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Impact of adrenal hormones, reproductive aging, and major depression on memory circuitry decline in early midlife.

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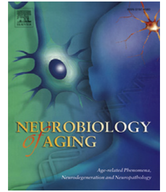

# Impact of BDNF and sex on maintaining intact memory function in early midlife

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ABSTRACT

Sex steroid hormones and neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), play a significant neuroprotective role in memory circuitry aging. Here, we present findings characterizing the neuroprotective effects of BDNF on memory performance, as a function of sex and reproductive status in women. Participants ($N = 191$; mean age $= 50.03 \pm 2.10$) underwent clinical and cognitive testing, fMRI scanning, and hormonal assessments of menopausal staging. Memory performance was assessed with the 6-Trial Selective Reminding Test and the Face-Name Associative Memory Exam. Participants also performed a working memory (WM) N-back task during fMRI scanning. Results revealed significant interactions between menopausal status and BDNF levels. Only in postmenopausal women, lower plasma BDNF levels were associated with significantly worse memory performance and altered function in the WM circuitry. BDNF had no significant impact on memory performance or WM function in pre/perimenopausal women or men. These results suggest that in postmenopausal women, BDNF is associated with memory performance and memory circuitry function, thus providing evidence of potential sex-dependent factors of risk and resilience for early intervention.

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## 1. Introduction

Faced with a rapidly aging population, cognitive deficits will become increasingly prevalent. Understanding factors contributing to memory impairment is crucial for the early prevention of memory decline. Men and women undergo different aging processes, especially in early midlife. In addition to chronological aging, women undergo reproductive aging, during which they experience a depletion of sex steroid hormones such as estradiol, which we previously demonstrated is directly related to decreased memory performance and reorganization of functional memory circuitries (Jacobs et al., 2016a, b; Rentz et al., 2016). The hippocampus (HIPP), a key region in the memory circuitry, is highly sexually dimorphic (Goldstein et al., 2001; Persson et al., 2014; Woolley and McEwen, 1993) and one of the few brain regions that continue to undergo neurogenesis with aging (Eriksson et al., 1998), albeit at a reduced rate (Kempermann et al., 1998). Sex steroid hormones and neurotrophic factors, such as the brain-derived neurotrophic factor (BDNF), play a significant neuroprotective role in memory circuitry aging through mechanisms of neurogenesis, cellular survival, axonal growth, dendritic growth, and synaptic plasticity (Brinton, 2009; Figurov et al., 1996; Liu et al., 2008; Ormerod et al., 2004; Scharfman et al., 2005; Tanapat et al., 1999; Tyler and Pozzo-Miller, 2003; Warren et al., 1995; Woolley and McEwen, 1994). However, despite growing evidence of this neuroprotective role, little is known about the sex-dependent role that BDNF plays on

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memory circuitry aging in the face of reproductive aging and ovarian function decline.

There is a long history of preclinical evidence demonstrating the role of estradiol in HIPP structure and function. For example, in rodents, HIPP CA1 neurons show excitatory synaptic density changes that are modulated by estradiol levels (McEwen et al., 1995; Woolley et al., 1996). Further, ovariectomization in rodents leads to degeneration in the HIPP, an effect which can be reversed with estrogen replacement (Dumitriu et al., 2010; Woolley et al., 1996). Estrogen replacement also enhances spatial memory in rodents (Daniel et al., 1997; Korol, 2004; Korol and Kolo, 2002; Luine et al., 1998; Packard and Teather, 1997), a function highly dependent on the HIPP. In rhesus monkeys, reproductive age, over chronological age, is associated with lower recognition memory and synaptic density in the HIPP dentate gyrus (Hara et al., 2012). In population-level studies, fluctuating levels of estradiol across the menstrual cycle correlate with verbal memory performance (Hussain et al., 2016; Protopopescu et al., 2008; Rosenberg and Park, 2002), HIPP volume (Lisofsky et al., 2015; Protopopescu et al., 2008), and HIPP fractional anisotropy (Barth et al., 2016). Furthermore, neuroimaging studies have demonstrated direct associations between sex steroid hormone levels and functional activity and connectivity in the memory circuitry (Jacobs et al., 2015; Lisofsky et al., 2015). Inconsistent with the preclinical literature, recent findings from hormone replacement therapy trials have found no treatment-related benefits to cognitive function compared to the placebo groups. However, there are several methodological considerations, such as sample selection and cognitive measures, which need to be further explored. In women APOE4-carriers, hormone replacement therapy decreased Aβ levels in the brain (Kantarci et al., 2016), suggesting that certain high-risk populations may benefit more from hormone replacement therapy than others.

Modulatory effects of estradiol are also seen across the menopausal transition (Epperson et al., 2013; Jacobs et al., 2016a, b; Morrison et al., 2006; Mosconi et al., 2017a, b; Rentz et al., 2016; Ryan et al., 2012; Shanmugan and Epperson, 2014; Wroolie et al., 2015). In a series of analyses comparing men and women in early midlife, we replicated the finding that women outperform men on verbal and associative memory tasks (Rentz et al., 2016). Furthermore, we demonstrated that female advantage was attenuated postmenopause due, in part, to estradiol decline, underscoring the impact of ovarian decline in shaping memory function in women. Reproductive age also had a pronounced regional and network level impact on task-evoked HIPP response, independent of chronological age (Jacobs et al., 2016a, b). During episodic memory encoding, we demonstrated that task-evoked HIPP responses decreased over the menopausal transition and correlated with decreasing levels of 17β-estradiol (Jacobs et al., 2016b). Postmenopausal women showed enhanced bilateral HIPP connectivity. Further, while performing a working memory (WM) task (n-back task), reproductive aging was associated with a failure to disengage the HIPP (Jacobs et al., 2016a), consistent with other studies of WM (Egan et al., 2003). Over the menopausal transition, neural pathways for maintenance of WM performance shifted in reliance from connectivity between the dorsolateral prefrontal cortex (DLPFC) and the inferior parietal cortex (iPAR) to the DLPFC and HIPP pathways. Together, these findings demonstrated that sex steroid hormones alter memory circuity function and that menopause has a significant impact on aging of memory circuitry in women. In the current analyses, we tested the role of BDNF in memory circuitry function by sex and across reproductive age in the same sample.

Similar to estradiol, there is an abundance of preclinical and clinical evidence for the role of BDNF in memory circuitry function. Estradiol and BDNF activate similar signaling pathways in the rodent HIPP (Scharfman and MacLusky, 2006). Further, estradiol also directly regulates BDNF transcription by binding to an estrogen response element on the *BDNF* gene (Scharfman and MacLusky, 2006). Although the cellular source of plasma BDNF is not clearly defined, BDNF is primarily produced in the brain and readily crosses the blood brain barrier (Pan et al., 1998). It is also found in vascular endothelial and smooth muscle cells as well as activated macrophages, lymphocytes, and dendritic cells. In the central nervous system, BDNF is most highly expressed in the HIPP and PFC (Murer et al., 2001). The genetic deletion of BDNF in mice leads to disruption of long-term potentiation (LTP) in the HIPP (Poo, 2001). Similarly, rats injected with BDNF antibodies are severely impaired at learning and recalling HIPP-dependent spatial information (Mu et al., 1999). BDNF mRNA levels also change during memory formation and play an essential role in the acquisition, retention, and recall of spatial memory (Mizuno et al., 2000). Furthermore, brain region-specific, epigenetic effects of estrogens may play a role in regulating BDNF, as direct administration of estradiol into HIPP has been reported to increase histone acetylation at BDNF promoters, thereby upregulating BDNF gene expression in association with improved memory consolidation (Fortress et al., 2014). In clinical studies, lower levels of BDNF in older adults was associated with poor memory performance (Erickson et al., 2010; Gunstad et al., 2008; Komulainen et al., 2008; Li et al., 2009), decreased HIPP volume (Erickson et al., 2010), steeper frontal white matter decline (Driscoll et al., 2012), and increased amyloid burden (Hwang et al., 2015). Some of these effects were sex-dependent, with significant findings only in women (Driscoll et al., 2012; Komulainen et al., 2008). BDNF levels can be highly variable and modulated by various factors such as physical exercise, circadian rhythm, and certain medications such as anti-depressants. Alterations in plasma levels of BDNF have also been found in numerous neurological and psychiatric diseases such as depression (Bus et al., 2015; Molendijk et al., 2014), schizophrenia (Chen et al., 2009; Toyooka et al., 2002), and Alzheimer's disease (AD) (Holsinger et al., 2000; Phillips et al., 1991). Thus, there is sufficient preclinical and clinical evidence suggesting a role for BDNF in learning and memory and HIPP structure and function. Furthermore, these effects closely parallel those of estradiol both through mechanisms of convergence and induction.

