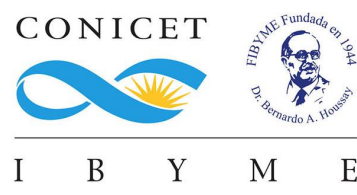


COGNITIVE FUNCTION, MICROGLIAL BALANCE AND SENESCENCE ARE RESTORED IN EXPERIMENTAL BRAIN AGING MODELS WITH METFORMIN

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Metformin represents a promising therapeutic intervention to counteract brain aging, effectively mitigating neurocognitive decline by suppressing microglial cellular senescence and restoring homeostatic balance

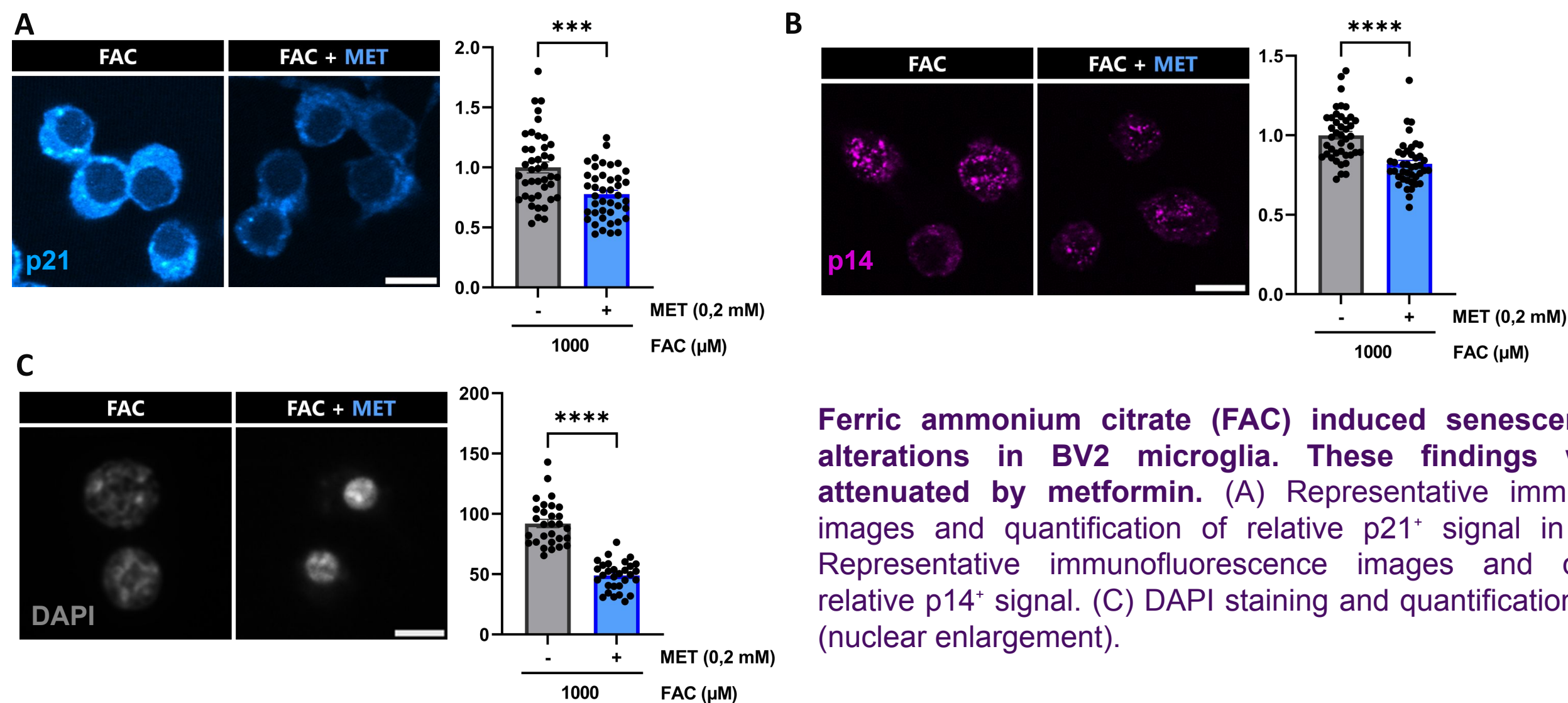
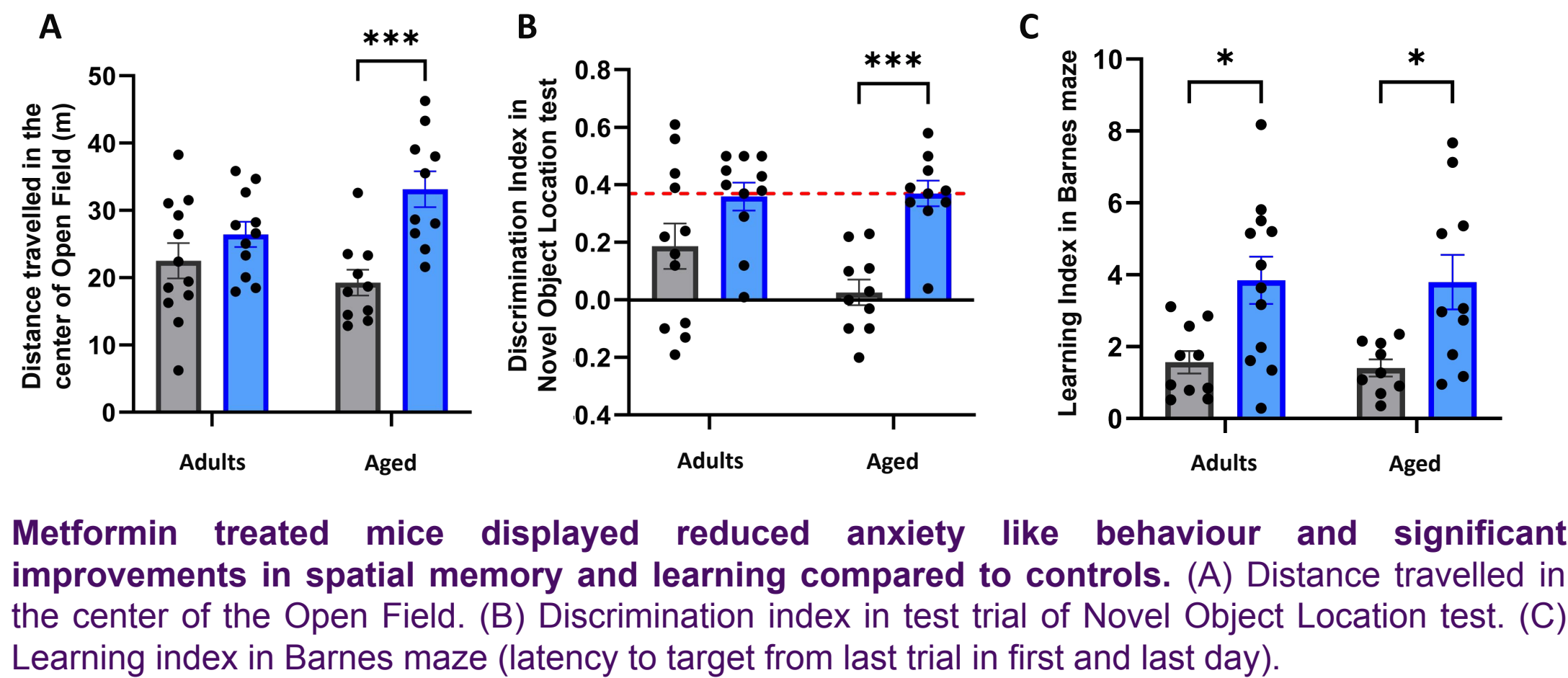
INTRODUCTION

