Neuropsychiatric symptoms are highly prevalent among systemic lupus erythematosus (SLE) patients, being clinically observed in up to 80% of adult and 95% of pediatric patients. Type 1 interferons, in particular interferon alpha (IFNα), have been implicated in the pathogenesis of SLE as well as its associated neuropsychiatric symptoms (NPSLE). The cellular components and molecular pathways affected within the central nervous system (CNS) in NPSLE remain unclear. Murine models of NPSLE with an elevated peripheral type 1 interferon signature are lacking, limiting studies of the mechanistic association between IFNα and behavioral phenotypes in this disease.

Methods Male and female B6.Sle1yaa mice were analyzed at varying ages from 10 days to 20 weeks. Both peripheral and CNS tissues were examined by RT-PCR for ISG expression.

MERFISH, a spacial transcriptomic approach, was used to identify ISG expression in whole brain sections and results validated using RNA scope. To identify differentially expressed genes single nuclei were isolated from cells of hindbrain and hippocampus and analyzed by RNA sequencing. Behavior assays were used examine symptoms of anxiety and fatigue.

Results We found using probe-based spatial transcriptomics that the type 1 interferon signature is present within the brain parenchyma of lupus mice as early as 3 weeks, with interferon stimulated genes (ISG) enriched in spatially distinct patches. ISG expression was validated by RT-PCR and RNA scope. Unbiased single nucleus sequencing of the murine hind brain and hippocampus revealed that ISGs as a group were the most highly differentially expressed genes. Sle1 yaa male mice developed symptoms of anxiety as early as 4 weeks and fatigue by 8 weeks relative to WT controls. Behavior and ISG patch formation were not dependent on the yaa mutation as female mice at 20 weeks were also positive for focal patches and development behavior change.

Conclusions We propose that the functional effects of interferon stimulated gene (ISG) patches play a mechanistic role in mediating behavioral phenotypes, and modulation of the type 1 interferon signaling pathway within the brain.

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Lay summary A common problem in lupus is being tired and absent minded. The cause is not known. We think it is due to the same factors released by the body during a cold. We want to know how the factors work in the brain and how they affect the tissues. By using mutant mice that have lupus symptoms, we hope to find out how the factors work in the brain.