METHODS/STUDY POPULATION: We searched PubMed, CINAHL, and SCOPUS through September 15, 2024, using keywords and appropriate subject headings related to AD, fluid biomarkers, and sleep. The search was developed and conducted in collaboration with a medical librarian. We also searched Google Scholar and screened the reference lists of relevant reviews. Two independent reviewers screened 1,657 peer-reviewed articles, of which 21 met the inclusion criteria (14 with biomarkers measured in cerebrospinal fluid [CSF] and 7 in blood). Two review authors independently extracted study details from included articles using a standardized data extraction template. RESULTS/ANTICIPATED RESULTS: Sample sizes ranged from 18 to 4,712 participants. Sleep duration was assessed using self-reported measures in 8 studies and objective measures in 13. For the 14 studies using CSF biomarkers, lower Aβ42 (3/14), Aβ40 (1/14), or the ratio (1/14) were associated with either short or long sleep duration; t-tau (3/14) and p-tau181 (4/14) levels were mostly associated with short sleep. For the 7 blood-based biomarker studies, Aβ42 (2/7), Aβ40 (2/7), and the ratio (3/7) had mixed results with either short or long sleep. T-tau (1/7) and p-tau181 (1/7) levels were associated with long sleep; NfL (2/7) was associated with both short and long sleep. Six studies reported nonlinear relationships, with both short and long sleep associated with unfavorable biomarker profiles. None of the studies investigated p-tau 217 or GFAP. DISCUSSION/SIGNIFICANCE OF IMPACT: Our results suggest that the relationship between sleep duration and AD fluid biomarkers is very complex, and it highlights the importance of sleep in AD risk assessment and prevention. The inconsistency in findings stresses the need for standardized study design and measurement methods to clarify causality and inform clinical guidelines.

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## Targeting negative-self-referential processing with transcranial magnetic stimulation: Feasibility studies

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OBJECTIVES/GOALS: Neuromodulation strategies like transcranial magnetic stimulation (TMS) can target specific neural circuits underlying particular psychiatric symptoms, potentially 1) enhancing understanding of mechanisms of illness and recovery and 2) acting as novel therapeutics. These feasibility studies lay foundation for a study of major depression. METHODS/STUDY POPULATION: Four healthy volunteers completed structural and functional MRI (fMRI). fMRI included a trait-adjective task, a negative self-referential processing task known to activate VMPFC, which is known to be abnormal in major depression. During the task, participants respond on a task pad whether they feel that each of a series of displayed adjectives (positive, negative, or neutral) applies to them. Three participants then participated in a simulated image-guided TMS session using their MRI data to target their VMPFC. Three-dimensional tracking of the participant's head and the TMS coil was used to position the coil for peak stimulation of the targeted brain region. RESULTS/ANTICIPATED RESULTS: Our team collected quality neural and behavioral data on the fMRI task; participants reported a tolerable experience. Simulated neuronavigated TMS showed feasibility and tolerability of positioning the device to stimulate VMPFC. The fMRI task activated the VMPFC as predicted. The MRI and TMS protocols were replicable and tolerable. These procedures can now be used experimentally by our team with confidence to test our hypothesis that targeting the VMPFC within the brain's default-mode network may normalize aberrant VMPFC activity seen in major depression, thereby improving excessive negative self-referential processing. DISCUSSION/SIGNIFICANCE OF IMPACT: This project lays essential groundwork for my K12 project, "Targeting Negative-Self Referential Processing in Depression with TMS," a longitudinal neuroimaging and behavioral study using these methods in the study population of people with major depression.

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## Follicle-stimulating hormone is reduced following a novel nutritional therapeutic in postmenopausal women with obesity

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OBJECTIVES/GOALS: Increased follicle-stimulating hormone (FSH) is linked to declines in ovarian and metabolic function in older women. Obesity is both a manifestation and a driver of aging pathologies. In animal models, FSH and insulin resistance (IR) were reduced after 6 mos. of a nutritional therapeutic (GLYLO). Our goal was to translate preclinical evidence to humans. METHODS/STUDY POPULATION: An integrated, precision medicine approach identified a unique phenotype of aging-related debility relative to older females. A non-comparer pilot study was conducted to translate GLYLO preclinical findings to postmenopausal women with obesity (n = 85; >55 years; body mass index [BMI] = 35.0 ±4.35; range: 30.3–42.8). Participants meeting the inclusion and exclusion criteria (n = 13) were enrolled and received two capsules of GLYLO (vitamins and natural products) daily for 6 mos. Assessments for FSH, estradiol (E2), IR (homeostatic model [HOMA-IR]), total cholesterol (TC), low- (LDL), high-density lipoproteins (HDL), safety biomarkers (e.g., red cell distribution width [RDW%], mean corpuscular volume [MCV]), and depression (Center for Epidemiologic Studies Depression Scale) were conducted prior to and after 6 mos. RESULTS/ANTICIPATED RESULTS: Mixed-effect models with intent-to-treat analysis were applied to compare outcomes prior to (n = 13) and following (n = 7) the intervention. Significant reductions in FSH were observed (-13.1 [2.47] Δ/SD; p = 0.002)) following the 6-month intervention. Interestingly, BMI, E2 (p = 0.412), HOMA-IR (p = 0.885), TC (p = 0.363), and LDL (p = 0.145) were unchanged, while HDL

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