

# Lithium Treatment Modulates Neuroinflammatory Protein Trajectories in Early Alzheimer’s Disease: Findings from the LATTICE Trial

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## INTRODUCTION

Lithium may slow Alzheimer Disease:

- Lithium is deficient in AD/MCI brains and sequestered by amyloid plaques
- Those exposed to lithium have lower prevalence of dementia
- Lithium treatment inhibits GSK-3α and GSK-3β, key kinases involved in Alzheimer Disease pathogenesis

| Characteristic | Overall (N=80) | Lithium (N=41) | Placebo (N=39) |
|----------------|----------------|----------------|----------------|
| Age            |                |                |                |
| [Mean(SD)]     | 72.1 (7.7)     | 72.9 (8.8)     | 71.2 (6.5)     |
| Sex [N(%)]     |                |                |                |
| Female         | 45 (56.3%)     | 23 (56.1%)     | 22 (56.4%)     |
| Male           | 35 (43.8%)     | 18 (43.9%)     | 17 (43.6%)     |
| Race [N(%)]    |                |                |                |
| White          | 71 (88.8%)     | 38 (92.7%)     | 33 (84.6%)     |
| Black/AA       | 8 (10.0%)      | 3 (7.3%)       | 5 (12.8%)      |
| Asian          | 1 (1.3%)       | 0 (0.0%)       | 1 (2.6%)       |
| Education      |                |                |                |
| [Mean(SD)]     | 16.0 (2.3)     | 15.5 (2.7)     | 16.5 (1.8)     |
| APOE4 [N(%)]   |                |                |                |
| Carrier        | 28 (35.0%)     | 15 (36.6%)     | 13 (33.3%)     |
| Non-carrier    | 52 (65.0%)     | 26 (63.4%)     | 26 (66.7%)     |
| PiB-PET [N(%)] |                |                |                |
| PiB-           | 54 (67.5%)     | 27 (65.9%)     | 27 (69.2%)     |
| PiB+           | 21 (26.3%)     | 11 (26.8%)     | 10 (25.6%)     |
| PiB Unknown    | 5 (6.3%)       | 3 (7.3%)       | 2 (5.1%)       |
| N at Timepoint |                |                |                |
| Baseline       | 73 (91.3%)     | 36 (87.8%)     | 37 (94.9%)     |
| One-year       | 63 (78.8%)     | 37 (90.2%)     | 26 (66.7%)     |
| Two-year       | 69 (86.3%)     | 38 (92.7%)     | 31 (79.5%)     |