Given the role that sex steroid hormones and BDNF play in memory formation and HIPP function, we investigated whether higher plasma levels of BDNF in postmenopausal women were neuroprotective against memory decline and functional changes in the memory circuitry. We hypothesized that in the face of reproductive aging and the depletion of sex steroid hormones, higher production of BDNF will be associated with better memory performance and memory circuitry function. Here, we present new findings characterizing the impact of BDNF on memory circuitry aging across the menopausal transition.

## 2. Material and methods

### 2.1. Participants

Adult participants were selected from 17,741 pregnancies in the New England Family Study (NEFS; subsidiary of the National Collaborative Perinatal Project), a representative sample of those receiving prenatal care in Boston - Providence from 1959 to1966. In a series of studies over 20 years, we followed subsets of NEFS offspring to investigate the fetal programming of adult psychiatric and general medical disorders and sex differences therein. We recently completed a study investigating the impact of prenatal maternal immune dysregulation on sex differences in memory circuitry in early midlife (NIMH R01 MH090291, Goldstein, PI). To insure variability in prenatal immune exposure, same-sex siblings

from NEFS discordant for prenatal inflammation were recruited, whereby one sibling was exposed to preeclampsia or fetal growth restriction and the other was not. When no sibling was available for an exposed offspring, an unexposed offspring was individually matched based on maternal age, ethnicity, socioeconomic status, offspring sex, and gestational age.

212 offspring (equally divided by sex) were recruited at 45–55 years of age and underwent clinical, cognitive, and neuropsychological assessments, of whom 201 completed functional and structural magnetic resonance imaging (fMRI/sMRI). The community-based sample was 88.6% White, 8.5% African American, 2.8% Other (primarily Hispanic). Exclusionary criteria included any history of neurological disease, CNS damage, head injury with loss of consciousness, endocrine disorders, heart disease, alcohol-related diseases, current or history of psychosis, other medical illnesses that may significantly alter CNS function, or any MRI contraindication. Demographic information, including BMI, marital status, race/ethnicity, psychiatric history, and alcohol and substance abuse dependence, were collected as part of the clinical interview via self-report using the Structured Clinical Interview for DSM-IV (SCID). The Partners Human Research Committee and Brown University's Institutional Review Board granted Human Studies participants' approval. All volunteers gave written informed consent and were paid for their participation.

### 2.2. Study design and procedures

Participants were seen at the Brigham and Women's Hospital Outpatient Clinical Research Center. Subjects were asked to refrain from taking pain medication and recreational drugs and drinking alcohol 24 hours prior to their visit. Women who were still menstruating were scheduled within the early follicular menstrual cycle phase (days 3–5). Participants fasted for ≥8 hours prior to morning baseline blood draw. They were offered a light standardized breakfast (excluding caffeine) before MRI scanning. MRI scanning was followed by neuropsychological testing and structured clinical interviews administered by an experienced clinical interviewer/clinician. Clinical interviews assessed history of alcohol or substance disorders, family medical history, and reproductive history.

### 2.3. Menopausal staging

Timing of menopause between the first clinical appearance of decreased ovarian function (i.e., shorter inter-menstrual time periods) to menstrual irregularity and final amenorrhea is highly variable and can occur over several years. Women in this sample were between the ages of 45–55 years and were expected to be in various states of ovarian decline, ranging from oligoamenorrhea to permanent amenorrhea as well as normal cycling. Reproductive histories and hormonal evaluations (see *Endocrine assessments* below) were used to determine reproductive stage following the Stages of Reproductive Aging Workshop (STRAW)-10 guidelines (Harlow et al., 2012). Women were categorized into late reproductive ("premenopause"), menopausal transition ("perimenopause"), and early postmenopausal ("postmenopause"). Eight women reported current use of hormone therapy and were excluded from analyses.

### 2.4. Sample collection

Trained nurses inserted a saline-lock IV line in the non-dominant forearm of participants to acquire serum and plasma samples. Approximately 18.5 mL of blood were collected at the Brigham and Women's Hospital (BWH) Center for Clinical Investigation. Fasting morning blood was drawn at approximately 0800h for optimal evaluation of hypothalamic-pituitary-gonadal axis hormone concentrations, including sex steroids (estradiol, progesterone, and testosterone) and gonadotropins (leutinizing hormone and follicle-stimulating hormone (FSH)). For endocrine assessments (see below), blood was collected into SST tubes. Serum samples were allowed to clot for 30–45 minutes, after which blood was centrifuged (1500 × g for 10 minutes) and sera aliquoted into 2-mL microtubes. Serum aliquots were stored at −80 °C for later evaluations. For BDNF assays, blood was collected into BD PST[TM] tubes with lithium heparin anticoagulant, processed to separate plasma by centrifugation at 1500 g at 4 deg C × 10 minutes, and aliquoted in 2-mL cryopreservation tubes. Serum and plasma aliquots were stored at −80 deg C for up to 4.5 years before use in assays. Serum samples were analyzed at BWH Research Assay Core (BRAC) for sex steroid determinations. Plasma samples were shipped frozen on dry ice to Columbia and stored at −80 °C until processing.

### 2.5. Endocrine assessments

17β-estradiol, progesterone, and testosterone concentrations were determined via LC-mass spectrometry at BRAC. Assay sensitivities, dynamic range and intra-assay coefficients of variation were as follows (respectively): Estradiol (1 pg/mL, 1–500 pg/mL, <5% RSD); Progesterone (0.05 ng/mL, 0.05–10 ng/mL, 5.75% RSD); Testosterone (1.0 ng/dL, 1–2000 ng/dL, <2% RSD). FSH levels were determined via chemoluminescent assay (Beckman Coulter), with assay sensitivity of 0.2 mIU/mL, dynamic range 0.2–200 mIU/mL, and intra-assay coefficient of variation 3.1%–4.3%.

### 2.6. BDNF assessment

To conserve sample volume, the concentration of BDNF was determined as part of an expanded set of analyses using a volume-sparing, magnetic bead-based, 60-plex immunoassay (customized Procarta immunoassay, Affymetrix/eBioscience, Santa Clara, CA, USA). Coded plasma samples from all participants were run in randomized fashion on assay plates manufactured in a single lot. Samples were thawed slowly on wet ice prior to use in immunoassays to protect protein integrity, and then spun to clear precipitate. All samples were run in duplicate along with an expanded set of serial standards (8 instead of 7), buffer controls (background) and the same in-house pooled human control plasma samples on each 96-well plate (Martins, 2002), following manufacturer's protocols. Median fluorescence intensities (MFI) of the analyte-specific immunoassay bead set were detected by the flow- and fluorescence-based Luminex 200 detection platform (Luminex Corporation, Austin, TX, USA) (Marques-Vidal et al., 2011; Vignali, 2000). BDNF concentrations were calculated by xPONENT build 4.0.846.0 and Milliplex Analyst software (v.3.5.5.0, Millipore) using a standard curve derived from the known reference concentrations supplied by the manufacturer. A five-parameter model based on weighted logistic regression curves was used to calculate final concentrations by interpolation, with values expressed in pg/mL. Data were processed in a custom-built quality control (QC) algorithm that calibrates performance of the expanded set of serial standard curves and the in-house plasma controls run on every assay plate, monitoring intra- and inter-plate covariance (CV), bead counts and proportion of values falling below the lower limit of quantitation (LLOQ) and above the upper limit of quantitation (ULOQ), incorporating both raw (MFI/xPONENT) and interpolated (Milliplex Analyst) data. Samples failing to meet QC criteria or falling above the ULOQ were designated for re-run (CVs >30%, bead counts <50, values >ULOQ). Values falling at or below the averaged MFI for buffer-only wells (background) were recoded to zero. Values below the LLOQ but exceeding background were recoded to

the mid-point between zero and the LLOQ (LLOQ/2) for statistical comparisons (Marques-Vidal et al., 2011; Uh et al., 2008). Samples generating values exceeding the ULOQ were diluted to bring them into the linear (detectable) range, and analyte concentrations were calculated accordingly.

