University of Pennsylvania Perelman School of Medicine

IMPRES: IMProving Executive function Study IRB #826981

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ABSTRACT
Risk-reduction bilateral salpingo-oophorectomy (RRSO) after completion of childbearing has become the standard-of-care for prevention of gynecologic and breast cancer in BRCA1 or BRCA2 gene mutation carriers. Although surgery reduces the risk of death due to cancer by over 75%, knowledge regarding the impact of this procedure and subsequent hypogonadism on brain structure, function and neurotransmitter systems is limited. Menopause before the age of 40 is associated with significant cognitive decline in the years that follow and an almost 2-fold increased risk of dementia if a woman does not supplement with estradiol (E2). However, E2 is not an option for many post-RRSO women due to enhanced risk of cancer. Systematic assessment of a large group of women who underwent RRSO suggests subjective deficits in executive functions (EF), with severity inversely correlated with age at RRSO. As the prefrontal cortex is impacted by loss of E2 and is critical for working memory and other EFs, we propose to examine the biological and behavioral impact of the psychostimulant lisdexamfetamine (LDX) in 100 women between the ages of 35 and 58 with post-RRSO EF complaints. LDX is FDA approved for the treatment of attention deficit hyperactivity disorder which is characterized by many of the symptoms reported by some peri- and postmenopausal women. Participants in this study will undergo multi-modal imaging (functional magnetic resonance spectroscopy, fMRI; and proton magnetic resonance spectroscopy, 1H-MRS) using the ultrahigh magnetic field strength of 7 Tesla pre- and post- a 6-week course of the psychostimulant lisdexamfetamine (LDX; Vyvanse®) or placebo followed by an approximate 2-week washout before crossing over to the other condition. Our overarching aim is to determine the impact of LDX treatment on brain function (neural activation and chemistry) as it relates to subjective and objective measures of EFs such as 1) organization and activation for work, 2) attention and concentration, 3) alertness, effort, processing speed, 4) managing affective interference, and 5) working memory, accessing recall. LDX has already demonstrated the potential to improve new-onset EF difficulties among women who underwent a natural menopause and has provided important information regarding a potential mechanism of therapeutic action, specifically LDX-induced changes in dorsolateral prefrontal cortex (dlPFC) glutamate (GLUT) levels.

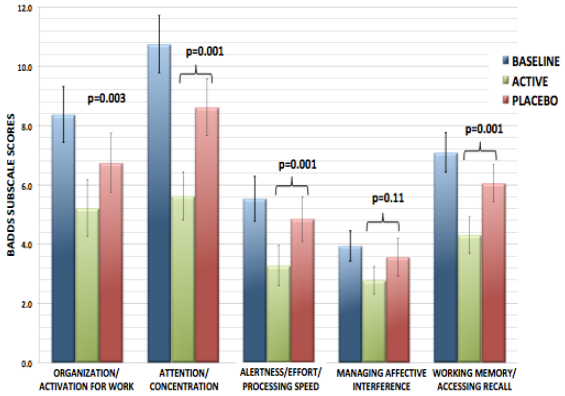
Background
It is becoming standard of care to recommend that premenopausal women who carry BRCA 1/2 gene mutation(s) undergo risk-reducing bilateral salpingo-oophorectomy (RRSO) upon completion of child bearing. Though RRSO before the age of 40 is associated with an 80% reduction risk of ovarian, fallopian tube, and peritoneal cancer, premature menopause is associated with significant cognitive decline in the short-term and an almost 2-fold increase risk for dementia in the long-term if subsequent intervention is not utilized (Finch et al., 2014; Domchek et al., 2010; Ryan et al., 2014). Preliminary data suggest varying degrees of executive function difficulties occur in 30% to 50% of women post-RRSO. Cognitive domains particularly affected by early menopause include verbal memory (Sherwin & Henry, 2008), verbal fluency and processing speed (Ryan et al., 2014), and executive functions such as attention, organization, and working memory in some women (Epperson, et al., 2011).

Treatment of executive function difficulties with estradiol therapy (ET) after surgery is relatively contraindicated for some women who undergo RRSO. Overall rates of ET use after RRSO are between 25% and 47% (Madalinska et al., 2006). Moreover, longer periods of time without ET after RRSO may diminish the potential positive impact of ET (Maki, 2013; Rocca et al, 2011,

2012). Women who experience cognitive difficulties after RRSO may put off use of ET due to fear of breast cancer, diminishing the potential benefits of ET should they reconsider treatment to mitigate cognitive changes. However, ET is only partially protective even if utilized within the first month of surgical menopause as certain domains of cognitive function such as spatial memory may not be amenable to ET (Ryan et al., 2014). Hence women and their oncologists must conduct a cost benefit analysis between a potential life-saving procedure and preservation of quality of life. Given that premature menopause has adverse effects on cognitive function at a time in a woman's life when she is experiencing the greatest demands professionally and personally, it is imperative to seek alternative interventions.

Our group has explored the use of other pharmacologic strategies to target executive systems with the goal of improving symptoms of executive function difficulties. We have conducted two RCTs with medication marketed for the treatment of attention deficit hyperactivity disorder (ADHD), one with the non-psychostimulant atomoxetine (ATX, Straterra®) and two with the pro-drug and psychostimulant lisdexamfetamine (LDX, Vyvanse®) in the treatment of executive function difficulties in perimenopausal and menopausal women. Women who participated in the ATX study reported a significant improvement in concentration/attention and working memory domains of the Brown Attention Deficit Disorder Scale (BADDS) (Epperson et al., 2011). Participants in both LDX studies were also invited to undergo the brain-imaging paradigm that is described for the current study.

