Effects of Lisdexamfetamine on prefrontal brain activation, glutamate concentration and executive function in menopausal women with memory complaints: A double-blind placebo controlled crossover study at 7T

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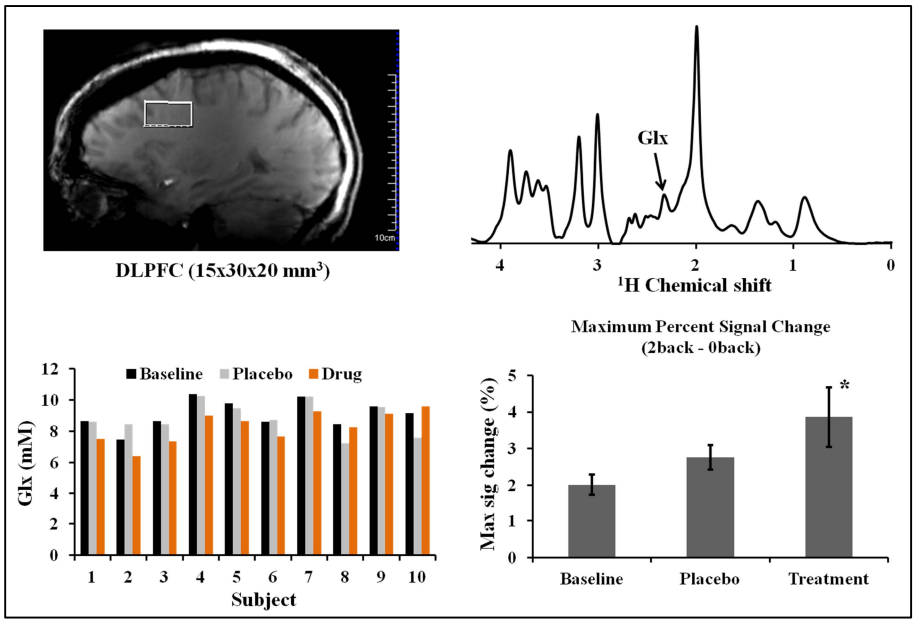
Introduction: During the menopause transition, many women report a decline in memory, focus, and organization, which are aspects of cognition referred to as executive functions (EFs). Loss of estradiol modulation of prefrontal dopamine systems may be one mechanism leading to this subjective decline in EFs at menopause. The psychostimulant lisdexamfetamine (LDX; Vyvanse®) may offset the effect of estradiol loss by enhancing dopamine function in the prefrontal cortex (PFC). We examined the effects of LDX on the left dorsolateral prefrontal cortex (DLPFC) using multimodal imaging including proton magnetic resonance spectroscopy (^{1}H-MRS) and functional magnetic resonance imaging (fMRI) in a subset of women participating in an on-going study of LDX in the treatment of EF difficulties during menopause.

Methods: A total of 15 healthy peri and early postmenopausal women (ages 45-60 years) reporting EF difficulties will be enrolled in this on-going, double-blind, placebo controlled, crossover study investigating the impact of LDX (40-60 mg/d) on brain glutamate and blood oxygen level dependent (BOLD) signal. Participants are healthy, right-handed, have a follicle stimulating hormone level of ≥20 and are within 5 years of their final menstrual period. Use of hormone therapy or psychotropic medications within the previous 6 months is exclusionary. All women provide signed informed consent for this study which is approved by the Perelman School of Medicine at the University of Pennsylvania Institutional Review Board. Severity of EF difficulties is determined by the Brown Attention Deficit Disorder Scale (BADDS) with all participants having a BADDS score of at least 20. Participants undergo fMRI and ^{1}H-MRS at baseline and at the end of each 4-week treatment arm (LDX, Placebo) with a 2 week wash-out between treatment arms. Left DLPFC glutamate concentrations are measured by ^{1}H-MRS immediately prior to performance of a working memory task (N-back task) while BOLD signal is measured during task performance. Scans were conducted using a Siemens 7T whole body scanner with a vendor supplied 32-Channel head coil. Automated placement of the ^{1}H-MRS voxel in left DLPFC (15x30x20 mm^3) was performed using the Imscribe (http://cmroi.med.upenn.edu/imscribe/) software package, which registered the subject's MPRAGE MRI to an MNI-space template. Automated shimming of the B_0 field was performed on the voxel in order to obtain localized water line width of ~20 Hz or less using FASTMAP shim method [1, 2] provided by SEIMENS as a works in progress (WIP) package. Single voxel spectra (SVS) for Glx were obtained with a PRESS sequence using the following parameters: number of points = 2048, averages = 16 (water reference)/64 (water suppressed), TR = 3000 ms and TE = 20 ms. Total acquisition time to obtain the spectra was 4 min. For post processing we used the raw multi-channel time domain data. From the water reference data, channel wise time dependent phase shifts due to eddy current and amplitude scale factors were obtained. All spectra were obtained after channel wise eddy current correction and adaptive combination [4]. Metabolite peaks from water suppressed spectrum were fitted as Lorentzian functions with non-linear least squares fitting (MATLAB "nlinfit" routine) by taking into account prior knowledge of eight macromolecular peaks and fourteen metabolite peaks over the frequency range of 0.5 to 4.3 ppm [5], followed by integration and then normalized by the water reference signal for absolute quantification of Glx. A BOLD imaging N-back task consisting of fractal images displayed in 0-back and 2-back blocks was acquired with the following parameters: TE/TR=27/3000ms, matrix=110x100, voxel size=2x2mm, slice thickness=2.2mm, slices=37, measurement=239. Maximum BOLD percent signal change in the left DLPFC for the contrast *2-back > 0-back* was computed.



Results: Ten women (52.7 ± 2.5 years old at time of admission) have completed all phases of the study. Mean (SD) glutamate levels are 9.09 (0.91) mM whereas the glutamate levels after the placebo and LDX administration were 8.85 (1.02) mM and 8.27 (1.02), respectively in the DFLPC region. Typical MRS spectra obtained as well as the fMRI BOLD results are provided in Figure 1. Five additional women were in the screening phase for both the treatment and brain imaging studies. BADDS scores at Baseline and during the Placebo arm are 43.10 ± 15.44 and 35.10 ± 16.29, respectively. Though BADDS scores (17.33 ± 9.67) and glutamate levels during the LDX treatment arm were lower, the findings were not statistically significant in this small sample. However, BOLD signal change in the LDX Treatment arm was associated with a significant increase in activation compared to the baseline scans ($p < 0.05$, df=9). There was no significant change in peak BOLD signal between Placebo and baseline.

Conclusions: Preliminary data (n=10) suggests that the psychostimulant LDX is well-tolerated and may reduce subjective executive functioning difficulties in certain menopausal women. Examining the impact of LDX on glutamate concentrations and brain activation during working memory in a larger sample will provide a more direct assessment of the impact of LDX on brain regions subserving executive functions in menopausal women and provide a more robust examination of LDX effects on cognitive performance in this population.

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