoid score[1]
Systemic Lupus International Collaborating Clinics - American College of Rheumatology Damage Index score[1,4]
History of any neuropsychiatric systemic lupus manifestations (excluding cognitive dysfunction)[2]
History of lupus nephritis[2]
Presence of additional risk factors not captured elsewhere (hypertension, obesity, and/or active smoker)[2]
Antiphospholipid antibody positivity[2,5]
Active use of an additional immunomodulator:
Antimalarial[2]
Belimumab[2]
Calcineurin inhibitor[2]
Cyclophosphamide[2]
Methotrexate[2]
Rituximab[2]
Prior use of an immunomodulator:
Antimalarial[2]
Azathioprine[2]
Calcineurin inhibitor[2]
Cyclophosphamide[2]
Mycophenolate[2]
Methotrexate[2]
Rituximab[2]
Beck Depression Inventory score[1]
Beck Anxiety Inventory score[1]
Age, years[1]
Sex (male versus female)[2]
Ethnicity (black, Caucasian, Chinese, other)[3]
Employment status (employed or full-time student versus other)[2]
Marital status (married or common-law partner versus other)[2]
Education level (completion of a College or University degree versus not)[2]

Participant Selection



Missing Values

Results

Table 2. Baseline characteristics of participants by cognitive function

	Total n=300	Non-CD[1] n=186 (62.0%)	CD[1] n=114 (38.0%)	p-values
Sex, n (%)				
Female	267 (89.0%)	168 (90.33%)	99 (86.8%)	0.35
Male	33 (11.0%)	18 (9.7%)	15 (13.2%)	
Age in years, mean ± SD	41.1 ± 12.1	41.3 ± 11.7	40.7 ± 12.7	0.49
Ethnicity				
Black	59 (19.7%)	24 (12.9%)	35 (30.7%)	**<0.01**
White	162 (54.2%)	114 (61.3%)	48 (42.1%)	**<0.01**
Chinese	33 (11.0%)	20 (10.8%)	13 (11.4%)	0.86
Others	46 (15.3%)	28 (15.1%)	18 (15.8%)	0.86
Education Level, highest achieved, n (%)				
12th Grade or lower	60 (20.0%)	31 (16.7%)	29 (25.4%)	
College or University Degree[2]	240 (80.0%)	155 (83.3%)	85 (74.6%)	0.07
Employment Status, n (%)				
Employed or student	195 (65.0%)	129 (69.4%)	66 (57.9%)	**0.04**
Other	105 (35.0%)	57 (30.7%)	48 (42.1%)	
Marital Status, n (%)				
Married or common Law	119 (39.9%)	81 (43.8%)	38 (33.9%)	0.10
Other	179 (60.0%)	105 (56.5%)	74 (66.1%)	

Results

SLE Manifestations, n (%)				
Antiphospholipid positivity[3]	46 (15.3%)	29 (15.6%)	17 (14.9%)	0.87
Nephritis	91 (30.3%)	53 (28.5%)	38 (33.3%)	0.69
Mucocutaneous	172 (57.5%)	105 (56.8%)	67 (58.8%)	0.73
Musculoskeletal	112 (37.5%)	63 (34.1%)	49 (43.0%)	0.12
Other NPSLE manifestation[4]	75 (25.0%)	44 (23.7%)	31 (27.2%)	0.49
Serositis	26 (8.7%)	18 (9.7%)	8 (7.0%)	0.42
Additional CD risk factors[5], n (%)				
Hypertension	124 (41.3%)	79 (42.5%)	45 (39.4%)	0.61
Obesity	97 (32.3%)	57 (30.7%)	40 (35.1%)	0.43
Smoker	18 (6.0%)	11 (5.9%)	7 (6.1%)	0.94
Disease Duration in years, median (IQR)	12.4 (6.0, 21.6)	14.4 (6.5, 22.2)	11.6 (3.9, 19.1)	0.06
SDI score				
Median (IQR)	1.0 (0.0-2.0)	0.0 (0.0-1.1)	1.0 (0.0-2.0)	
Mean ± SD	1.0 ± 1.4	1.0 ± 1.4	1.1 ± 1.5	0.35
SLEDAI-2K score				
Median (IQR)	2.0 (0.0, 4.0)	2.0 (0.0, 4.0)	2.0 (0.0, 5.0)	
Mean ± SD	3.3 ± 3.8	3.0 ± 3.4	3.7 ± 4.4	0.45
Glucocorticoid dose, mg/day				
Mean ± SD	4.3 ± 8.1	3.9 ± 7.4	5.1 ± 9.1	0.42
Immunosuppressant use, n (%)				
Antimalarials	224 (82.4%)	140 (82.8%)	84 (81.6%)	0.79
Azathioprine	52 (17.3%)	32 (10.7%)	20 (6.7%)	**0.03**
Belimumab	14 (4.7%)	10 (5.4%)	4 (3.5%)	0.46
Cyclophosphamide	2 (0.7%)	2 (1.1%)	0 (0.0%)	0.27
Cyclosporine	2 (0.7%)	1 (0.5%)	1 (0.9%)	0.73
Glucocorticoids	132 (48.5%)	80 (47.3%)	52 (50.5%)	0.61
Methotrexate	25 (8.8%)	13 (7.0%)	12 (10.5%)	0.28