Figure 1 shows the main outcome of the published results, specifically that LDX was more effective than placebo at decreasing scores in 4 of the 5 BADDS subscales (Epperson et al., 2015). Findings from the imaging sub-study indicated that baseline glutamate (Glut) levels were correlated with baseline severity of total BADDS scores, meaning that individuals presenting at baseline with higher severity of executive function difficulties also had higher Glut levels within the left dorsolateral prefrontal cortex (DLPFC) at baseline. Additionally, the decline in BADDS subscale 1 (Organization and Activation) scores during LDX vs. placebo treatment was negatively associated with increase in left DLPFC blood oxygen dependent (BOLD) signal during a working memory task (N-Back). That is, the increase in left DLPFC BOLD signal to active drug compared to placebo was greater in people who had greater improvement in BADDS score on LDX vs. placebo. These findings provide important evidence of co-occurring behavioral and brain changes with LDX treatment. Applying this paradigm in a larger sample of women from whom we will also acquire neurocognitive data to assess objective changes in function will provide important information regarding the mechanism of therapeutic action of LDX in this unique population.



1 Study Objectives

1.1 *Overall Objectives*

The overarching aim of this study is to determine the impact of LDX treatment on brain function (neural activation and chemistry) as it relates to subjective and objective measures of executive functioning.

1.2 *Primary Outcome Variable(s)*

LDX effects on subjective report of executive function difficulties. Brown Attention Deficit Disorder Scale (BADDS) is a clinically administered 40-item questionnaire that assess the frequency and severity of five clusters of symptoms: 1) organization and activating for work, 2) sustaining attention, 3) sustaining alertness, 4) managing affective interference, and 5) using working memory and accessing recall. The total BADDS score will serve as the primary outcome variable, while sub-scale scores will be examined to more fully determine the impact of LDX treatment on various domains of executive function and to determine whether any sub-categories of executive difficulty are more responsive to LDX treatment in this particular population.

1.3 *Secondary Outcome Variable(s)*

LDX effects on objective report of executive function difficulties. Proton magnetic resonance spectroscopy (1H-MRS) and functional magnetic resonance imaging (fMRI) will be utilized to assess the relative importance of dorsolateral prefrontal cortex (DLPFC) glutamate (Glut) levels and blood oxygen dependent (BOLD) signals during working memory task performance and the effect of LDX on the executive system activation.

2 Study Design

2.1 *General Design*

To further our understanding of the mechanism of LDX treatment in women with executive function complaints after risk-reducing bilateral salpingo-oophorectomy (RRSO), participants will undergo multi-modal imaging (fMRI and 1H-MTS at 7 Tesla) pre- and post- a 6-week course of LDX (20-60mg/d) or placebo followed by an approximate 2-week washout before crossing over to the other condition. This study utilizes a double-blind, placebo-controlled, cross-over design. We will recruit 100 women who are between the ages of 35 and 58 years old. Subjects will be recruited from flyers posted around campus, paid advertisements, referrals from collaborators at FORCE (Facing Our Risk of Cancer Empowered), the Basser Center, and other medical settings where women who have undergone RRSO may seek treatment. Study subjects will be screened by a member of the research staff who can gauge whether the individuals are likely to meet study criteria. Potential participants who appear to meet criteria and express an interest in the study will have the option of completing the screening visit remotely or completing the visit in-office. Participants will also have the option to complete a remote version of the study.

In-Office Screening: Participants who report for an in-office screening will be presented with the full, written ICF where they will have the chance to review and sign it with the study CRC. After giving full, written informed consent, subjects will undergo screening for past and current psychiatric disorders with the Mini International Neuropsychiatric Interview (M.I.N.I) and complete several behavioral ratings and questionnaires concerning personal history. A urine sample will be collected from participants to do a urine drug screen. Subjects will then undergo a brief medical evaluation and electrocardiogram (EKG) conducted by the study PI (Epperson, M.D.) or key study personnel. Vital signs including blood pressure and pulse will be recorded. Women with a consistent systolic blood pressure of >145mm Hg or diastolic blood pressure >90 mm Hg after three readings at screening will not be enrolled and referred to their primary care doctors for further evaluation. Routine laboratory studies will include TSH, FSH and estrogen assays. If potential subjects have had these tests performed within the previous 6 months and can present their results, they will forgo additional blood work except that for genetics studies (4 mL)

to examine genes related to estrogen metabolism and various neurotransmitter systems involved in cognition. These tests will assess general health and confirm postmenopausal status. The study PI will be responsible for the final decisions regarding enrollment.

Remote Screening: Participants who decide to complete the screening visit remotely must have access to telecommunication applications (i.e., Skype) that would enable the research team and participants to communicate via video chat in real-time. Furthermore, participants must have access to a scanner/fax machine so that they can send documents to the study CRC during the screening visit. Subjects who meet these stipulations will be presented with the full, written informed consent form via email and will have the opportunity to review the document in its entirety with the study CRC in real-time. After providing consent, subjects are expected to scan/fax the ICF document with their signatures to the CRC before completing other study-related procedures. The CRC will sign the document, attesting that she obtained consent, and scan/fax the document back to the subjects so that they have a copy for their records. Subjects will then undergo screening for past and current psychiatric disorders with the Mini International Neuropsychiatric Interview (M.I.N.I) and complete several behavioral ratings and questionnaires concerning personal history. Subjects will have the option of completing the brief medical evaluation, electrocardiogram (EKG), and routine laboratories studies (TSH, FSH, and estrogen levels) with their physician of choice or with key study personnel before their baseline visit. If applicable, participants will not proceed to the MRI portion of the visit until they have received medical clearance from study personnel. If potential subjects have had the blood work performed within the previous 6 months and can present their results, they will forgo additional blood work except that for genetics studies (4 mL). The study PI will be responsible for the final decisions regarding enrollment.

Participants will also review a supplemental informed consent form with a study physician, pertaining to the purpose, procedures and risks/benefits of using both of the study medications. This form will be reviewed and signed in anticipation of the participant's first dose of study medication.

Participants either unable to travel or unable to complete an MRI will be offered a remote non-imaging alternative which removes the MRI and blood draws from the required study procedures.