## METHODOLOGY

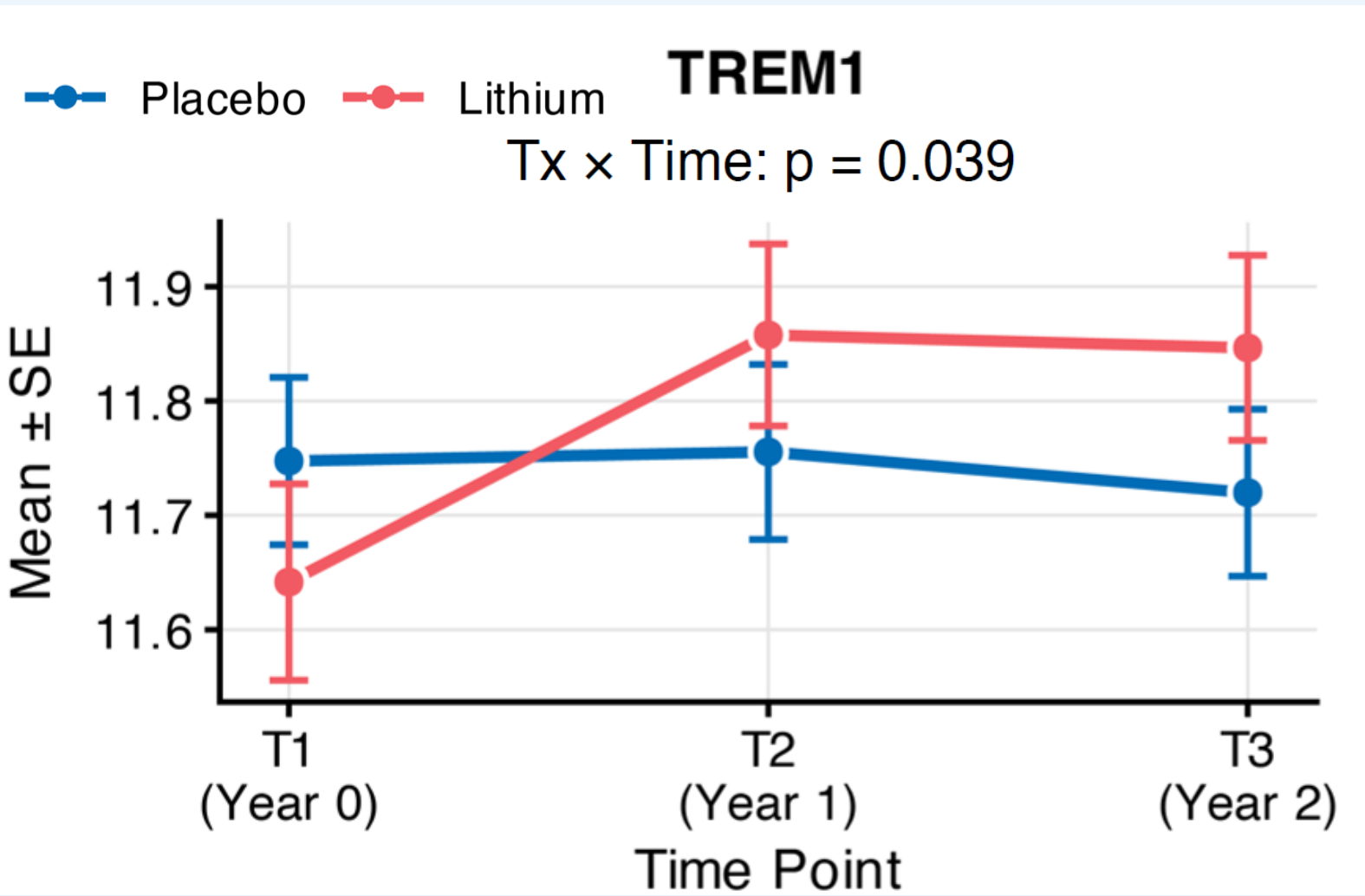
The LATTICE study:

- Double-blind pilot RCT
- N=80 with adjudicated MCI diagnosis
- Randomized to lithium carbonate or placebo for 2 years.
- Amyloid PET (PiB) imaging at baseline
- Plasma samples at baseline, 1-year, and 2-year visits.
- NULISaseq CNS 120 panel applied to N=210
- Longitudinal biomarker trajectories were analyzed using linear mixed-effects models with random intercepts, testing treatment-by-time interactions in the full cohort and stratified by PiB status.