### 2.7. Working memory fMRI paradigm

180 participants performed a verbal working memory N-back task during fMRI scanning. The task consisted of 2 conditions, 0-back and 2-back. In each condition, participants were presented with a sequence of white upper-case letters on a black background presented centrally (200 msec duration, 1800 msec interstimulus interval) in a pseudo-random order. Participants performed 2 experimental runs of the task, with each run lasting 5 min 44 sec. Each run contained six 32 sec blocks. Each block was preceded by a 20 sec fixation period and a 4 sec instruction screen. During 0-back blocks, participants responded to every letter using one of 2 buttons to indicate whether or not the target letter (X) appeared. During 2-back blocks, participants responded to every letter using one of 2 buttons to indicate whether it matched or did not match the letter seen 2 previously. Response times and accuracy (*d' 2back*) were recorded. Response time (RT) values <100 msec were considered null and not included in the computation of participants' average RT. The sensitivity index *d' 2back* was calculated (Wickens, 2001) as *d' 2back* = *z* [probability (hits)] - *z* [probability (false alarms)].

### 2.8. fMRI data acquisition

MRI data were acquired with a Siemens 3T Tim Trio scanner (Siemens, Erlangen, Germany), equipped with a 12-channel head coil. Functional data were obtained using a T2*-weighted echo-planar imaging sequence sensitive to blood oxygenation level-dependent (BOLD) contrast (repetition time, 2000 msec; echo time, 30 msec; field of view, 200 mm; flip angle, 90°; voxel size, 3.1 × 3.1 × 3.0). Each functional volume consisted of 33 (3 mm) oblique axial slices. A T1-weighted image was collected using a high-resolution 3D Multi-Echo (ME) MPRAGE sagittal sequence with an isotropic resolution of 1 $mm^3$. Following acquisition, MRI data were converted to Nifti format and preprocessed in SPM8 (Wellcome Department of Cognitive Neurology, London, UK). Preprocessing included realignment and geometric unwarping of echo-planar imaging images using magnetic field maps, correction for head motion, nonlinear volume-based spatial normalization (Montreal Neurological Institute template MNI-152), and spatial smoothing with a Gaussian filter (6 mm [full width at half maximum]). Additional software (http://web.mit.edu/swg/software.htm) was used to identify and exclude outliers in the global mean image time series (threshold 3.0 standard deviation (SD) from the mean) and movement (threshold 1.0 mm; measured as scan-to-scan movement, separately for translation and rotation) parameters. Statistical parametric maps of BOLD activation were calculated in SPM8 using the general linear model approach-Worsley and Friston, (1995).

### 2.9. fMRI data analyses

Hemodynamic responses were modeled using a gamma function and convolved with onset times of 2-back and 0-back blocks to form the general linear model (GLM) at the single subject level. Outlier time points and the 6 rigid-body movement parameters were included in the GLM as covariates of no interest. To test a priori hypotheses targeting the HIPP and DLPFC, anatomically-defined masks of the HIPP and bilateral DLPFC (BA9/46; MNI coordinates, left: −42, 26, 30; right: 44, 32, 28) (10-mm spheres around peak loci) were used. Functional regions of interest (ROIs) in the DLPFC were defined from "supergroup" whole-brain analyses in the larger sample (N = 180; Fig. 1) based on peak task-evoked activity generated at $p < 10^{-10}$, T = 7.16, df = 179.The left and right HIPP ROIs was anatomically defined using a manually segmented MNI-152 brain (based on methods previously published by the Center for Morphometric Analysis at Massachusetts General Hospital and Harvard Medical School; (Makris et al., 2013)). ROIs were created with the Wake Forest University PickAtlas ROI toolbox for SPM (Maldjian et al., 2003). β weights from the right and left HIPP were extracted for each participant as a function of WM load (2-back > 0-back) using the REX toolbox (Whitfield-Gabrieli, 2009) and were used for subsequent analyses. For each participant and ROI, β estimates were entered into a linear mixed model analysis

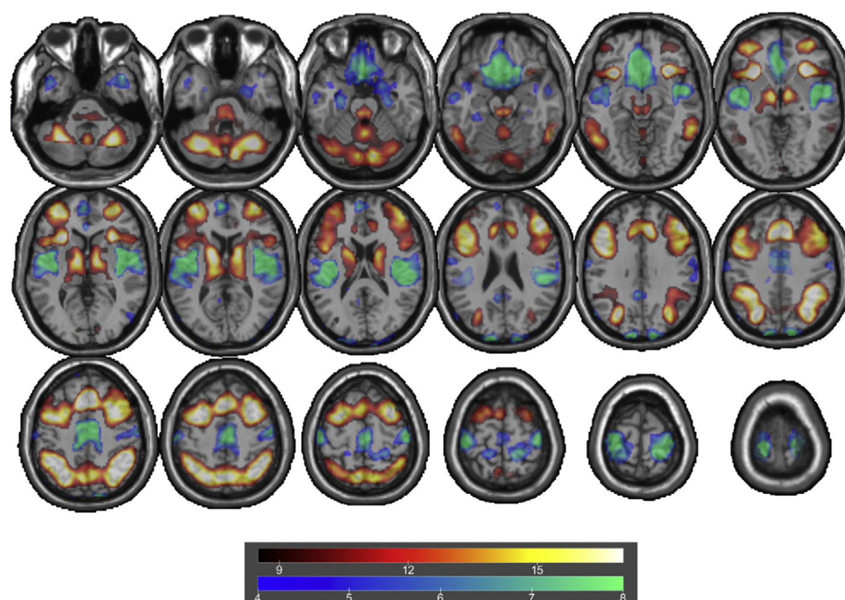


**Fig. 1.** Task-evoked BOLD responses throughout working memory circuitry, 2-back > 0-back, of total sample N = 180. Abbreviation: BOLD, blood oxygenation level dependent.

with sex or reproductive status and plasma BDNF levels as independent variables.

### 2.10. Neuropsychological assessments

Participants were administered a neuropsychological battery to assess episodic memory and estimated verbal intelligence (IQ). Measures of episodic memory included the 12-item Face-Name Associative Memory Exam (FNAME) (Papp et al., 2014; Rentz et al., 2011) and the 6-trial Selective Reminding Test (SRT) (Buschke, 1984; Masur et al., 1989). These tests were chosen because they are particularly challenging and sensitive to memory and learning deficits associated with early aging. The FNAME is a paired-associative face-name task that is sensitive to temporolimbic integrity. Using associative learning paradigms, in contrast to list learning procedures, has the benefit of controlling attention within the learning process by pairing items together, thus requiring the participant to make associations between them. Memory impairments on associative learning paradigms are often consistent with temporolimbic amnestic dysfunction (Grober et al., 2000; Sarazin et al., 2010).

As reported by Papp et al. (2014) the FNAME asks the participant to study 12 unfamiliar face-name-occupation groupings. The test consists of 2 learning exposures, followed by the presentation of the face and the request to recall the name and occupation associated with that face. After a 10-minute delay during which participants are shown 12 generationally-specific celebrity faces and asked to provide their name and occupation as an interference trial, participants are shown the face and asked to recall the name and occupation. A multiple-choice format was presented that asked the participants to choose the name and occupation from 3 choices of names and 3 choices of occupations. While forming face-name associations is particularly difficult, pairing the face with an occupation is an inherently easier task because of its association with previously stored semantic knowledge (Rentz et al., 2011). Performance on the FNAME was previously found to decline with age (Grober et al., 2000) and other factors that impact memory performance, such as depression (Lockwood et al., 2002). Furthermore, FNAME is thought to isolate medial temporal lobe memory function capacities apart from frontal executive mechanisms involved in memory processing and is thus a good choice to elucidate memory vulnerabilities associated with menopausal transition.

