Selective Estrogen Enhancement of Cholinergic-Related Cognitive Performance In Women With/Without Subjective Cognitive Decline After Menopause
Kimberly Albert1, Julie Dumas3, Savannah Boyd1, Andrew Saykin4, Brenna McDonald4, Joon Hyuk Park5, Magdalena Naylor3, Paul Newhouse1,2
1Center for Cognitive Medicine, Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, 2GRECC VA-TVHS, University of Vermont, 3University of Indiana, 4Jeju National University, South Korea

INTRODUCTION
- Changes in cognitive performance noticed by an individual, so-called subjective cognitive decline (SCD), has emerged as a marker for increased risk of late life objective cognitive decline and dementia (Jessen et al., 2014). Women appear at higher risk for late life cognitive impairment (Halbreich et al., 1995).
- Cognitive symptoms reported by postmenopausal women may be linked to the loss of estradiol (E2) support to basal forebrain cholinergic systems (Newhouse and Dumas 2015).
- Epidemiologic studies suggest that exposure to estrogen (E2) in the early years after menopause is associated with reduced risk of being diagnosed with dementia/Alzheimer’s disease in later life (Shao et al., 2012).
- We have demonstrated that E2 effects on cognitive processes after menopause are mediated partially through salutary effects on brain cholinergic systems (Dumas et al., 2006). Estradiol effects on brain cholinergic system-mediated cognitive performance are age-dependent (“critical window hypothesis”) (Dumas and Newhouse 2008).
- We have shown that postmenopausal women with SCD show increased cortical activity during working memory tasks (Dumas et al., 2013) and increased cortical connectivity (Vega et al., 2106).
- To further clarify the source of these cortical activity differences in SCD, we examined the effects of 3 months of E2 administration on the response to cholinergic blockade compared to non-SCD women.

RESEARCH QUESTION
Does SCD impact the ability of estrogen treatment to enhance cognitive performance after cholinergic blockade in women with or without post menopausal SCD?

METHODS
Participants: Thirty four (34) normal early postmenopausal women were cognitively and behaviorally screened and classified as cognitive compliers (SCD; n = 18, Age: 56.2 ± 2.8) if they endorsed more than 20% of cognitive symptom items in an extensive self-report battery validated in a study of subjective cognitive impairment (Saykin et al., 2006), or non-compliers (Non-SCD; n = 16, Age: 55.9 ± 3) otherwise.

Procedures:
- Participants were scanned (structural and fMRI) and performed a baseline cognitive battery that included tests of attention, speed, and memory.
- Participants were then administered 1 mg of oral 17-β estradiol (E2) or placebo daily for 3 months. Follow-up scanning and cognitive testing then took place 3 months later, followed by anti-cholinergic drug challenges.
- Participants completed 4 drug challenge days throughout a time span of 2 weeks, at least 48 hours apart. For each participant, the drug sequence was randomized.
- Drugs administered during challenge days were:
  - Scopolamine (SCOP) is a muscarinic cholinergic antagonist intravenously administered at a dose of 2.5µg/kg body weight.
  - Mecamylamine (MECA) is a nicothinergic antagonist with oral doses of 20 mg.
- Combination of scopolamine and mecamylamine
- Matching placebo
- Working memory performance was assessed during cholinergic challenge days through the use of the N-Back Task (NBT).

RESULTS
Statistically significant group differences (p<0.01) were seen in cognitive complaints, depression scores and cognitive ratings, although not in cognitive performance scores, that were in the normal range for both groups. No participants met criteria for active depression.

Main effect of challenge medication (F (3,480) = 12.83, p < 0.001), with worse mean performance during high-dose SCOP (F (34) = 2.72, p < 0.05) and SCOP+MECA (F (34) = 3.85, p < 0.01) compared to placebo.

Interaction between SCI status and E2 treatment (F(3,480) = 19.70, p < 0.001) and a three way interaction between SCI status, E2 treatment, and N-Back task condition (F(3,480) = 2.71, p < 0.05).

SCI status and E2 treatment interaction: 3-Back performance following mecamylamine (F(1,33) = 14.68, p < 0.005).

DISCUSSION
- A significant beneficial effect was seen on working memory performance after chronic E2 treatment following nicotinic blockade, but only in women who had not experienced postmenopausal cognitive changes. No such beneficial effect was seen in women with postmenopausal SCD.
- These results suggest that the basis of such subjective dysfunction may be in part secondarily altered in cholinergic system activity, specifically nicothinergic receptor changes.
- Beneficial effects of the E2 administration on cholinergic-related cognitive functioning may be restricted to women without menopausal-related cognitive changes, consistent with the healthy cell bias of estrogen effect hypothesis (Brinton 2008).
- Postmenopausal SCD may be a marker of cholinergic vulnerability and/or E2 unresponsiveness and suggests that the ability of E2 to decrease the risk of late-life cognitive impairment may be selective.

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