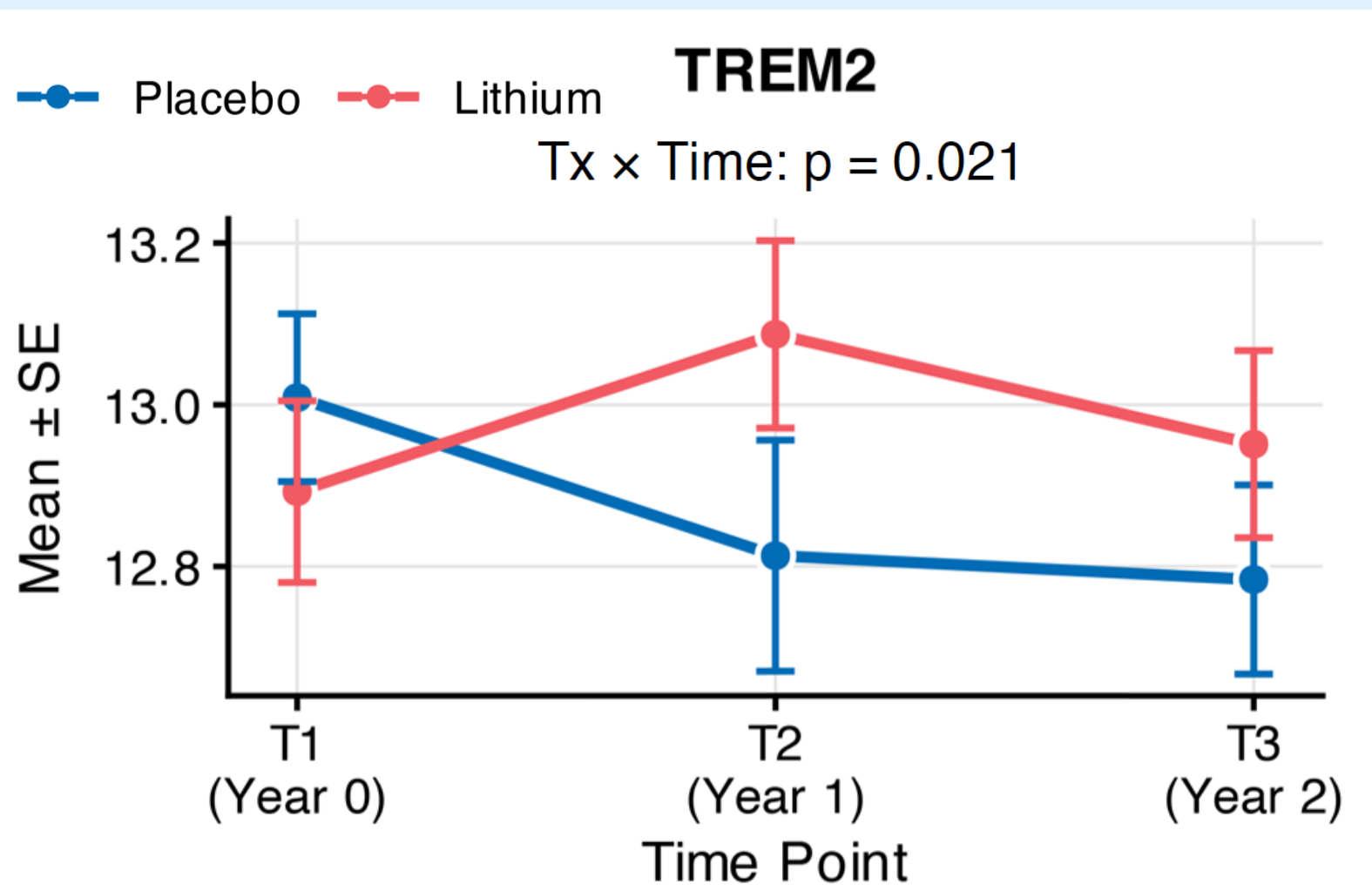
- All p-values were adjusted for multiple comparisons using the Benjamini-Hochberg false discovery rate (FDR).