Results

Mycophenolate	96 (32.0%)	53 (28.5%)	33 (29.0%)	0.93
Rituximab	14 (4.7%)	1 (0.5%)	1 (0.9%)	0.73
Immunosuppressive use, g/kg cumulative dose, mean ± SD				
Azathioprine	0.67 ± 2.17	0.98 ± 2.66	0.39 ± 1.57	**0.02**
Mycophenolate	16.32 ± 35.63	14.16 ± 33.09	18.31 ± 37.83	0.18
Prior Immunosuppressant Use, n (%)				
Azathioprine	2 (0.7%)	1 (0.7%)	1 (0.6%)	0.76
Cyclophosphamide	0	0	0	-
Cyclosporine	0	0	0	-
Methotrexate	2 (0.7%)	0	2 (1.8%)	0.07
Mycophenolate	23 (7.7%)	11 (7.7%)	12 (7.6%)	0.31
Beck Depression Inventory[6] score				
Median (IQR)	14.9 (7.2, 18.3)	13.7 (7.0, 16.1)	14.9 (10.3, 24.4)	**0.01**
Beck Anxiety Inventory[7] score				
Median (IQR)	15.6 (7.0, 20.0)	15.0 (7.0, 18.0)	15.6 (11.0, 23.0)	**0.01**

Results

Table 3. Baseline characteristics of participants by azathioprine and mycophenolate use

	Total n=300	No AZA use n=248	AZA use n=52	p-value	No MMF use n=204	MMF use n=96	p-value
SDI score							
Median score (IQR)		1.0 (0.0, 1.0)	1.0 (0.0, 2.0)	0.40	0.0 (0.0, 1.1)	1.0 (0.0, 2.0)	0.32
Mean score ± SD		1.0 ± 1.4	1.2 ± 1.5		1.0 ± 1.5	1.1 ± 1.4	
Disease Duration in years, median (IQR)		12.7 (5.8, 21.9)	11.9 (6.7, 16.6)	0.48	13.2 (6.0, 22.2)	11.6 (6.0, 19.4)	0.22
SLEDAI-2K							
Median score (IQR)		2.0 (0.0, 4.0)	4.0 (2.0, 6.0)	**<0.01**	2.0 (0.0, 4.0)	3.5 (0.0, 6.0)	**0.03**
Mean score ± SD		3.1 ± 3.8	4.3 ± 3.6		2.9 ± 3.5	4.0 ± 4.2	
SLEDAI-2KG							
Median score (IQR)		2.3 (0.0, 6.0)	2.1 (1.5, 7.3)	**<0.01**	2.0 (0.0, 6.0)	4.0 (2.0, 7.8)	**<0.01**
Mean score ± SD		4.2 ± 4.9	5.5 ± 3.8		3.8 ± 4.1	5.7 ± 5.7	
Other Immunosuppressant use, n (%)							
Antimalarials		183 (82.1%)	41 (83.7%)	0.79	152 (82.6%)	72 (81.8%)	0.87
Belimumab		11 (4.4%)	3 (5.8%)	0.68	10 (4.9%)	4 (4.2%)	0.78
Cyclophosphamide		2 (0.8%)	0	0.52	2 (1.0%)	0	0.33
Cyclosporine		2 (0.8%)	0	0.52	2 (1.0%)	0	0.33
Methotrexate		23 (9.3%)	2 (3.9%)	0.20	23 (11.3%)	2 (2.1%)	**0.01**
Rituximab		2 (0.8%)	0	0.52	1 (0.5%)	1 (1.0%)	0.58
Prior Immunosuppressant Use, n (%)							
Azathioprine		-	-	-	2 (1.0%)	0	0.33
Cyclophosphamide		0	0	-	0	0	-
Cyclosporine		0	0	-	0	0	-
Methotrexate		2 (0.8%)	0	0.52	2 (1.0%)	0	0.33
Mycophenolate		5 (2.0%)	18 (34.6%)	**<0.01**	-	-	-

