Background One of the most prevalent, but least understood aspects of SLE is the fact that patients commonly develop neuropsychiatric symptoms, a condition referred to as central nervous system (CNS) lupus. The mechanisms driving neuropsychiatric disorders remain enigmatic; moreover, CNS lupus symptoms are variable and complicated by the systemic nature of the disease. The molecular mechanisms of CNS lupus thus remain a major gap in the lupus field. Interestingly, CNS lupus patients can show reduced grey matter volume, suggestive of neuron or synapse loss; however, the mechanisms underlying this neuron and synapse loss have yet to be fully explored. We looked to other CNS diseases for mechanistic clues relevant for CNS lupus. In Alzheimer’s disease, synapse loss is an early event and microglia have been identified as major mediators of the process. Type I interferon signalling has also emerged as a modulator of microglia activation and is commonly elevated in SLE patients. Therefore, we hypothesize that type I interferon may stimulate microglia dysfunction and promote aberrant microglia-mediated synapse loss.

Materials and methods We addressed this hypothesis using genetic and pharmacological approaches to block interferon alpha receptor (IFNAR) signalling in lupus models (564 lgi and NZB/W). Immunohistochemistry based assays were used to determine microglia activation state combined with RNAseq to characterise microglia gene expression changes. Flow cytometry, confocal, and electron microscopy were used to assay microglia engulfment of neuronal material and synapse density.

Results Gene expression analysis of microglia isolated from lupus mice identified significant upregulation of interferon stimulated genes and genes associated with microglia function. Consistent with these data, significant increases were observed in activated microglia in lupus mice relative to wild type littermates. Moreover, reminiscent of early development where microglia are important in synaptic pruning, microglia could be found engulfing neuronal material. In MX1 reporter mice, MX1+ microglia were more reactive than MX1− microglia in lupus mice and showed increased engulfment. Lupus mouse models also showed reduced synapse density at ages concurrent with increased microglia engulfment, suggesting aberrant microglia pruning of synapses. Treatment in vivo with anti-interferon receptor antibody protected against reactive microglia and engulfment of neuronal material. Injection i.v. with IFN-α or -β was sufficient to stimulate microglia engulfment of neuronal material.

Conclusion Taken together, these results suggest that type I interferon is necessary and sufficient to stimulate microglia dysfunction in SLE and identifies a novel potential mechanism promoting synapse loss and neuropsychiatric symptoms in CNS lupus patients.