## RESULTS

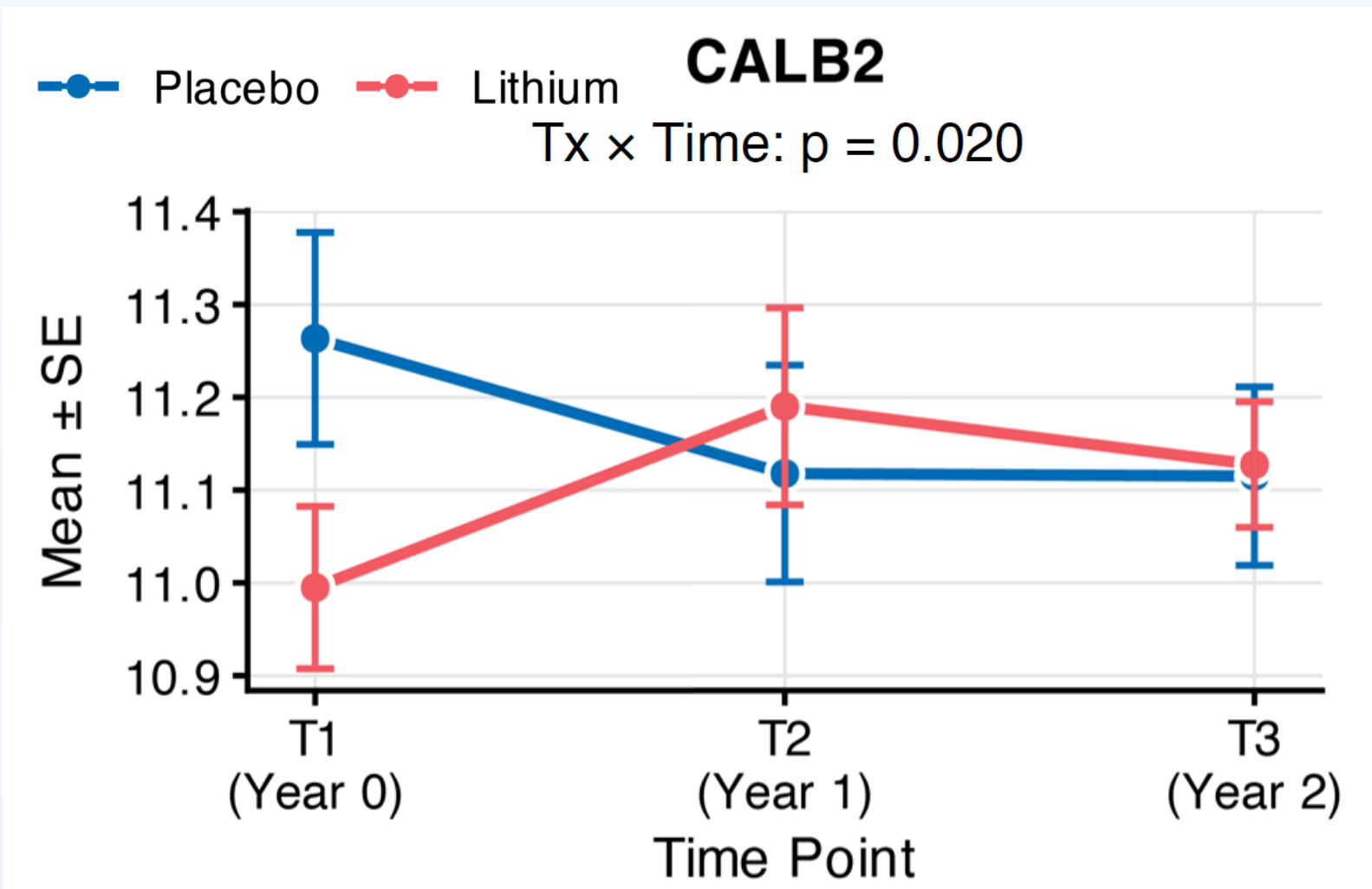
In the full cohort, lithium modulated trajectories in three neuroinflammatory proteins: treatment by time interactions were significant for TREM1 (p=0.039), TREM2 (p=0.021), and CALB2 (p=0.020).