The SRT, on the other hand, is a selective reminding procedure that relies on feedback tailored to the individual, i.e., individuals are only reminded of words they failed to recall in the previous trial. This procedure taps into executive processing because it requires the individual to hold information online, within working memory, as only a portion of the list that was not immediately recalled is presented for learning. More specifically, once the individual is exposed to all the words in trial 1, they are reminded only of the words that were not immediately recalled in the previous trial. While more challenging than a traditional list learning test, the SRT was chosen because it taps into executive compromise (Loring and Papanicolaou, 1987), an important component to learning and memory and potentially relevant to menopausal vulnerabilities. Thus, our rationale for utilizing these 2 specific episodic memory tests was to determine whether menopausal memory changes were related to frontal executive retrieval deficits common in aging (i.e., as detected on the SRT) or HIPP dysfunction (i.e., as detected on the FNAME).

Z-score composites were created for FNAME including: 1) Initial learning of names and occupations; 2) Cued recall of names and occupations and; 3) FNAME summary score combining both initial learning and cued recall of names and occupations. Finally, we explored SRT performance that included list learning over 6 trials (Total Recall), delayed recall at 30 minutes (Masur et al., 1989), and an SRT summary z-score combining both list learning and delayed recall. The American National Adult Reading Test (AMNART) (Nelson, 1982) was used to assess estimated verbal intelligence (IQ).

### 2.11. Statistical analyses

Descriptive statistics of study sample characteristics - age, BMI, education (above v. below a 4-year college level of attainment), ethnicity (Caucasian v. not Caucasian), substance or alcohol abuse or dependence (history of or current, yes v. no), current smoking status (yes v. no), marital status (married, yes v. no), and BDNF plasma level—were reported by sex (male v. female) and reproductive status (pre- and peri-menopausal, post-menopausal). BDNF was examined both as a continuous and categorical measure, the latter indicating what has been referred to as a deviant subgroup analysis. The binary measure of high plasma BDNF v. not high was operationalized as BDNF levels in the highest third (above the 67th percentile) of the total sample versus in those below: pre/perimenopause (High BDNF: n = 21 v. low BDNF: n = 41), postmenopause (High BDNF: n = 10 v. low BDNF: n = 19), and men (High BDNF: n = 32 v. low BDNF: n = 68). We found no significant association comparing the first and second tertiles (there instead appeared to be a threshold effect at tertile 3), and thus the 2 groups were combined to double the sample size of the reference group and increase power. Comparisons by group status were calculated using nonparametric Wilcoxon rank-sum or chi-square test, for continuous and categorical data, respectively.

The associations between BDNF levels (as a continuous and binary variable) and measures of adult memory performance (FNAME, SRT) and fMRI BOLD activity were assessed overall and by individual group status using linear mixed models adjusted for intrafamilial correlation among siblings, along with age, ethnicity, and substance or alcohol abuse or dependence. fMRI BOLD activity models additionally controlled for task performance. We tested education, SES, marital status, BMI, substance and alcohol abuse or dependence, and ethnicity as potential confounding variables. Potential confounding was determined if a covariate was associated with both the outcome and exposure with a $p < 0.2$. To examine whether estradiol modified the association between BDNF and cognitive performance and brain activity, we included estradiol as a covariate in the model to observe whether effects were attenuated. Analysis of the right DLPLC was performed on the natural log (ln) transformation of the measure (plus a constant of 1 to address negative values) to normalize the model residuals. In models where BDNF was assessed as a continuous variable, BDNF was natural log (ln) transformed (plus a constant of 1 to address values below the limit of detection coded as 0) to normalize model residuals. Normality was formally assessed using the Shapiro-Wilk test. Group differences in the association between BDNF and adult memory performance, along with fMRI BOLD activity, were assessed with the inclusion of an interaction term between group status and BDNF. Wald chi-square tests were used to assess interactions. All analyses were performed using SAS 9.4 software (SAS institute, Cary, NC, USA).

## 3. Results

### 3.1. Participant demographics

The sample included 212 participants (106 women and 106 men). Three participants did not complete the cognitive tests (2 men and one woman). In addition, 8 women reported current use of hormone replacement therapy and 4 women reported past hormone use. Estradiol levels in postmenopausal women currently on hormone replacement therapy did not significantly differ from pre/peri menopausal women ($z = -1.08$, $p = 0.28$) and thus these

women were removed from subsequent analyses. Estradiol levels in postmenopausal women with a past history of hormone use were significantly lower than pre/perimenopausal women ($z = -2.39$, $p = 0.02$) and thus these women were included in subsequent analyses. In postmenopausal women, past hormone use was not associated with significantly higher or lower plasma levels of BDNF ($z = -1.71$, $p = 0.24$). Plasma BDNF measures were missing for 5 participants (2 men and 3 women) and BDNF data were lost for an additional 5 participants (2 men and 3 women) due to coding and data transfer errors and as such, a final sample of 191 participants (91 women and 100 men; Fig. 2) were included in the final analyses.

All participants were in early midlife (mean age = 50.03 ± 2.10), with an average verbal IQ of 116.54 ± 10.50. 76% of the participants had a high school diploma/GED or higher. Among women, some were already in menopause with permanent amenorrhea, low estradiol levels, and elevated gonadotropins; some exhibited signs of follicular failure (elevated FSH and oligoamenorrhea); and some showed normal cycling. Thirty-five women (38.5%) were premenopausal, 27 (29.7%) were perimenopausal, and 29 (31.9%) were postmenopausal. Given the small sample sizes, we combined the premenopausal and perimenopausal women into one pre/perimenopausal group to achieve sufficient power for assessing associations. In previous studies with this cohort (Jacobs et al., 2016a, b; Rentz et al., 2016), pre- and perimenopausal women had similar performances on memory tests. In the current study, we found no significant differences in the relationship between BDNF and memory between the 2 groups ($p_{chsq} > 0.05$ for all outcome measures) and thus, we combined the 2 groups to achieve adequate power for subsequent analyses.

Table 1 reports demographic characteristics of the sample and group comparisons. Groups were comparable on plasma levels of BDNF, body mass index, education, and estimated verbal IQ. Groups differed in ethnicity, substance and alcohol abuse, and there was a slight difference in age. Pre/perimenopausal women were slightly younger in age than postmenopausal women and men. There was a higher percentage of African American women in postmenopausal women and a higher percentage of substance and alcohol abuse/dependence in men compared to women, specifically pre/perimenopausal women. In the current sample, there was a high rate of history of alcohol and substance abuse/dependence, especially in men (64%). This was primarily due to one of the criteria in the DSM-IV for alcohol or substance abuse, which is “recurrent substance use in a situation in which it is physically hazardous”. This means that any individual who had repeatedly engaged in driving under the influence, at any point in their life, would be categorized as having a history of alcohol or substance abuse. Many of our participants, and presumably the general population for this age group, have a history of suchbehavior, especially when they were younger and regulations were different. This classification changed in the new DSM V and will presumably result in a significantly lower number of diagnoses. Although asked to refrain, 9 subjects reported taking pain medication prior to the scan. However, pain medication did not impact plasma levels of BDNF ($z = -0.96$, $p = 0.34$).

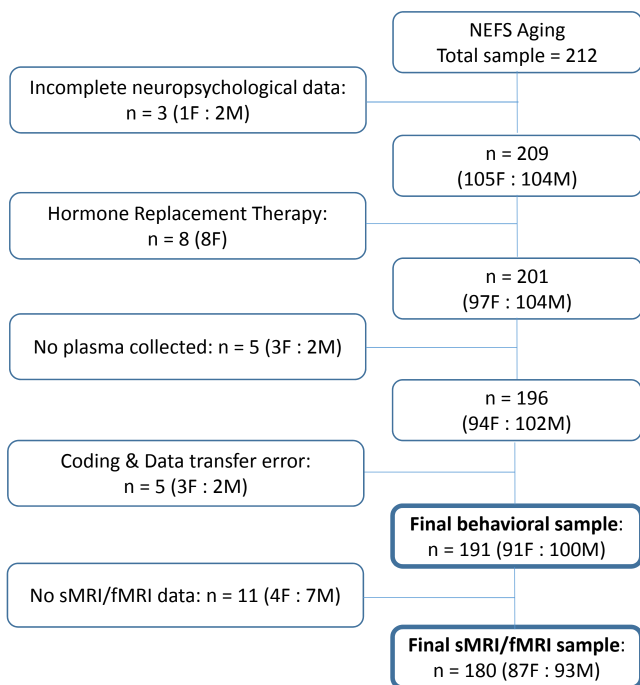


**Fig. 2.** Flow chart of subject recruitment and selection. Abbreviations: F, female; fMRI, functional magnetic resonance imaging; M, male; NEFS, New England Family Study; sMRI, structural magnetic resonance imaging.