Baseline MRI Scan (Visit 2): Upon completion of the screening visit, subjects will be scheduled to undergo their baseline ^{1}H-MRS and fMRI scan session, which will take approximately 75 minutes. Subjects will be instructed to present to the Penn Center for Women's Behavioral Wellness approximately 2.5 hours before their scheduled scan to complete behavioral assessments regarding their mood and emotions and to complete out-of-scanner cognitive testing. Subjects will then be escorted to the Center for Magnetic Resonance and Optical Imaging (CMROI) by the study CRC where they will be scanned and asked to perform a series of tasks assessing their memory and attention. Subjects will then be given the study drug for the entirety of Trial A (either placebo or LDX) and instructed to begin taking the medication as directed by the study provider. If the participant needs additional study drug in order to complete the trial an additional script will be submitted to IDS for dispensation. Upon completion of the visit, the subject will be given a scale and blood pressure cuff for future remote vital sign collections. In total, the baseline scan visit will require approximately 4 hours to complete.

Additional Study Procedures for MRI eligible Subjects who Completed Screening Remotely: All subjects who completed the screening visit remotely will be reminded to bring the original version of the ICF to their Baseline MRI Scan (Visit 2) so that the original copy can be stored at PCWBW. A urine sample will be collected from all subjects to do a urine drug screen and an additional tube of blood will be collected for those who consented to genetics studies (4 mL) on the ICF before they start their scan. Subjects who indicated that they prefer research personnel to complete their required EKG and medical evaluation will be instructed to present to the Penn Center for Women's Behavioral Wellness approximately 3.5 hours before their scheduled scan to complete said procedures in addition to the assessments stipulated by Visit 2. In total, the baseline scan visit will require approximately 5 hours to complete for those that still need medical clearance.

Remote Baseline (Visit 2): Upon completion of the screening process, subjects will be scheduled for the baseline visit which will require approximately two hours. Medication will be mailed directly to the patient's home through appropriate and approved direct-to-patient services. Subjects will be prescribed study drug for the entirety of Trial A (either placebo or LDX) and instructed to begin taking the medication as directed by the study provider. If the participant needs additional study drug in order to complete the trial an additional script will be submitted to IDS for dispensation. The subject will be sent a scale (if needed) and blood pressure cuff for future remote vital sign collections. On the day of the remote baseline visit, subjects will meet remotely with a member of the study team to complete behavioral assessments regarding their mood and emotions and complete cognitive testing.

Week 2 Phone Check-In: At the end of week 2 of medication use, the CRC will check in with the participant by phone to assess for side effects. Subjects who are having more than mild side effects will be instructed to reduce their dose back to one pill per day.

Week 3 Mid-Trial Check-In: Halfway through Trial A, during their third week, subjects will be scheduled for a remote follow-up visit where they will be monitored by the CRC for potential side effects of the medication and medication compliance. If no or mild side effects are reported, subjects will be instructed to increase the study drug to three pills per day. Subjects who are having more than mild side effects will be instructed to reduce their dose back to one pill per day. The study CRC can exercise her discretion regarding medical personnel involvement at this check-in. Subjects will be instructed to complete various mood and symptoms ratings during the visit. In total, the visit will require approximately 60 minutes and will include measures of blood pressure, pulse, and weight.

Week 4 Phone Check-In: During week 4, the CRC will check in with the participant by phone to assess for side effects. Subjects who are having more than mild side effects will be instructed to reduce their dose back to 2 pills per day for the remainder of the trial.

End of Trial Scan: After the 6-week period, subjects will be scheduled to undergo their end of Trial A ^{1}H-MRS and fMRI scan session, which will take approximately 75 minutes. Subjects will be instructed to present to the Penn Center for Women's Behavioral Wellness approximately 2.5 hours before their scheduled scan to complete cognitive testing and behavioral assessments

regarding their mood and emotions. Subjects will then be escorted to the CMROI by the study CRC where they will be scanned and asked to perform a series of tasks assessing their memory and attention. In total, the end of Trial A scan will require approximately 4 hours to complete. The completion of this visit concludes all visits for Trial A. Upon completion of the visit and Trial A, subjects will be given the study drug for the entirety of Trial B (either placebo or LDX) and instructed to begin taking the medication after the washout period, as directed by the study provider.

Following an approximate 2-week washout period, subjects will complete their Trial B Baseline Visit, initiating the start of Trial B and medication usage. With the exception of the first baseline scan and cognitive testing, subjects will undergo the same study procedures for Trial B as they did for Trial A. Subsequent to their last scan, subjects will be required to bring their scales, blood pressure cuffs and unused capsules/empty bottles back to the study team so that they can be returned to Penn Investigational Drug Service (IDS).

The primary investigator and research staff will unblind themselves to the drug treatment that was administered in each trial upon each participant's completion or discharge from the study.

Remote End of Trial Visit: After the 6-week period, subjects will be scheduled to undergo their end of trial visit which will require approximately two hours. On the day of the remote end of trial visit, subjects will meet remotely with a member of the study team to complete behavioral assessments regarding their mood and emotions and complete cognitive testing. The completion of this visit concludes all visits for Trial A. Upon completion of the visit and Trial A, subjects will return the prescription bottle and any remaining study drug from Trial A so that they can be returned to Penn Investigational Drug Service (IDS). At this point, all subjects will be instructed to complete an approximate 2-week wash out period before continuing to Trial B.

Following an approximate 2-week washout period, subjects will be mailed their prescription for Trial B and complete their Trial B Baseline Visit remotely, initiating the start of Trial B and medication usage. Subjects will undergo the same study procedures for Trial B as they did for Trial A.

At the completion of the remote End of Trial B visit, subjects will be required to bring return the scale (if applicable), blood pressure cuffs and unused capsules/empty bottles back to the study team so that they can be returned to Penn Investigational Drug Service (IDS).

The primary investigator and research staff will unblind themselves to the drug treatment that was administered in each trial upon each participant's completion or discharge from the study.