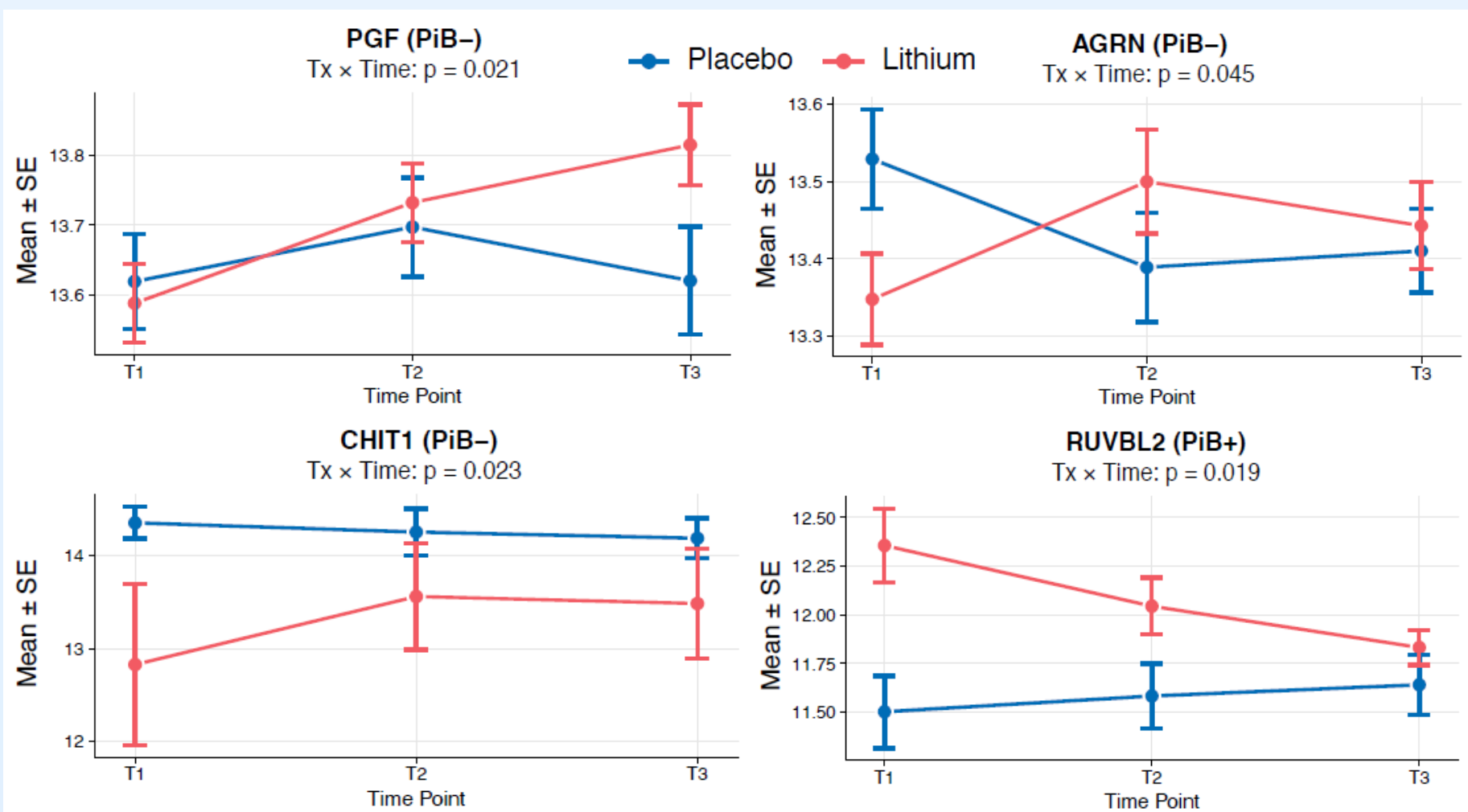
Relative to baseline, TREM1, TREM2, and CALB2 levels at 2-year visit were 1.76%, 0.46%, and 1.21% higher in the treatment group compared to -0.24%, -1.73%, and -1.32% in placebo, respectively.



These proteins showed stronger effects among PiB-negative individuals, with treatment-by-time interaction p-values of 0.070 for TREM1, 0.077 for TREM2, and 0.017 for CALB2.



Stratified by PiB status, PGF (p = 0.021), CHIT1 (p = 0.023), and AGRN (p = 0.045) exhibited significant treatment-by-time effects among PiB-negative participants (n = 27/arm; greater increase with lithium). RUVBL2 (p = 0.019) was significant among PiB-positive participants (n = 10-11/arm; greater decrease with lithium).