BDNF val66met and APOE genotypes did not differ between men and women (BDNF val66met: men (27% met-carrier) v. women (28% met-carrier), $X^2 = 0.08$, $p = 0.78$; APOE: men (26% APOE4) v. women (22% APOE4), $X^2 = 0.97$, $p = 0.62$) or between menopause groups (BDNF val66met: pre/peri (28% met-carrier) v. post (29% met-carrier), $X^2 = 0.02$, $p = 0.89$; APOE: pre/peri (24% APOE4) v. post (17% APOE4), $X^2 = 2.44$, $p = 0.30$). We found no significant difference in plasma levels of BDNF between APOE (E2: mean = 2.45 (1.32), E3: 2.36 (1.60), E4: 2.13 (1.65); $F_{(1, 186)} = 0.43$, $p = 0.65$) and BDNF genotype groups (met-carrier: mean = 2.27 (1.56), val/val: 2.33 (1.60); $F_{(1, 186)} = 0.05$, $p = 0.83$).

### 3.2. Hormonal evaluations

Not surprising, postmenopausal women (estradiol: median = 12.10 pg/mL; progesterone: median = 0.07 ng/mL; FSH: median = 67.09 mIU/mL) had significantly lower levels of serum estradiol ($z = -5.34$, $p < 0.001$) and progesterone ($z = -3.89$, $p < 0.001$) and significantly higher levels of FSH ($z = -5.76$, $p < 0.001$) compared to premenopausal (estradiol: median = 86.00 pg/mL; progesterone: median = 1.46 ng/mL; FSH: median = 5.70 mIU/mL) and perimenopausal women (estradiol: median = 29.50 pg/mL; progesterone: median = 0.13 ng/mL; FSH: median = 28.82 mIU/mL). Premenopausal women had significantly higher levels of estradiol ($z = -4.12$, $p < 0.001$) and progesterone ($z = -3.51$, $p < 0.001$) and lower levels of FSH ($z = -6.50$, $p < 0.001$) compared to perimenopausal women.

Overall in women, estradiol levels did not correlate with plasma levels of BDNF ($r = 0.15$, $p = 0.15$). Stratified by menopausal staging, there was no association in pre/perimenopausal women ($r = 0.18$, $p = 0.18$). However, in postmenopausal women, there was a non-significant positive correlation between estradiol levels and BDNF ($r = 0.35$, $p = 0.07$).

### 3.3. Adult memory performance

In our previous work with the same cohort presented here (Rentz et al., 2016), we demonstrated that women performed significantly better than men on tasks of associative and verbal memory. This female advantage was attenuated over the menopausal transition. Postmenopausal women performed worse than pre/perimenopausal women on the FNAME test and SRT and performed similar to men (Rentz et al., 2016). In the current study, we extended these findings to examine adult memory performance in the context of BDNF.

Overall, and within men and women separately, plasma BDNF levels were not associated with memory performance on the FNAME and SRT (Table 2: all $p_{chsq} > 0.1$). Further, there was no interaction between sex and BDNF on memory performance

**Table 1**
Demographic and clinical characteristics of a sample of N = 191 men and women assessed at age 45–55

| Measure | Men (n = 100) | Women (n = 91) | Pre/peri (n = 62) | Post (n = 29) | Comparisons: Men versus women | Men verus pre/peri | Men versus post | Pre/peri versus post |
|---|---|---|---|---|---|---|---|---|
| | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | *p* value | *p* value | *p* value | *p* value |
| Age | 50.21 (2.19) | 49.82 (1.99) | 49.52 (1.81) | 50.48 (2.21) | 0.24 | 0.05[e] | 0.54 | 0.05[e] |
| BMI | 29.29 (5.57) | 28.09 (5.96)[a] | 28.29 (5.96) | 27.68 (6.05) | 0.08 | 0.13 | 0.20 | 0.71 |
| Verbal IQ | 116.29 (10.9) | 116.74 (9.9) | 117.34 (9.3) | 115.45 (11.2) | 0.96 | 0.85 | 0.69 | 0.61 |
| d' 2back performance | 2.00 (0.69)[b] | 1.96 (0.66)[c] | 1.96 (0.65)[c] | 1.97 (0.69) | 0.54 | 0.65 | 0.80 | 0.87 |
| | Median (p25,p75) | Median (p25,p75) | Median (p25,p75) | Median (p25,p75) | | | | |
| | n (%) | n (%) | n (%) | n (%) | | | | |
| BDNF plasma levels (pg/mL) | 8.84 (1.6,27.7) | 11.54 (1.4,34.8) | 10.92 (2.0,43.9) | 14.30 (1.2,24.6) | 0.58 | 0.48 | 0.95 | 0.61 |
| Education (% > 4 Y College) | 68 (68%)[a] | 54 (59%)[b] | 38 (61%) | 16 (55%)[b] | 0.25 | 0.34 | 0.36 | 0.86 |
| Ethnicity (Caucasian) | 89 (89%) | 79 (87%) | 56 (90%) | 23 (79%) | 0.12 | 0.49 | 0.03[e] | 0.19 |
| Current smoking status (Yes) | 14 (14%) | 16 (18%) | 11 (18%) | 5 (17%) | 0.50 | 0.52 | 0.67 | 0.95 |
| Marital status (Married) | 63 (63%)[a] | 53 (58%) | 37 (60%) | 16 (55%) | 0.45 | 0.61 | 0.41 | 0.69 |
| Substance or alcohol abuse/dependence (Yes)[d] | 64 (64%) | 40 (44%) | 26 (42%) | 14 (48%) | 0.005[e] | 0.006[e] | 0.13 | 0.57 |
| BDNF categorical (High) | 32 (32%) | 31 (34%) | 21 (34%) | 10 (34%) | | | | |

p25,p75: 25th and 75th quartiles.
[a] Missing n = 1.
[b] Missing n = 2.
[c] Missing n = 6.
[d] History of or current.
[e] $p \leq 0.05$.

(Table 2: all $p_{chsq} > 0.1$). When women were divided based on menopausal staging, we found BDNF was significantly associated with memory performance, specifically in postmenopausal women (FNAME: initial learning: $\beta = 0.80$, SE = 0.34, $\chi^2 = 5.64$, $p_{chsq} < 0.05$; cued recall: $\beta = 0.90$, SE = 0.36, $\chi^2 = 6.21$, $p_{chsq} < 0.05$; and summary score: $\beta = 0.85$, SE = 0.32, $\chi^2 = 6.98$, $p_{chsq} < 0.01$; SRT: 30 min delayed recall: $\beta = 2.13$, SE = 1.01, $\chi^2 = 4.44$, $p_{chsq} < 0.05$), whereby higher levels of BDNF were associated with better memory performance. There was no significant relationship between plasma levels of BDNF and memory performance in pre/perimenopausal women (Table 2: all $p_{chsq} > 0.1$).

To examine whether postmenopausal women differed significantly from pre/perimenopausal women, we conducted interaction analyses between menopausal staging (pre/peri v. post) and BDNF on memory performance, controlling for age, ethnicity, substance and alcohol abuse, and sibship. We found significant interactions in measures of associative memory (FNAME summary: $\chi^2 = 5.44$, $p_{chsq} < 0.05$; FNAME initial learning: $\chi^2 = 3.51$, $p_{chsq} = 0.06$; FNAME cued recall: $\chi^2 = 6.55$, $p_{chsq} < 0.05$; Fig. 3) and verbal memory (SRT summary: $\chi^2 = 3.30$, $p_{chsq} = 0.07$; $\chi^2 = 7.02$, $p_{chsq} < 0.01$; Fig. 4), suggesting that the relationship between BDNF and memory was significantly different between postmenopausal women v. pre/perimenopausal women. Controlling for estradiol levels, effects in postmenopausal were slightly attenuated but remained significant (FNAME initial learning: $\beta = 0.70$, SE = 0.36, $\chi^2 = 3.81$, $p_{chsq} = 0.05$; FNAME cued recall: $\beta = 0.88$, SE = 0.39, $\chi^2 = 5.09$, $p_{chsq} < 0.05$; and FNAME summary: $\beta = 0.79$, SE = 0.35, $\chi^2 = 5.22$, $p_{chsq} < 0.01$; SRT 30 min delayed recall: $\beta = 2.08$, SE = 1.10, $\chi^2 = 3.61$, $p_{chsq} = 0.06$), suggesting that the impact of BDNF was not wholly dependent on estradiol, despite the correlation between BDNF and estradiol levels.