2.2 *1H-MRS Methods*

All the single-voxel ^{1}H-MRS experiments to measure glutamate will be performed on a 7.0T whole body MRI scanner (Siemens Medical Systems, Erlangen, Germany) with a vendor supplied volume coil transmit/32 channel receive proton head phased array coil. BOLD signal change will be measured during performance of cognitive task and during rest.

2.3 *Medical Administration*

Subjects will be prescribed lisdexamfetamine (LDX) 20mg capsules or a look-alike placebo (microcellulose) by the study PI (Epperson, M.D.) or her designee. Subjects will be instructed to take one pill (LDX = 20 mg) each morning for 7 days and then will be asked to increase to two pills (LDX = 40 mg) each morning for 14 days. If the study drug is well tolerated by the end of week 3 (as per medication monitoring by the CRC), participants will be asked to increase to three pills (LDX = 60 mg) each morning until the completion of the trial. Participants will be instructed to contact the study team if they experience any side effects and may decrease their medication as instructed. At the end of week 6, which is the end of the trial, participants will be evaluated and instructed to stop their study drug. After an approximate 2-week washout, participants will be crossed over to the other condition and the procedure will repeat. See table below for dosing instructions when the substance is well tolerated.

Week	1	2	3	4	5	6
Dosage	20mg	40mg	40mg	60mg	60mg	60mg

2.4 *Medication Dispensation*

Subjects will receive one medication bottle at their Trial A Baseline MRI Scan (Visit 2), which should last through the entirety of Trial A (6 weeks). Upon completion of their End of Trial A MRI Scan (Visit 4), subjects will receive their second medication bottle for Trial B. Subjects will be instructed to begin taking the medication after their Trial B Baseline Visit.

In the event that a subject would require additional capsules, another prescription will be submitted on her behalf for the exact number of capsules needed to get her through the remainder of her trial.

2.5 *Compensation*

Participants will be compensated for their participation in all study visits. If the participant completes all parts of the study, is on time for appointments, and takes her medication, total payment for participants is $650.

The breakdown of subject payment by visit is as follows:

Visit Name	Visit Number	Amount
Screening Visit*	Visit 1	$50
Trial A		
Baseline (with Scan)	Visit 2	$150
Week 3*	Visit 3	$50
End of Trial A (with Scan)	Visit 4	$150
Trial B		
Baseline (without Scan)*	Visit 5	$50
Week 3*	Visit 6	$50
End of Trial B (with Scan)	Visit 7	$150

Note: "" indicates that study visit can be complete remotely.*

Subject reimbursement is available for:

- Transportation to and from required in-office visits (Visits 2, 4, and 7).

- Hotel accommodations provided by the research team for up to two nights for required in-office visits (Visits 2, 4, and 7)
- Study-related procedures completed with the subject's physician that were NOT covered by the subject's insurance (i.e., EKG, blood work, and physical exam).

2.6 ***Study Duration***
We anticipate completion of recruitment within 5 years of study inception. Each subject will spend approximately 4-5 months completing all study related procedures.

3. Subject Selection and Withdrawal

3.1 ***Target Population***
We will recruit 100 women, aged 35 to 58 years old, who have undergone a RRSO within the previous 15 years and are currently reporting impairment in some aspect of their daily function. We anticipate a drop-out rate of 10%. Given that the composition of the proposed study population will reflect the Greater Philadelphia referral base, we will make attempts to enhance the recruitment of minorities, but we are limited by the racial and ethnic make-up of women who typically seek oophorectomy for prevention of breast and ovarian cancer.

3.2 ***Accrual***
We anticipate that we will meet our recruitment goals by working with our longstanding collaborators in the Department of Oncology at Penn and the support group: Facing Our Risk of Cancer Empowered (FORCE) for women who are at genetic risk for breast and ovarian cancer and/or gynecologic cancer survivors. Based on previous recruitment efforts, the organization could provide 30% of our participants from the FORCE membership of 25,000 women. Also, 500 BRCA-1/2 gene carriers are followed yearly at the Basser Center for BRCA at the Abramson Cancer Center and the Basser registry of post-RRSO women includes 1800 individuals. Another 50-60 women undergo RRSO each year at one of the University of Pennsylvania Health System hospitals. Additionally, Philadelphia has several other nationally ranked cancer centers from which we can recruit.

We have found advertisements on the local Philadelphia public radio station (WHYY) to be enormously productive for our menopause studies, yielding 1-2 new qualifying participants with each run. Hence, we plan to advertise on WHYY at least twice a month. Also, we have already conducted an online evaluation of the severity of executive function difficulties among post-RRSO women in the greater tri-state area and were granted IRB approval to re-contact these women to inform them about the proposed study. With access to clinical samples and referrals from FORCE and the Basser Center, we could complete our study enrollment if even 5% of the genetically at-risk population in the area were to meet study criteria and agree to participate.

3.3 ***Key inclusion criteria***
1. Females aged 35 to 58 years;
2. Have undergone risk-reducing bilateral salpingo-oophorectomy (RRSO) within the previous 15 years AND were premenopausal at the time of RRSO;
3. Score of ≥ 20 on the Brown Attention Deficit Disorder Scale (BADDS);
4. Onset of executive function difficulties occurred post RRSO;

5. Clean urine drug screen (nicotine and marijuana are permissible). Potential false positive screenings will be reviewed and exclusionary based on PI discretion;
6. Are fluent in written and spoken English;
7. Are able to give written informed consent (obtained at screening visit);
8. Have a high school diploma or equivalent degree (i.e., GED), as per subject report;
9. *If using aromatase inhibitors or tamoxifen:* Must have been on a stable dose for at least 6 months;
10. *If completing visits remotely*: Must have access to a telecommunications application (i.e., Skype), email, scanner/fax machine, and a private area that enables the protection of participant confidentiality.