Results

Glucocorticoid Dose, mg/day						
Mean ± SD	4.4 ± 8.5	4.2 ± 5.8	0.23	3.1 ± 5.5	7.0 ± 11.4	**<0.01**
SLE manifestations, n (%)						
Cognitive dysfunction	137 (55.2%)	20 (38.5%)	**0.03**	102 (50.0%)	55 (57.3%)	0.24
Antiphospholipid positivity[1]	34 (13.7%)	12 (23.0%)	0.09	28 (13.7%)	18 (18.8%)	0.26
Nephritis	68 (27.5%)	25 (48.1%)	**<0.01**	43 (21.1%)	50 (52.6%)	**<0.01**
Mucocutaneous	137 (55.5%)	35 (67.3%)	0.12	117 (57.4%)	55 (57.9%)	0.93
Musculoskeletal	90 (36.4%)	22 (42.3%)	0.43	76 (37.3%)	36 (37.9%)	0.92
Other NPSLE manifestation[2]	66 (26.6%)	9 (17.3%)	0.16	50 (24.5%)	25 (26.0%)	0.78
Serositis	20 (8.1%)	6 (11.5%)	0.42	15 (7.4%)	11 (11.6%)	0.23
Additional CD Risk Factors[3], n (%)						
Hypertension	100 (40.3%)	24 (46.2%)	0.44	76 (37.3%)	48 (50.0%)	**0.04**
Obesity	83 (33.5%)	14 (26.9%)	0.36	63 (30.9%)	34 (35.4%)	0.43
Smoker	14 (6.1%)	3 (5.8%)	0.94	16 (7.8%)	2 (2.1%)	**0.05**
Ethnicity						
Black	50 (20.2%)	9 (17.3%)	0.64	36 (17.6%)	23 (24.0%)	0.20
White	132 (53.2%)	30 (57.7%)	0.56	111 (54.4%)	51 (53.1%)	0.84
Chinese	27 (10.9%)	6 (11.5%)	0.89	18 (8.8%)	15 (15.6%)	0.08
Others	39 (15.7%)	7 (13.4%)	0.68	39 (19.1%)	7 (7.3%)	**0.01**
Education Level, highest achieved, n (%)						
12th Grade or lower	45 (18.1%)	15 (28.8%)		40 (19.6%)	20 (20.8%)	
College or University Degree[4]	203 (81.9%)	37 (71.2%)	0.08	164 (80.4%)	76 (79.2%)	0.80

Results

Table 4. Mixed logistic regression models for medication use predicting cognitive dysfunction[1]

	Cumulative dose, g/kg n=676		Use for ≥6 months n=676		Treatment duration, years n=676	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Azathioprine	**0.76 (0.58, 0.98)**	**0.04**	0.47 (0.12, 1.76)	0.26	**0.72 (0.54, 0.97)**	**0.03**
Mycophenolate	1.03 (0.93, 1.13)	0.58	0.76 (0.32, 1.79)	0.53	1.12 (0.96, 1.31)	0.15

OR: odds ratio, CI: confidence interval.

[1] Defined as a z-score of ≤-1.5 on ≥2 domains as determined by comprehensive cognitive testing.

Interpretation of Azathioprine Results

Despite significantly higher SLEDAI scores, cumulative AZA dose & duration of treatment were associated with decreased odds of CD.

- Median cumulative AZA dose 2.29g/kg → 55.0% assoc. decreased odds CD.

Retrospective study: caution in interpreting results.

- Many unknown/unaccounted confounders – no causal conclusions.
- Did not capture incident CD – timing of CD vs AZA use unclear.
- No information regarding medication adherence.
- Single center; predominantly College-educated, White population; English-speaking.

Additional and prospective studies are needed.

Interpretation of Mycophenolate (MMF) findings

Despite neuroprotective qualities in prior studies, our study found no association with MMF and cognitive function.

- Increased disease severity?
- Higher steroid dose in participants taking MMF?
- Inadequate statistical power?
- Uncovered neurotoxic effect?
- No association?

Study Strengths

To our knowledge, first study to investigate the association of AZA, MMF and SLE-CD.

Despite the retrospective analysis completed for this study, data was collected prospectively, limiting misclassification and recall biases.

Longitudinal design allowed us to account for both intra- and inter- individual effects.

Cumulative dose and treatment duration of AZA may support a ‘dose-dependent’ association, strengthens a potential relationship between AZA use & CD.

Potential mechanism: Microglial inhibition.