### 3.4. Regional BOLD response in WM circuitry

In our previous work on working memory circuitry activity in our cohort (Jacobs et al., 2016a), we demonstrated that the N-back paradigm evoked robust responses throughout the working memory circuitry. We demonstrated that task-evoked activity in DLPFC increased over the menopausal transition, with postmenopausal women exhibiting greater activity relative to pre/perimenopausal women. Similarly, pronounced deactivation in the HIPP was observed in pre/perimenopausal women, with attenuated deactivation (failure to disengage) in postmenopausal women. In the current study, we extended these findings to examine working memory function in the context of BDNF.

Behavioral performances on the WM task (d' 2back) were comparable across sex/menopausal staging groups (Table 1). There was no association between performance on the WM task and BDNF levels in the total sample ($r = -0.03$, $p = 0.71$) as well as within each sex/menopausal staging group (Men: $r = 0.09$, $p = 0.40$; Women: $r = -0.14$, $p = 0.17$; Pre/Peri: $r = -0.18$, $p = 0.18$; Post: $r = -0.10$, $p = 0.61$).

$\beta$ weights from the HIPP and DLPFC ROIs were extracted for each participant as a function of WM load (2-back > 0-back) and used for subsequent analyses of fMRI BOLD activity. Overall, higher levels of BDNF, as a continuous measure, were significantly associated with lower fMRI BOLD activity in the left HIPP ($\beta = -0.04$, SE = 0.02, $\chi^2 = 4.08$, $p_{chsq} < 0.05$). Within men and women separately, plasma BDNF levels were not associated with fMRI BOLD activity in the HIPP or DLPFC (Table 2: all $p_{chsq} > 0.1$). There was also no interaction between sex and BDNF on fMRI activity for any of the ROIs (Table 2: all $p_{chsq} > 0.1$).

However, when women were divided based on menopausal staging, we found BDNF was significantly associated with activity in the left HIPP and right DLPFC, specifically in postmenopausal women (left HIPP: $\beta = -0.11$, SE = 0.04, $\chi^2 = 6.58$, $p_{chsq} < 0.05$; right DLPFC: $\beta = -0.08$, SE = 0.03, $\chi^2 = 8.43$, $p_{chsq} < 0.005$), whereby higher levels of BDNF were associated with lower fMRI BOLD activity. Typically, the HIPP is systematically deactivated during the n-back task. Here we found dysfunction in the HIPP in postmenopausal women with lower plasma levels of BDNF. There was no significant relationship between plasma levels of BDNF and BOLD activity in HIPP or DLPFC in pre/perimenopausal women (Table 2: all $p_{chsq} > 0.1$). To examine whether postmenopausal women differed significantly from pre/perimenopausal women, we conducted interaction analyses between menopausal staging (pre/peri v. post) and BDNF on BOLD activity in HIPP or DLPFC, controlling for age, ethnicity, substance and alcohol abuse, sibship, and task performance. We found significant interactions in left HIPP

**Table 2**
Interaction between BDNF and sex/reproductive status on adult memory performance

| Measure | Total (N = 191) | | | | Men (n = 100) | | | | Women (n = 91) | | | | Pre-/Peri-menopause (n = 62) | | | | Post-menopause (n = 29) | | | | Comparisons | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | | | | | | | Men v. Women | | Men v. Pre/Peri- | | Men v. Post- | | Pre-/Peri- v. Post- | |
| | β | SE | χ2 | $p_{chsq}$ | β | SE | χ2 | $p_{chsq}$ | β | SE | χ2 | $p_{chsq}$ | β | SE | χ2 | $p_{chsq}$ | β | SE | χ2 | $p_{chsq}$ | χ2 | $p$ | χ2 | $p_{chsq}$ | χ2 | $p$ | χ2 | $p_{chsq}$ |
| Face-Name Association Test | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Summary score | 0.15 | 0.15 | 1.11 | 0.29 | 0.12 | 0.20 | 0.37 | 0.54 | 0.22 | 0.21 | 1.16 | 0.28 | −0.05 | 0.26 | 0.04 | 0.84 | 0.85 | 0.32 | 6.98 | 0.01[c] | 0.01 | 0.91 | 0.74 | 0.39 | 3.35 | 0.07[b] | 5.44 | 0.02[c] |
| Initial recall | 0.12 | 0.16 | 0.54 | 0.46 | 0.10 | 0.20 | 0.23 | 0.63 | 0.16 | 0.24 | 0.45 | 0.50 | −0.16 | 0.31 | 0.28 | 0.60 | 0.80 | 0.34 | 5.64 | 0.02[c] | 0.01 | 0.90 | 0.45 | 0.50 | 2.97 | 0.08[b] | 3.51 | 0.06[b] |
| Cued recall | 0.19 | 0.15 | 1.60 | 0.21 | 0.15 | 0.22 | 0.45 | 0.50 | 0.30 | 0.20 | 2.33 | 0.13 | −0.03 | 0.23 | 0.02 | 0.90 | 0.90 | 0.36 | 6.21 | 0.01[c] | 0.01 | 0.92 | 0.80 | 0.37 | 2.83 | 0.09[b] | 6.55 | 0.01[c] |
| Buschke Selective Reminding Test | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Summary score | 0.07 | 0.14 | 0.23 | 0.63 | 0.10 | 0.20 | 0.24 | 0.62 | 0.03 | 0.19 | 0.03 | 0.87 | −0.20 | 0.24 | 0.72 | 0.40 | 0.48 | 0.35 | 1.92 | 0.17 | 0.34 | 0.56 | 1.19 | 0.28 | 0.25 | 0.62 | 3.30 | 0.07[b] |
| Total recall | 0.18 | 1.37 | 0.02 | 0.89 | 0.33 | 1.96 | 0.03 | 0.87 | −0.06 | 1.87 | 0.00 | 0.97 | −0.75 | 2.27 | 0.11 | 0.74 | 1.67 | 3.50 | 0.23 | 0.63 | 0.16 | 0.69 | 0.30 | 0.58 | 0.01 | 0.92 | 0.58 | 0.45 |
| 30 min Delayed recall | 0.35 | 0.43 | 0.65 | 0.42 | 0.45 | 0.61 | 0.54 | 0.46 | 0.22 | 0.58 | 0.14 | 0.71 | −0.91 | 0.72 | 1.60 | 0.21 | 2.13 | 1.01 | 4.44 | 0.04[c] | 0.22 | 0.64 | 2.14 | 0.14 | 0.95 | 0.33 | 7.02 | 0.01[c] |
| N-back Task fMRI BOLD activity | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Hippocampus | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Right | 0.00 | 0.02 | 0.01 | 0.92 | −0.01 | 0.04 | 0.02 | 0.89 | 0.00 | 0.03 | 0.03 | 0.87 | 0.05 | 0.03 | 2.21 | 0.14 | −0.08 | 0.05 | 2.71 | 0.10 | 0.12 | 0.73 | 1.63 | 0.20 | 1.33 | 0.25 | 3.33 | 0.07[b] |
| Left | −0.04 | 0.02 | 4.08 | 0.04[c] | −0.04 | 0.03 | 2.18 | 0.14 | −0.04 | 0.02 | 0.05 | 0.83 | 0.00 | 0.03 | 0.00 | 0.99 | −0.11 | 0.04 | 6.58 | 0.01[c] | 0.02 | 0.88 | 1.04 | 0.31 | 1.11 | 0.29 | 3.91 | 0.05[c] |
| Dorsolateral Prefrontal Cortex | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| [a]Right | −0.01 | 0.01 | 1.03 | 0.31 | −0.02 | 0.02 | 0.83 | 0.36 | −0.01 | 0.02 | 0.19 | 0.66 | 0.02 | 0.02 | 0.86 | 0.35 | −0.08 | 0.03 | 8.43 | 0.004[c] | 0.56 | 0.45 | 2.19 | 0.14 | 1.02 | 0.31 | 6.12 | 0.01[c] |
| Left | 0.04 | 0.03 | 1.08 | 0.30 | 0.04 | 0.04 | 1.50 | 0.22 | 0.05 | 0.05 | 1.17 | 0.28 | 0.08 | 0.06 | 1.98 | 0.16 | −0.01 | 0.08 | 0.01 | 0.92 | 0.24 | 0.62 | 0.43 | 0.51 | 0.03 | 0.85 | 0.72 | 0.40 |

Linear mixed model adjusted for age, ethnicity, current substance dependence, and intrafamilial correlation between siblings.
[a] Analysis of the right DLPLC was performed on the natural log (ln) transformation of the measure (plus a constant of 1 to address negative values) to normalize the model residuals.
[b] $p \le 0.1$.
[c] $p \le 0.05$.