3.4 ***Key exclusion criteria***

1. Current untreated psychiatric disorder;
2. Substance use disorder within the previous 3 years;
3. Lifetime history of ADHD or psychotic disorder including bipolar disorder, schizoaffective disorder, and schizophrenia;
4. Lifetime history of stimulant abuse or dependence;
5. Regular use of psychotropic medications except selective serotonin reuptake inhibitors (SSRI), serotonin noradrenergic reuptake inhibitors (SNRI), bupropion, zolpidem, gabapentin, or buspirone;
6. Chemotherapy within the past year;
7. Previous history of sensitivity or adverse reaction to lisdexamfetamine (LDX);
8. History of seizures or unstable medical condition;
9. Known heart disease or clinically significant abnormal electrocardiogram during screening as determined by the study MD;
10. Uncontrolled hypertension;
11. Presence of a metallic implant contraindicative to scanning at the 7T level;
11. Claustrophobia;
12. Consistent systolic blood pressure of >145mm Hg or diastolic blood pressure >90 mm Hg after three readings at time of screening;
13. Known renal impairment and End Stage Renal Disease (ESRD).

Note: Chemotherapy and RRSO are commonly paired as a treatment plan for feminine cancers. Participants who underwent relatively concurrent treatments of chemotherapy and RRSO, such as when chemotherapy immediately precedes RRSO, will be considered by the principal investigator and be included at the PI's discretion.

3.5 ***Populations vulnerable to undue influence or coercion***

University of Pennsylvania students and employees (both of appropriate age and study criteria) and economically disadvantaged persons are welcome to participate in this study. Potential subjects will be provided with information about the study and will have the opportunity to ask questions of study staff prior to signing consent. They will be informed that their decision to participate or decline will not affect their care, or their employment or education (if an employee or student of UPenn). The participants will be appropriately consented and their information will be kept in a locked cabinet, filed by code, in a locked room that only the research study personnel has access to.

3.6 *Subject Recruitment*
Subjects will be recruited by word of mouth, referrals by collaborators at FORCE, the Basser Center, and other medical practices, flyers/brochures, paid advertisements, and direct calling of qualified, prescreened women who agreed to future contact for the proposed study.

3.7 Non-Imaging Subsection of Participants
Subjects will be evaluated for their eligibility to participate in the full list of protocol procedures. However, there may be some subjects that are not eligible due to MRI incompatibility. Therefore, we will have a subsection of participants who are not eligible to complete the MRI due to having metal in their body, claustrophobia, or handedness, but are still eligible to complete all other study procedures at the PIs discretion. The non-imaging subsection will serve as an alternative for anyone unable or not interested in completing the MRI. This subsection of participants will have to meet all other study criteria in order to be included in this subsection and will be reviewed by the PI. Participants eligible for the non-imaging subsection of this study will receive a separate consent form that details the study procedures, risks/benefits, and compensation.

4 Analysis Plan
4.1 *Statistical Analysis*
Summaries of each outcome (BADDS scores, performance on the cognitive tasks, Glut, and BOLD signal) under each treatment condition (baseline, LDX, and placebo) will be examined using histograms, boxplots, and normal probability plots. Transformations of the outcomes will be considered as necessary to meet modeling assumptions. General linear regression (mixed models) will be employed to estimate the association between each outcome, treatment condition and cross-over sequence while accounting for the nonzero correlation among the repeated observations within individuals.

Aim 1: Total BADDS score at each time point will be examined for an interaction effect between time (pre vs. post) and treatment (LDX vs. placebo) to assess whether within-subject total BADDS score is significantly reduced post LDX treatment rather than post placebo. Baseline BADDS scores will be dichotomized at the median score and considered as a covariate in the mixed effects models. Additional interaction terms for baseline group by time (pre vs. post) and baseline group by treatment (LDX vs. placebo) will be added to the model to test whether treatment effects differentially affect those with higher baseline scores.

Aim 2: Similar models will evaluate BADDS subscores, cognitive task performance, and L-DLPFC Glut levels. Similar mixed models will assess associations between change in specific BADDS domains with identified deficits in executive function and change in DLPFC Glut levels.

Aim 3: We will quantify associations between baseline percentage BOLD signal change during performance of the n-back (3-back) and L-DLPFC Glut.

Current methods for fMRI analyses are as follows: Functional scans will be realigned, normalized, time-corrected, and spatially smoothed by an 8 mm FWHW Gaussian kernel. The time series will be high-pass filtered to correct for drift across the scan. For blocked designed experiments (3-back), regressors will represent trial conditions; for the event-related design

experiments regresses will represent individual trials and trial outcomes. At the individual level, voxel-wise fixed-effects contrast analyses will be performed for each subject to assess the magnitude of pair wise difference in blood oxygen dependent (BOLD) signal between the emotional and the neutral control condition. At the group-level, a second stage of the process will use a random effects model to create spatial parametric maps (SPM) depicting loci that are active across subjects. Movements parameters derived from the realignment correction (for all six possible directions) will be entered into the design matrix as covariates of no interest. For a priori regions of interests, clusters will be reported if they are significant at P=0.05 corrected, using a small volume correction (SVC). Clusters will also be reported if they are significant at a threshold of P=0.001, uncorrected, with an extend threshold of 10 voxels. Repeated measures analysis of variance (ANOVA) will then be performed to test the effect of LDX on brain activation patterns and simple effects analyses will reveal overall effects of LDX treatment.

fMRI/MRS Analysis: Percent BOLD signal changes in the left DLPFC will be entered in a correlational analysis with corresponding Glut concentrations. Size and orientation of regions included for analysis of BOLD signal and Glut concentration will be identical. Percent BOLD signal change will be calculated for each regressor of interest and correlation coefficients will be obtained. Voxel wise regression of BOLD signal vs. mean Glut concentration will be performed for each functional voxel.

4.2 *Rationale for sample size*

Sample size is estimated for the 3 primary outcome measures: BADDS scores, DLPFC Glut levels, BOLD signal activation during the N-Back Task.

