Cholinergic blockade increased functional connectivity in Occipital and Insular cortices in healthy postmenopausal women

Juliann Sargis, Magdalena Naylor, Peter Casson, Paul Newhouse, & Julie Dumas

Disruption of the cholinergic system is thought to be the main cause of memory disorders such as Alzheimer's disease(AD) and Mild Cognitive Impairment(MCI). Prior studies have shown that cholinergic enhancement decreased connectivity of the medial prefrontal cortex(MPF) to visual association areas, creating more efficient information processing and reduced effort in attention demanding tasks. The use of cholinergic antagonists mecamylamine(MECA) and scopolamine(SCOP), have been used to impair attention and memory encoding and this is a proposed model of normal aging and AD. We utilized these pharmacological manipulations to further understand how these processes affect connectivity in brain regions important for cognitive processes. Twelve healthy, cognitively normal postmenopausal women (mean age(SD)= 59.5(5.2) took part in three fMRI testing sessions in which they received placebo, 20mg MECA or 2.5μg/kg SCOP. After drug administration the women underwent a baseline fMRI to observe the effects of MECA and SCOP on functional connectivity in the brain. We used a seed based method to examine functional connectivity and seeded the posterior cingulate cortex(PCC) and MPF which are both believed to be the main cortical areas affected by normal aging and AD. We examined correlations of time course of activation in each seed with the time course of activation in all other voxels in the brain. Both MECA and SCOP compared to placebo increased connectivity from the PCC to visual association areas and insular cortices, as well as decrease connectivity to frontal lobes, parietal lobes, and anterior cingulate cortex. These data show the ability of mecamylamine and scopolamine to affect cholinergic networks, specifically by decreasing connectivity of the PCC and MPF to the frontal lobes. These results may have implications for the role of the cholinergic system in controlling the attentional resources, a cognitive process that declines in normal aging, MCI, and AD.