($\chi^2 = 3.91$, $p_{chsq} < 0.05$; Fig. 5A) and right DLPFC ($\chi^2 = 6.12$, $p_{chsq} < 0.05$; Fig. 5B), suggesting that the relationship between BDNF and memory circuitry function was significantly different between postmenopausal women v. pre/perimenopausal women. Controlling for estradiol levels, effects in postmenopausal remained significant (left HIPP: $\beta = -0.11$, SE = 0.05, $\chi^2 = 5.10$, $p_{chsq} < 0.05$; right DLPFC: $\beta = -0.09$, SE = 0.03, $\chi^2 = 9.2$, $p_{chsq} < 0.005$), again signifying that these effects were not wholly dependent on estradiol, despite the correlation between BDNF and estradiol levels.

## 4. Discussion

In this population-based study, we identified the impact of BDNF on memory performance in early midlife as a function of sex and reproductive status in women. Specifically, in postmenopausal women, memory performance and functional BOLD activity in the WM circuitry were related to plasma levels of BDNF. Higher plasma levels of BDNF were associated with better associative and verbal memory performance. In early midlife, these effects were particularly strong for associative memory. Further, in postmenopausal women, lower BDNF levels were associated with failure to disengage the HIPP and higher BOLD activity in DLPFC during the WM task. In contrast, BDNF levels did not significantly impact memory performance or memory circuitry function in early middle-aged pre/perimenopausal women and men.

Reproductive aging in women presents a critical period for neurological changes that have long-term implications for the risk of cognitive impairment and AD. Over the menopausal transition, some women experience a decline in memory performance (Bleecker et al., 1988; Kerschbaum et al., 2017; Rentz et al., 2016), functional changes in episodic and working memory networks (Jacobs et al., 2016a, b), reduced cerebral glucose metabolism (Mosconi et al., 2017a), increased amyloid beta deposition (Mosconi et al., 2017b), and reduced volumes of gray and white matter in regions vulnerable in AD (Mosconi et al., 2017b). These studies suggest that pathological changes occur in women over menopause, which chronologically aligns with the emergence of early AD-related pathology. A major contributor to neuronal changes over menopause is the depletion of ovarian steroid hormones. Our group (Jacobs et al., 2016b) and others (Kerschbaum et al., 2017; Wolf et al., 1999) have demonstrated that there is a direct association between decline in 17β-estradiol and memory performance. Further, early surgical menopause is significantly associated with increased risk of AD (Bove et al., 2014; Phung et al., 2010; Rocca et al., 2007, 2011). Given the neuroprotective properties of estradiol on HIPP neurogenesis, synaptogenesis, and learning and memory (Brinton, 2009; Liu et al., 2008; McEwen et al., 1995; Ormerod et al., 2004; Tanapat et al., 1999; Warren et al., 1995; Woolley and McEwen, 1994; Woolley et al., 1996), the depletion of estradiol may be a critical period for revealing which women are at higher risk for AD later in life, contributing to our broader understanding of AD risk in women.

Despite strong preclinical evidence for the neuroprotective effects of estradiol, there is considerable debate in the clinical literature regarding the effects of estradiol on cognitive performance, especially based on evidence from recent hormone replacement therapy randomized control trials (RCTs) (Espeland et al., 2013; Gleason et al., 2015; Henderson et al., 2016). Overall, these RCTs found that hormone therapy did not improve cognitive performance. This is not surprising given that hormone therapy may help maintain intact memory function with aging but not necessarily improve cognitive function. Interestingly, the placebo groups in these studies did not decline in cognitive performance, suggesting either a selection bias of healthy women who were not symptomatic or vulnerable to cognitive decline over menopause or that the cognitive tests administered were not sensitive to cognitive changes

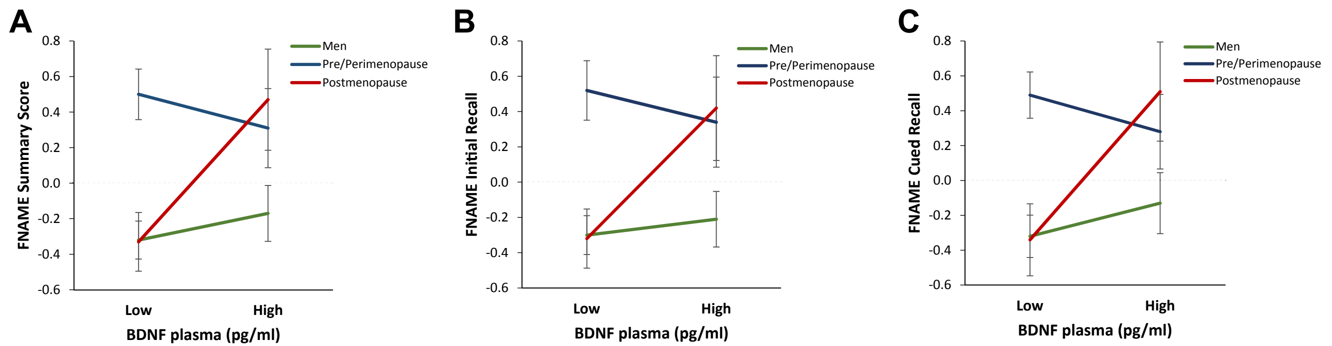


**Fig. 3.** Performance on the FNAME by reproductive stage/sex and plasma BDNF levels. Z-scores are reported by group and BDNF status for FNAME (A) summary score, (B) initial learning of names and occupations, and (C) cued recall of names and occupations. The FNAME summary score combines both initial learning and cued recall of names and occupations. Error bars represent SEM. Abbreviations: BDNF, brain-derived neurotrophic factor; FNAME, Face-Name Associative Memory Exam; SEM, standard error of the mean.

over menopause. As noted above, we and others have demonstrated that some women experience a decline in memory function, especially verbal memory, with reproductive aging. These RCTs were primarily conducted in healthy women and little is known about the impact of hormone therapy in women with chronic diseases, such diabetes, depression, and hypertension, 3 diseases that are independent risk factors for Alzheimer's disease. It is important to understand factors that contribute to memory decline over menopause and which women may benefit most from hormone therapy. Long-term follow-up studies of these cohorts are necessary to determine whether hormone therapy decreases dementia risk, as recently demonstrated in the WHI cohort of women $\leq$65 years of age. As such, it is critical to continue work on the impact of hormone therapy on maintaining intact memory function, including the most effective form, route, and duration of administration.

Although all women undergo menopause, whether naturally or surgically, not all women experience cognitive decline. Like all aging processes, there is heterogeneity in outcomes, suggesting mechanisms for risk and resilience. In the current study, we demonstrated that higher levels of BDNF may be a nerve growth pathway through which resilience against memory decline could be targeted. Higher levels of BDNF in postmenopausal women were associated with better memory performance and functional patterns in the working memory network that were similar to pre/perimenopausal women (i.e., lower HIPP and DLPFC activity). Interestingly, the neuroprotective effects of BDNF were only evident in postmenopausal women. Memory performance was not related to BDNF levels in pre/perimenopausal women. In the absence of estradiol, higher levels of BDNF (downstream from estradiol) may have a greater impact on memory function, whereas in premenopausal women, regulation of memory function by estradiol itself may reduce the impact of BDNF. In postmenopausal women, when we controlled for estradiol levels, effects remained significant, suggesting that BDNF effects were not wholly dependent on estradiol. Rodent studies suggest that estradiol and BDNF activate similar signaling pathways that are involved in axonal and dendritic growth, cellular survival, synaptic plasticity, and learning (for a review, see Scharfman and MacLusky, 2006). Given that women experience depletion of ovarian hormones, while men experience a more gradual decline with age, these results suggest that certain neuroprotective factors may play a more crucial role early in midlife in women.