Assuming a type I, alpha, error of 5%, and 80% power, we anticipate being able to detect a 0.3 SD difference between within subject change under active LDX and placebo conditions with 88 participants. Based on our pilot data for total BADDS score, we will have 80% power to detect as small as an 8.4% difference in BADDS total score when comparing placebo to LDX administration. Given our pilot data from naturally menopausal women, this effect size corresponds to a 19% difference between active LSX and placebo in organization and activation for work, and 15% for attention/concentration BADDS subscales. We are conservatively powered for an effect size of 0.3 SD, meaning that we have sufficient power to examine a number of different covariates and possible predictors of outcome in this study.

Given our pilot data for levels of Glut in the left DLPFC, we will have 80% power to detect as small as a 2.6% reduction in Glut for active LDX administration compared to placebo. A similar 0.3 SD can be detected for BOLD signal in left DLPFC. This corresponds to a 25% difference in BOLD signal change between placebo and LDX for 3-back task.

5 Safety and Adverse Events

5.1 *Potential Risks*

Risk of Vyvanse® (LDX): The reported adverse reactions to LDX treatment include: constipation, decreased appetite, diarrhea, dizziness, dry mouth, headache, increased sweating, mild irritability, nervousness, or restlessness, nausea, trouble sleeping, unpleasant taste, upper stomach pain, vomiting and weight loss.

The most common side effects reported by adults are decreased appetite, difficulty falling asleep, and dry mouth. LDX can cause an increase in blood pressure and heart rate, although it is not contraindicated in the treatment of individuals with stable hypertension (Huffman & Stern, 2004). While the likelihood that individuals will develop peripheral vasculopathy is very small, subjects will be monitored at each assessment for tingling and numbing sensations in their extremities. Sudden death has been reported in adults using stimulant medications within the normal dosing range. This type of serious event has not occurred with Vyvanse® but will be discussed with subjects as a potential adverse event of this class of medication. Although rare, the risk of serotonin syndrome increases when co-administered with other serotonergic agents (i.e., SSRIs, SNRIs, triptans). Women taking serotonergic medications will be briefed on potential symptoms and monitored at each visit for any side effects. Serious side effects will be minimized by short-term treatment, exclusion of women who would be at heightened risk for participation, and careful monitoring of the treatment.

Risk of ^{1}H-MRS operating at 7T: To date, no persistent adverse effects have been reported by facilities with magnetic field strengths at 7.0T. A metallic taste in the mouth, dizziness or nausea upon being moved into the magnetic field is not uncommon. This dizziness and nausea typically last less than 10 minutes and can be reduced by reducing the speed at which the subject is placed into the magnet. If experienced, the metallic taste usually goes away within minutes. In rare cases individuals may experience brief, intermittent sensations such as tingling in parts of their body during the scan. The FDA has authorized the use of the 7.0T magnets in humans. Some of the pulse sequences and/or RF coils are not FDA authorized but are considered non-significant risk investigational devices. All subjects will be informed of the possibility of having these sensations during the informed consent process. The 7.0T scanners are not approved in pregnant women and they are to be excluded from trials utilizing the 7.0T magnet. As the women in this study are not of child bearing potential, they will not be subjected to a urine pregnancy test before scans. All subjects will be screened for the presence of any metallic objects that they may be holding or have implanted in their bodies, and all potential subjects with metallic implants contraindicative to scanning at the 7.0T level will be excluded.

> Experimental Device Clause: Some of the pulse sequences and/or RF coils are not FDA approved but are considered non-significant risk investigational devices.
>
> Pregnancy Clause: Women in this study will be postmenopausal and are therefore unable to conceive.

Use of venipuncture for blood sampling: Inserting a needle into a vein is safe when done by professionals under clean conditions. Sometimes a bruise will occur at the puncture site and on rare occasions fainting, a blood clot, or an infection may form in the vein. If this occurs, appropriate treatment will be instituted immediately.

Clinical Assessments: Subjects will be administered a number of cognitive and behavioral assessments during the screening process and at follow-up visits. However, there is no risk associated with administering these assessments. Knowing the outcome of the assessments should

not make the subject feel any differently about themselves. We will not be sharing the results with anyone besides the subjects and the research team.

Genetics: In the laboratory, genetic samples will be labeled with a number only. Subject name or any other identifying information will not be attached to the samples in the research laboratory. This measure is taken to protect confidentiality, in addition to the following specific measures:

a.) The genetic testing of all samples will be used for research purposes only. No results of genetic testing from this study will appear in any subject's medical record.
b.) Genetic test results will not be made available to subjects, to their doctors, or to the other clinicians or any other clinical staff.
c.) To protect confidentiality as much as possible, no computer records will be created that could be used to identify a subject's genetic or medical information individually. Thus, even if a "hacker" breaks into the laboratory computer system, there will be no information stored there that can identify any individual subject.
d.) Information about genes will only be stored in Dr. Epperson's laboratory, using procedures described above to protect your confidentiality, unless the information has become completely stripped of information that could identify an individual subject.

In our experience at a previous academic institution, in which many hundreds of samples have been collected, no outside agency has ever tried to gain access to any research subject's genetics samples. Dr. Epperson believes that the risk of this happening to any sample collected as part of this study is extremely small.

The goal of the genetic testing for the study is exploratory, not predictive.

5.2 ***Potential Study Benefits***
There are no intended direct benefits for subjects in this study however participants may experience an improvement in their perceived cognitive functioning during the course of the study trials. Results from this clinical trial may help add to our understanding of treatment options for individuals experiencing executive function difficulties as a result of RRSO.

5.3 ***Risk/Benefit Assessment***
This study represents more than minimal risk to the subject, as individuals will undergo neuroimaging and treatment with LDX, which they may never have otherwise taken. Should this study show that LDX administration improves executive function outcomes of interest and is correlated with changes in left DLPFC glut concentrations and BOLD signal, we will have additional evidence that psychostimulant –related changes in brain neurochemistry and neuronal function are clinically relevant.