Brain aging involves chronic neuroinflammation, oxidative stress, and mitochondrial dysfunction, with **microglial impairment** and cellular senescence driving the subsequent cognitive decline. Although the antidiabetic drug **Metformin** exhibits notable geroprotective properties, its capacity to rescue microglial homeostasis remains unclear. This study evaluated whether metformin treatment could **attenuate age-associated cognitive impairment** and suppress microglial senescence using complementary *in vivo* and *in vitro* models.

METHODS

To evaluate metformin’s neuroprotective effects, complementary *in vivo* and *in vitro* aging models were utilized. **Male C57BL/6 mice** (9 and 16 months old) received **intraperitoneal metformin (320 mg/kg)** or saline three times weekly for three weeks, followed by **Open Field, Novel Object Location, and Barnes maze tests** to assess anxiety and cognitive performance. Concurrently, **BV2 microglial cells** were exposed to ferric ammonium citrate for 24 hours to induce iron-associated senescence, with **metformin (0.2 mM)** administered during the final hour of treatment to evaluate cellular and senescence-associated markers

RESULTS



Ferric ammonium citrate (FAC) induced senescence associated alterations in BV2 microglia. These findings were markedly attenuated by metformin. (A) Representative immunofluorescence images and quantification of relative p21⁺ signal in BV2 cells. (B) Representative immunofluorescence images and quantification of relative p14⁺ signal. (C) DAPI staining and quantification of nuclear area (nuclear enlargement).