using a model of anti-cholinergic drug-induced cognitive dysfunction. We hypothesized that TMX would, in the absence of estrogen, enhance cholinergic function and blunt the effects of muscarinic and nicotinic blockade on attention, delayed memory, and spatial learning and memory.
Methods: Twenty-one postmenopausal women were administered 20 mg of oral TMX or placebo for three months. Participants then took part in five drug challenges using the anticholinergic antinicotinic agent mecamylamine (MECA) and anti-muscarinic agent scopolamine (SCOP) and were tested on a comprehensive battery including tasks of attention and psychomotor function, verbal episodic memory, and spatial navigation utilizing the computerized Virtual Morris Water task. After a three-month placebo washout, participants were then crossed over to the alternate treatment and repeated the challenge days after three months.
Results: TMX compared to placebo treatment significantly attenuated the impairment from cholinergic blockade on tasks of verbal episodic memory and spatial navigation, but worsened performance on attentional/psychomotor tasks. Analysis by APOE genotype showed that APO ε4+ women showed a greater beneficial effect of TMX on reversing the cholinergic impairment than APO ε4- women on most tasks.
Conclusions: This study provides evidence that TMX may act as an estrogen-like agonist to enhance cholinergic system activity and hippocampally-mediated learning. SERMs such as TMX may have promise for maintenance of cognitive functioning in older women after menopause.

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Grey Matter Atrophy Associated With Delusional Onset In Mild Cognitive Impairment Patients

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Introduction: Mild Cognitive Impairment (MCI) patients may present with delusions and other psychiatric symptoms, which significantly contribute to greater caregiver burden and functional impairment. It is unknown whether the development of delusions in patients with MCI is associated with atrophy in specific neuroanatomical structures associated with cognitive inhibition. Previous research suggests that the right frontal areas are involved in inhibition of inappropriate thoughts and the monitoring of emotions. We therefore hypothesized that enhanced atrophy in the right frontal areas of the brain would attenuate the monitoring/inhibitory function of these areas, contributing to delusional onset.
Methods: Twenty-four non-delusional MCI patients who developed delusions within 6 months to a year were subject to within-group comparisons, using 1.5 Tesla structural magnetic resonance images. The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a longitudinal, international collaboration providing curated structural neuroimaging data for research purposes. We conducted a longitudinal voxel-based morphometry (VBM) analysis on a well-defined cohort of ADNI participants with MCI who developed delusions. Specialized scripts in the VBM8 toolbox running on Statistical Parametric Mapping 8 were used to modify the typical VBM processing pipeline to accommodate longitudinal analysis; post-delusional onset images were warped to the pre-delusional onset analogs. Individual grey matter images were normalized and smoothed with an isotropic Gaussian kernel of 8 mm full-width half maximum. The modulated images were entered into a General Linear Model for a two-sample dependent t-test.
Results: In total, fourteen significantly different voxel clusters were detected in the analysis (Table 1). Half of the fourteen clusters were located in the right hemisphere. The five most significantly different voxel clusters, in decreasing order were in the left precuneus (cluster size, Kc = 3011), right cerebellar culmen (103), left superior temporal gyrus (902), left cerebellar culmen (252), and left insula (350). As criteria for significance, we corrected for multiple comparisons using the False Discovery Rate (FDR) approach at $p < 0.05$ and only reported clusters with a size greater than fifty.
Conclusions: In our ADNI cohort of MCI patients over time, the onset of delusions was accompanied with characteristic decreases in cortical and cerebellar grey matter. Although our VBM analysis did not reveal significant asymmetry in atrophy patterns overall, areas such as the precuneus and insula have been associated with consciousness processes and emotional regulation. The right insular cortex was also the most significantly atrophied structure in our previous work cross-sectionally with ADNI MCI patients with and without delusions. In addition, various studies in schizophrenic patients have shown an association between cerebellar dysfunction and psychotic symptoms. Our results localize areas of brain atrophy associated with the longitudinal onset of delusions in the same group of MCI patients. We look forward to verifying and extending these results in a greater cohort of MCI patients from other similar collaborations.

Table 1. Suprathreshold voxel clusters in longitudinal VBM analysis of ADNI MCI participants who developed delusions, FDR corrected $p < 0.05$ with cluster size greater than or equal to fifty

SUPRATHESHOLD VOXEL CLUSTERS, $p < 0.05$ FDR Corrected								
	Coordinates (Talairach)			Cluster Size				
Cluster No.	X	Y	Z	k_c	Location (Nearest Grey Matter)	T	$q_{FDR\ corr.}$ (peak)	$P_{uncorr.}$ (cluster)
1	−2	−58	32	3011	Left Precuneus	5.59	0.022	0.000
2	18	−52	−13	103	Right Cerebellar Culmen	5.16	0.022	0.274
3	−57	−40	17	902	Left Superior Temporal Gyrus	5.12	0.022	0.004
4	−38	−44	−19	252	Left Cerebellar Culmen	5.12	0.022	0.095
5	−38	4	1	350	Left Insula	4.99	0.022	0.054
6	−29	−38	−7	633	Left Parahippocampal Gyrus	4.94	0.022	0.013
7	5	44	18	62	Right Medial Frontal Gyrus	4.93	0.022	0.397
8	29	16	−5	1180	Right Insula	4.85	0.022	0.001
9	−40	−31	15	90	Left Superior Temporal Gyrus	4.11	0.023	0.306
10	35	−41	−23	90	Right Cerebellar Culmen	4.07	0.023	0.306
11	−45	−8	5	53	Left Insula	3.80	0.025	0.436
12	23	−38	−12	75	Right Cerebellar Culmen	3.79	0.025	0.351
13	3	−18	12	200	Right Thalamus	3.55	0.028	0.133
14	19	−53	6	74	Right Posterior Cingulate	3.51	0.028	0.354

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Inflammaging: associated with physical frailty in late-life depression

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Introduction: The prevalence of physical frailty is significantly higher in depressed older persons compared to non-depressed older persons, even when corrected for overlapping criteria of both constructs (Collard et al, 2013). As low-graded inflammation is associated with both frailty and depression, we examined inflammatory markers in depressed and non-depressed persons stratified for frailty status. We hypothesize highest levels of inflammatory markers in frail, depressed persons.
Methods: This cross-sectional study was embedded in the Netherlands Study of Depression in Older people (NESDO), a prospective cohort study. A total of 378 subjects suffered from a depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) as assessed with the Composite International Diagnostic Interview (CIDI 2.1). A comparison group of 132 non-depressed subjects were included. The components of the Fried criteria, weight loss, weakness, poor endurance and energy, slowness and low physical activity level, were used as physical frailty markers. Principal