5.4 ***Data Safety and Monitoring***
The Principal Investigatory (Dr. C. Neill Epperson) will be the primary source for data and subject safety monitoring. The research staff will meet weekly to discuss recruitment, retention, breaches of confidentiality, adverse events, and collected data. Subjects will be instructed to call study personnel as soon as possible in the event of side effects. If we have concerns about their physical and emotional health, we will share these concerns with the subjects' primary care physicians.

5.5 *Resources Necessary for Human Research Protection*

Dr. Epperson, the study Principal Investigator has had more than 20 years of experience conducting translational neuroscience research in human subjects focusing on the impact of sex hormones and neurosteriods on behavior and cognition in women. Dr. Epperson is the recipient of 3 RO1 grants from the NIMH, NIDA, and NIA. She is also the recipient of several K awards from the NIH. Dr. Epperson has extensive experience overseeing the conduct of research in her laboratory. She is personally responsible for all aspects of the study or delegation of duties to individuals she has trained over the years.

If an individual were to demonstrate the need for mental health services, they would first be referred to the Penn Center for Women's Behavioral Wellness (PCWBW) for evaluation by one of the Center's psychologists or psychiatrists. An appropriate treatment plan and/or referral would be developed as necessary. The PCWBW is housed in a large office building with 24-hour security. The Center's main offices at 3535 Market St. are comprised of 8 clinical offices, one laboratory space, copy, fax and mail room, reception area and kitchen. In addition, there is both clinical and administrative space at Pennsylvania Hospital in the same area as Maternal Fetal Medicine outpatient services.

6 Data Handling and Record Keeping

6.1 *Subject Confidentiality*

This study will utilize directly-identifiable protected health information (PHI). PHI, as defined by HIPAA, means individually identifiable health information about an individual that is transmitted or maintained by electronic media or in any other form or medium. PHI includes demographic information that is created or received by a health care provider, health plan, employer, or health clearinghouse. PHI relates to the past, present, or future physical or mental health or condition of an individual; the provisions of health care to an individual; or the past, present, or future payment for the provision of health care to an individual; and identifies the individual or can reasonably be used as a basis to identify an individual. The following PHI will be collected for this study:

- Name
- Postal address information
- All elements of dates, such as birthdate and date of visit, (except year) for dates directly related to an individual and all ages over 89)
- Telephone and fax number
- Electronic mail addresses
- Social security numbers *(for study compensation)*
- Medical record numbers (*for ordering MRIs and medications*)

In accordance to University of Pennsylvania's policy regarding how PHI is handled, managed, and disseminated, study personnel will utilize an institutionally secured and managed network drive.

Institutionally secured and managed network drive: The PCWBW utilizes a departmental shared drive to securely store PHI. The PCWBW shared drive is managed and secured by The Penn Medicine Academic Computing Services (PMACS). Access to the shared drive requires password

access to a departmental device (PCWBW desktop or laptop) then additional password access to the departmental shared drive. After being granted access to the shared drive, one must have an encryption code to access the files storing PHI. Therefore, the only PCWBW employees that will have access to the PHI connected to this study will be the approved study personnel (Principal Investigator, Project Supervisor, Clinical Research Coordinators).

Any paperwork that includes PHI (such as SSN on subject compensation forms) will be kept in a locked draw within a locked office. To reduce the possibility of breaches in subject confidentiality, subjects will be given a unique identifier to place on their demographic information, questionnaires, behavioral ratings, and data from scan sessions. Only the study personnel will have access to the code. Five years after completion of the study, the subject code will be destroyed. Data will be destroyed 8 years after study completion.

6.*2 Subject Privacy*

The study personnel will maintain a high level of privacy for this research study. To respect those boundaries, several safeguards will be in place. Subjects will be screened and interviewed in a private office at the PCWBW offices located at 3535 Market Street. When contacting subjects, information about mental and physical health will not be disclosed; telephone messages or voicemails will be worded so as to not reveal the subjects study status, diagnoses, or any other confidential information.

7 Investigational Agent

7.1 *Investigational Agent*

- *Drug name: Vyvanse® (lisdexamfetamine; LDX)*
- *Pharmacological class: STIMULANT*
- *Structural formula (if known):* $C_{15}H_{25}N_3O(CH_4O_3S)_2$
- *Formulation and dose: Capsules 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg*
- *Route of Administration: Oral*

Planned exposure (e.g. duration of study drug administration): One hundred, otherwise healthy, adult women (age range 35 to 55 years) who have undergone RRSO and are currently reporting some impairment in daily functioning will be enrolled in this study to determine the impact of LDX treatment on brain function as it relates to subjective and objective measures of executive function such as 1) organization and memory, 2) attention and concentration, 3) alertness, effort, processing speed, 4) managing affective interference, 5) working memory, accessing recall. Participants will undergo multi-modal imaging-fMRI and 1H-MRS pre and post a 6-week course of LDX or placebo followed by a 2-week washout before crossing over to the other condition.

7.2 *Overview of Previous Human Experience*

Please see section 10 of this protocol for data regarding human experience with LDX.

7.2.1 *Reference to previously submitted IND application(s)*

Please see section 10 of this protocol for information regarding IND applications for LDX.

7.3 *Overview of Preclinical Data*

Please see FDA Labeling for Protocol 812470.

8 Investigational Agent: Chemistry and Manufacturing

8.1 *General Method of Preparation and packaging*

Vyvanse® (LDX) is designed as a capsule for once-a-day oral administration. LDX is commercially available from the manufacturer.

All study drugs used n this study will be obtained directly from the manufacturer and dispensed by the Penn Investigational Drug Service (IDS).

8.2 *Drug Components and Drug Product*

Vyvanse® capsules contain LDX as the active ingredient in dosages of 20mg, 30mg, 40mg, 50mg, 60mg, and 70mg. Each capsule contains the following inactive ingredients; microcrystalline cellulose, coscamellose sodium and magnesium stearate. The capsule shells contain gelatin, titanium dioxide and one or more of the following: D&C Red #28, D&C Yellow #10, FD&C Blue #1, FD&C Green #3, and FD&C Red #40.