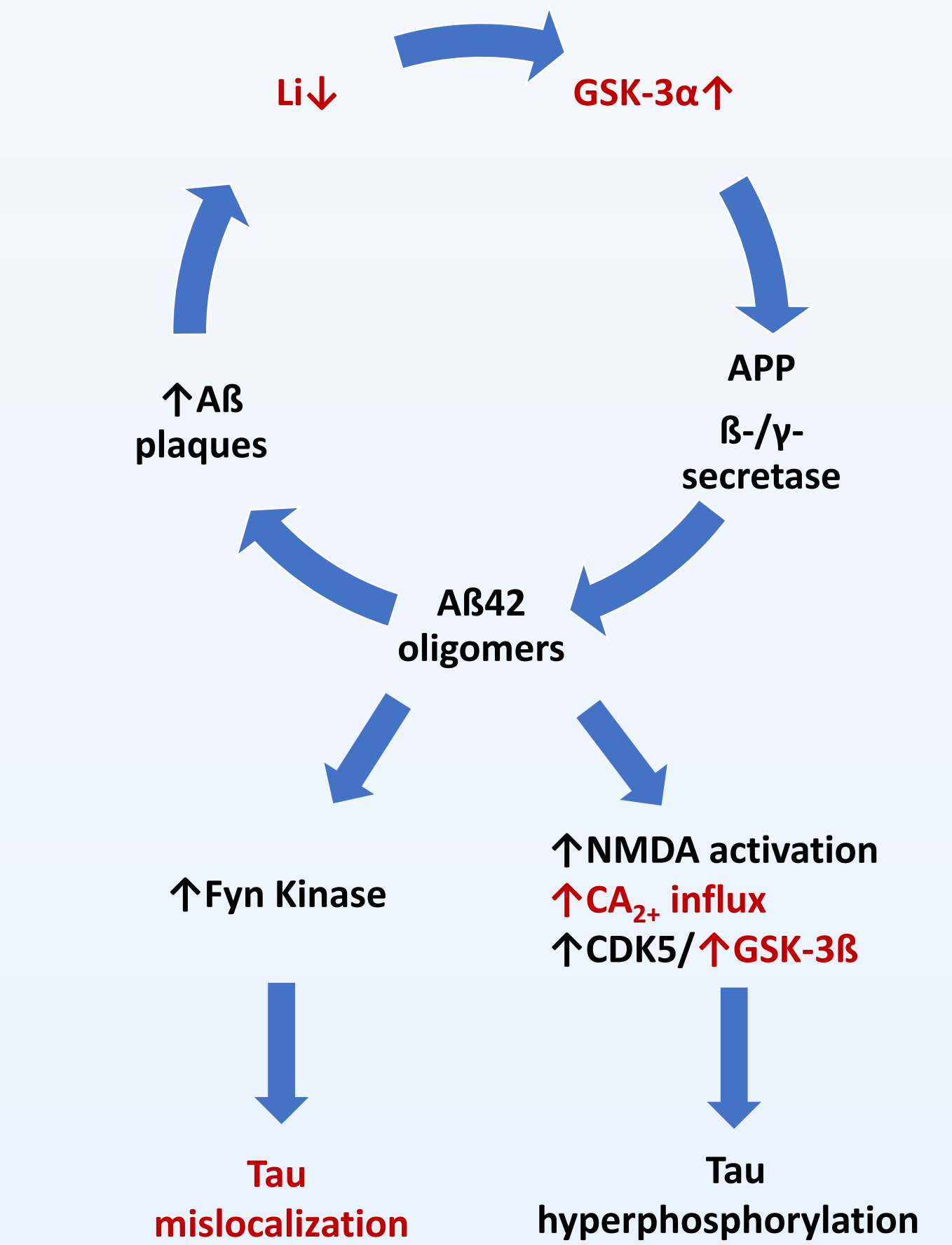
## DISCUSSION

Lithium treatment modulated the trajectories of neuroinflammatory proteins TREM1, TREM2, and CALB2. Additional effects on PGF, CHIT1, AGRN, and RUVBL2 were observed following stratification by PiB status.

No direct effects were detected on core amyloid-β or tau biomarkers, likely reflecting the early disease stage, limited follow-up duration, or small sample size

These findings suggest that lithium may exert protective effects against dementia by modulating neuroinflammatory and stress-related pathways.

## Lithium’s Role in Alzheimer Disease Pathophysiology



- Red text indicates possible effects of lithium treatment on AD pathology
- Lithium inhibits **GSK-3α** and **GSK-3β**
- Increases in TREM2 signaling may enhance responses involved in clearing **mislocalized tau** and promote compensatory injury-response pathways
- Increases in TREM1 expression may amplify the TREM2 response
- Increased CALB2 expression may alter interneuron calcium buffering (Chronic **CA<sub>2+</sub> influx**) and influence network stability

## CONCLUSION

Our findings suggest lithium may modulate neurodegenerative processes, including neuroinflammation and synaptic function, particularly in preclinical AD. Larger studies are needed to confirm these results.

## ACKNOWLEDGEMENTS

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