Outline

1. Background
2. Association of Mycophenolate and Azathioprine Use with Cognitive Dysfunction in Systemic Lupus
3. Summary
4. Future Directions
5. Questions

https://dictionaryblog.cambridge.org/2022/09/14/thinking-outside-the-box-talking-about-creativity/

Conclusions

1. Lupus cognitive dysfunction is common: occurs in 40%.

2. Reduced quality of life and reduced rates of employment.

3. Pathophysiology imperfectly understood, but likely multiple mechanisms including:
   - Pathologic microglial activity.
   - Cell and autoantibody mediated damage; tertiary lymphoid structures.
   - Facilitated by multiple neuroimmune interfaces.

4. Our new study showed:
   - Azathioprine use associated with decreased odds of CD in a cohort of 300 SLE patients from a single-center.
   - Mycophenolate use was not associated with CD.
   - Further studies are needed to replicate these findings and to further explore the relationship of AZA, MMF and SLE-CD.

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Future Directions

Comprehensive cognitive testing in a diverse SLE cohort in NYC.

- Toronto cohort predominantly Caucasian with post-secondary education.

Pilot study for effectiveness of cognitive rehabilitation:

- Low risk intervention studied for other etiologies of cognitive dysfunction.
- Could be immediately implemented vs drug trials will take years.
- Plan to focus on cognitive domains most affected.

Examining the association of each individual cognitive test with medication use.

Future Directions

ACEi (centrally-acting) also inhibit microglia.

- Additional study completed with Toronto lupus cohort to examine association of ACEi use with cognitive dysfunction.
- Clinical trial is also underway in New York.

Neuroimaging study.

- Microglial activity determined by PET imaging
  - targeting translocator protein 18 kDa – a specific, established marker located on outer mitochondrial membrane of microglia during periods of activation.

Genetic markers of lupus cognitive dysfunction & microglial dysfunction.

Further delineate how SLE can stimulate neurotoxic microglia.

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Thank you!

Albert Einstein College of Medicine:

- Clinical Research Training Program
  - NIH CTSA Grant Number UL1TR002556
- Aileen McGinn
- John McGinley
- Melissa Fazzari
- Chaim Putterman

University of Toronto – University Health Network:

- Jiandong Su
- Nicole Anderson
- Dennisse Bonilla
- **Zahi Touma**

- Arthritis Society of Canada
- Canadian Institutes of Health Research
- Physician’s Services Incorporated
- Province of Ontario Early Research Award
- Lupus Research Alliance
- Lupus Ontario
- Schroeder Arthritis Institute.
- Canadian Rheumatology Association (CIORA)
- Arthritis Society

Table 4 | **Cytokines in NPSLE**

Cytokine	Effects	Refs
TNF	• Conflicting data regarding elevated CSF levels in NPSLE • Treatment with TNF inhibitors can induce SLE-like symptoms • Increased levels can impair the BBB via increased local inflammation	115,211–214
BAFF	• Mediates B cell survival and promotes immunoglobulin class switching (important in SLE pathogenesis) • Anti-BAFF (belimumab) antibody treatment is approved for the treatment of SLE, but efficacy in NPSLE has not been established	215,216,189
IFNα	• Important in SLE pathogenesis • Strong systemic interferon signature in patients with NPSLE • Induced in vitro by CSF from patients with NPSLE • Activates microglia leading to synaptic pruning • Can induce depression (most common adverse effect), psychotic features, confusion, focal neurological deficits and seizures	149–151,217–219
TWEAK	• Mediates BBB disruption, choroid plexus cellular infiltration and neuronal damage • Elevated in the CSF of patients with SLE	49,156,220
IFNγ	• Mainly produced by T cells and found in high levels in sera from patients with SLE • Elevated in the CSF of patients with NPSLE, which can distinguish NPSLE from demyelinating neurological conditions	160
IL-6	• Secreted primarily by myeloid cells, activated astrocytes and endothelial cells • Stimulates B cells, promotes immunoglobulin secretion by plasma cells, promotes differentiation of T_H17 cells and inhibits differentiation of regulatory T cells • Elevated in the CSF of patients with NPSLE, but similarly elevated in CSF from patients with demyelinating neurological conditions and septic meningitis	152,160,213,221
IL-8	• Secreted by several cell types, including activated endothelial cells • Elevated in the CSF of patients with NPSLE, but similarly elevated in CSF from patients with demyelinating neurological conditions and septic meningitis	152,160,211

BAFF, B cell activating factor; BBB, blood–brain barrier; CSF, cerebrospinal fluid; NPSLE, neuropsychiatric systemic lupus erythematosus; SLE, systemic lupus erythematosus; T_H17 cell, T helper 17 cell; TWEAK, TNF-like weak inducer of apoptosis.

Schwartz N, Stock AD and Putterman C. Neuropsychiatric lupus: new mechanistic insights and future treatment directions. Nat Rev Rheumatol 2019; 15: 137-152. 2019/01/20.