8.3 *Placebo Product*

Capsules will be filled with microcellulose. The placebo capsules will also be administered by IDS.

8.4 *Labeling*

The drug used for this study will be placed in a bottle labeled with the subject's name, instructing them to take the capsule(s) by mouth. The capsules will be ordered through the IDS at UPenn and brought to the PCWBW by research staff and then distributed to the subject.

8.5 *Environmental Analysis Requirements*

As LDX is a marketed medication we believe an environmental analysis is not required.

9 Pharmacology and Toxicology

LDX is a product of dextroamphetamine. After oral administration, LDX is rapidly absorbed from the GI tract and converted to dextroamphetamine, which is responsible for the drug's activity. Amphetamines are non-catecholamine sympathomimetic amines with CNS stimulant activity. The mode of therapeutic action in ADHD is not known. Amphetamines are thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monamines into the neural space. The parent drug, LDX does not bind to the sites responsible for the reuptake of norepinephrine and dopamine in vitro.

Pharmacokinetic studies of dextroamphetamine after oral administration id LDX have been conducted in healthy adults

10 Previous Human Experience with Investigational Agent

10.1 *Marketed experience*

The study investigator has received an IND exemption from FDA for IRB #812470 and IRB #817628 and therefore would be expected to receive an exemption for this protocol as well. Shire's IND, #67,482, provides important information about LDX, including marketing experience with humans.

10.2 ***Prior Clinical Research Experience***
Shire's IND, #67,482, provides important information about LDX, including clinical research experience with human subjects. In addition, the FDA approved prescribing information includes a brief summary of clinical trials of LDX in both children and adults. Pertinent to the present project, the information regarding adults from IND#67,482 is presented here.

A double blind, randomized, placebo-controlled, parallel-group, study was conducted in adults (N=420) who met DSM-IV criteria for ADHD. In this four-week study, patients were randomized to fixed dose treatment groups receiving final doses of 30, 50, or 70 mg of Vyvanse® or placebo. All subjects receiving Vyvanse® were initiated on 30mg for the first week of treatment. Subjects assigned to the 50 and 70 mg dose groups were titrated by 20 mg per week until they achieved their assigned dose. Significant improvements in ADHD symptoms, based upon investigator rating on the ADHD Rating Scale (ADHD-RS), were observed at endpoint for all Vyvanse® doses compared to placebo.

A second study was a multi-center randomized double-blind, placebo-controlled, cross-over design, modified analog classroom study of Vyvanse® to simulate a workplace environment in 142 adults who met DSM-IV TR criteria for ADHD. There was a 4-week open-label, dose optimization phase with Vyvanse (30, 50, or 70 mg/d in the morning). Subjects were then randomized to one of two treatment sequences: 1) Vyvanse® (optimized dose) followed by placebo, each for one week or 2) placebo followed by Vyvanse®, each for one week. Efficacy assessments occurred at the end of each week, using the Permanent Product Measure of Performance (PERMP). The PERMP is a skill-adjusted math test that measures attention in improvement in attention across all post-dose time points, as measured by average PERMP total scores over the course of one assessment day, as well as at each time point measured. The PERMP assessments were administered at pre-dose (-0.5 hours) and at 2,4,8,10,12, and 14 hours post-dose.

10.3 ***Clinical Care Experience***
While psychostimulants have been used to manage cancer related fatigue with variable success (Minton et al., 2010), there have been no controlled studies of psychostimulants in the treatment of new onset executive function difficulties after RRSO. Several placebo-controlled studies of psychostimulants have been conducted in children who experience cognitive deficits after surgery, chemotherapy and/or radiation, particularly for head and neck cancers. Benefits of active drug over placebo have been shown for domains such as attention, vigilance, working memory and processing speed (Castellino et al., 2014). Likewise, use of psychostimulants in adults with cancer treatment related to neurocognitive impairment has been met with variable success (Prommer, 2012), possibly due to the advanced age of the individuals studied. To our knowledge, there are no controlled studies examining the efficacy of psychostimulants in treatment of subjective or objective cognitive decline in young women after RRSO or other forms of premature menopause.

Of the few 1H-MRS studies of psychostimulant effects on brain neurochemistry most have been performed in pediatric populations with ADHD. A recent study in adults with ADHD found no difference in baseline GLX (glutamate+glutamine) levels in the DLPFC between adults with and without ADHD (Maltezos et al., 2014)

11 Additional Information

11.1 *Drug dependence and abuse potential*

Amphetamines have been extensively abused. Tolerance, extreme psychological dependence and severe social disability have occurred. There are reports of patients who have increased the dosage to levels many times higher than recommended. Abrupt cessation following prolonged high-dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines may include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

In a human abuse liability study, when equivalent oral doses of 100 mg lisdexamfetamine dismesylate and 40 mg immediate-release d-amphetamine sulfate were administered to individual with a history of drug abuse, lisdexamfetamine dismesylate 100 mg produced subjective responses on a scale of "Drug Liking Effects" (primary endpoint) that were significantly less than d-amphetamine immediate-release 40 mg. However, oral administration of 100 mg lisdexamfetamine dismesylate produced increases in positive subjective responses that were statistically indistinguishable from the positive subjective responses produced by the 40 mg of oral immediate-release d-amphetamine and 200 mg of diethpropion (C-IV) Intravenous administration of 50 mg lisdexamfetamine dismesylate to individuals with a history of drug abuse produced positive subjective response on scales measuring "Drug Liking Euphoria," "Amphetamine Effects," and "Benzedrine Effects" that were greater than placebo but less than those produced by an equivalent dose (20 mg) of intravenous d-amphetamine.

11.2 *Radioactive drugs*- Not applicable to this study.

11.3 *Pediatric studies*- not applicable for this study.

11.4 *Direct-to-Patient Services*

Participants who complete the remote option for this study will have the medication appropriately and legally shipped directly to their home for each trial. After the completion of each study trial, the participants will ship back their prescription bottle and any unused medication for return and destruction to Penn's IDS.

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