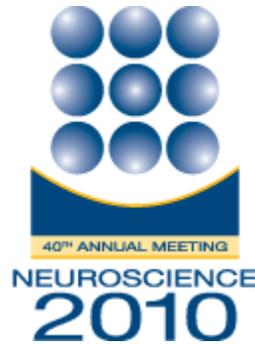


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## Presentation Abstract

Program#/Poster#: 192.15/FFF19

Title: In vivo study of abnormal neuronal  $\text{Ca}^{2+}$  activity in  $\alpha$ -synuclein transgenic mice model of Parkinson's disease using 2-photon microscopy

Location: Halls B-H

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Abstract: Although significant progress has been made in understanding molecular mechanism of Parkinson's disease, translation of these findings into clinically effective treatments remains a major challenge today. On the molecular level, it has been recently shown that  $\alpha$ -synuclein ( $\alpha$ -syn) might form channel-like oligomers that lead to an increase in intracellular  $\text{Ca}^{2+}$  in cell culture and *in vitro* assays. In this context, the central hypothesis of this study was that  $\alpha$ -syn dysregulates neuronal  $\text{Ca}^{2+}$  homeostasis *in vivo*. To test this hypothesis, 2-photon microscopy has been utilized to assess neuronal  $\text{Ca}^{2+}$  activity *in vivo* in transgenic (tg) mice expressing human  $\alpha$ -syn under the mThy-1 promoter. Neuronal response to a sensory stimulus (electrical whisker stimulation, 0.3-1 mA, 100  $\mu$ sec, a single pulse or 1-sec train at 10 Hz) was mapped using surface potential recordings with a silver ball electrode. Following the mapping, a mixture of calcium dye Oregon Green BAPTA-1 (OGB) AM and astrocytic marker SR101 were pressure injected 500  $\mu$ m below the cortical surface at the center of the neuronal response.  $\text{Ca}^{2+}$  activity in neurons at depths of 150 and 250  $\mu$ m was imaged in 1 year old  $\alpha$ -syn tg mice (fully developed disease) and compared to age-matched WT littermates ("controls").

We imaged stimulus-evoked  $\text{Ca}^{2+}$  activity in 5 and 5 tg and control mice, respectively. In 85% of the tg neurons ( $n=216$  at  $150\ \mu\text{m}$  and  $n=213$  at  $250\ \mu\text{m}$ ), stimulus-evoked  $\text{Ca}^{2+}$  responses were characterized by an increase in peak amplitude. In this population, trial-averaged  $\text{Ca}^{2+}$  response amplitude was up to 190% and 145% relative to the mean control responses at  $150\ \mu\text{m}$  and  $250\ \mu\text{m}$ , respectively ( $n=206$  at  $150\ \mu\text{m}$  and  $n=164$  at  $250\ \mu\text{m}$ ). In addition, prolonged  $\text{Ca}^{2+}$  decays were detected in 28% of the imaged tg neurons after the termination of the stimulus. This was assessed by fitting the decay with an exponential function  $y=ae^{-x/\tau}$ , where  $y$  - change in fluorescence of OGB,  $x$  - time,  $a$  and  $\tau$  - constants. The fitted time constant  $\tau$  indicated significantly longer decays in tg neurons imaged at the depth of  $150\ \mu\text{m}$  (up to 150% vs. controls). No significant difference in  $\tau$  was evident in neurons imaged at  $250\ \mu\text{m}$ . These results imply an increase in  $\text{Ca}^{2+}$  entry and slow clearance of the excess of  $\text{Ca}^{2+}$  in tg neurons. Further studies will be required to address the mechanisms through which  $\alpha$ -syn provokes neuronal  $\text{Ca}^{2+}$  dysregulation.

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