Consistent with our findings, others have found that higher levels of BDNF were positively associated with memory performance (Erickson et al., 2010; Komulainen et al., 2008; Li et al., 2009), executive function (Li et al., 2009), general cognitive function (Gunstad et al., 2008; Komulainen et al., 2008), and HIPP volume (Erickson et al., 2010) in older adults. These results were consistent across methods of BDNF assessment (plasma, serum, and CSF) (Erickson et al., 2010; Gunstad et al., 2008; Komulainen et al., 2008; Li et al., 2009) and in some cases were specific to postmenopausal women. However, some population-level studies in older adults found no significant association between BDNF and memory or HIPP volume or found effects only specific to patients with AD (Driscoll et al., 2012; Kim et al., 2015; O'Bryant et al., 2011).

Many factors can contribute to discrepancies between studies including the consideration of sex or reproductive age, as we demonstrated in the present study. It is important to note that although in the current study we did not find differences in plasma

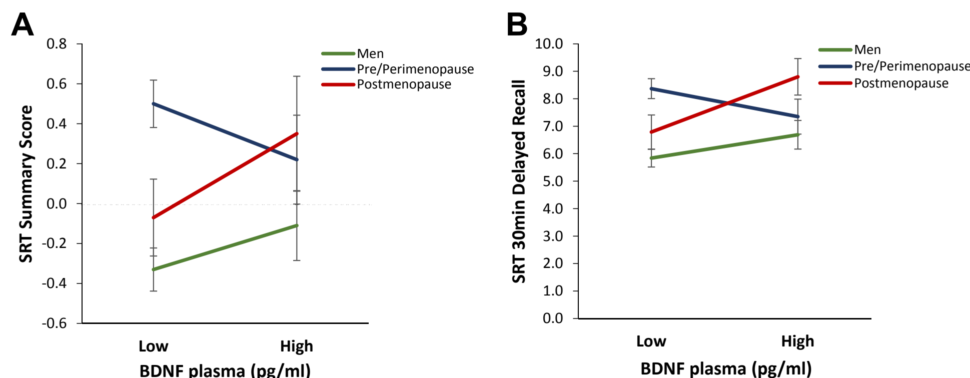


**Fig. 4.** Performance on the trial SRT by reproductive stage/sex and plasma BDNF levels. (A) Z-scores are reported by group and BDNF status for SRT summary score. (B) Scores are reported by group and BDNF status for SRT 30 min delayed recall. The SRT summary score combines both list learning and delayed recall. Error bars represent SEM. Abbreviations: BDNF, brain-derived neurotrophic factor; SEM, standard error of the mean; SRT, Selective Reminding Test.

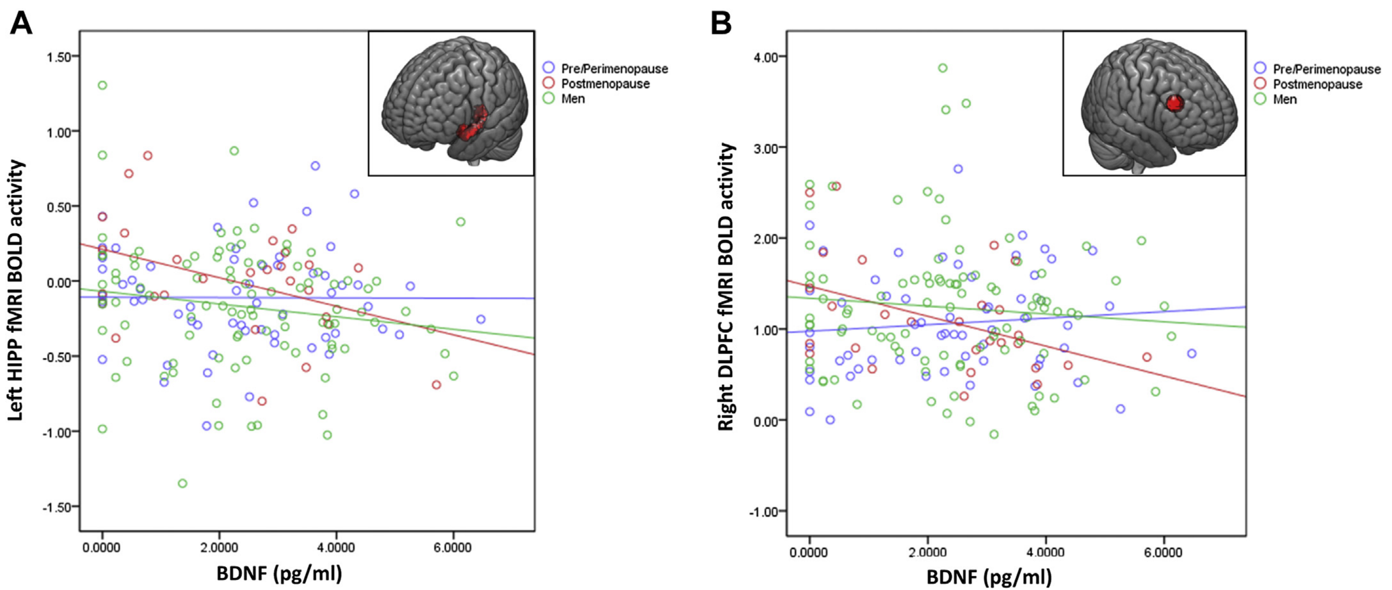


**Fig. 5.** Modulation of working memory-related HIPP and DLPFC activity by reproductive stage/sex and plasma BDNF levels. (A) Surface location of functionally defined mask of HIPP on a rendered brain. Task-related HIPP deactivations diminished with increasing levels of plasma BDNF in postmenopausal women. (B) Surface location of functionally defined masks of DLPFC on a rendered brain. Functional ROI was generated from a supergroup activity map in a larger sample (2-back > 0-back; N = 180). Task-evoked activity in right DLPFC increased with increasing levels of BDNF in postmenopausal women. Abbreviations: BDNF, brain-derived neurotrophic factor; BOLD, blood oxygenation level dependent; DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; HIPP, hippocampus.

levels of BDNF between sex and menopause groups (i.e., postmenopausal women did not have lower plasma levels of BDNF than pre/perimenopausal women), BDNF expression is highly regulated by gonadal hormones (Sohrabji et al., 1995). The *BDNF* gene has an estrogen response element to which estrogen hormone-receptor complexes bind to stimulate transcription (Sohrabji et al., 1995). Studies have found that BDNF expression changes across the estrous cycle, mirroring levels of estradiol (Scharfman et al., 2003; Spencer et al., 2008; Spencer-Segal et al., 2011). Furthermore, in ovariectomized rats, there is a decrease in BDNF expression that is restored following the administration of estradiol (Singh et al., 1995). In contrast, depletion of testosterone in rodents is associated with upregulation of BDNF immunoreactivity in the HIPP mossy fiber pathway (Skucas et al., 2013). Studies have also found that women tend to have higher levels of BDNF compared to men (Driscoll et al., 2012; Li et al., 2009). These investigations emphasize the importance of taking into consideration sex and reproductive age when examining the relationship between BDNF and memory. Findings in the current study emerged only when sex and reproductive age were incorporated into the analyses.

Past studies have found alterations in HIPP and DLPFC fMRI BOLD activity on working memory tasks in a number of different conditions (Chen et al., 2017; Fernandez-Corcuera et al., 2013; Miskowiak et al., 2016; Smith et al., 2017). Notably, our team showed that on a group level, postmenopausal women have increased fMRI BOLD activity in the HIPP and DLPFC compared to pre/perimenopausal women (Jacobs et al., 2016a). Egan et al. (2003) found that carriers of the BDNF met allele, the allelic isoform associated with decreased activity-dependent release of BDNF, also have increased fMRI BOLD activity in the HIPP on the n-back working memory task. Consistent with this, in the study presented here, we found that low plasma BDNF levels in postmenopausal women were associated with higher BOLD activity in the HIPP and DLPFC. On the n-back task, activation of the DLPFC is normally accompanied by a robust deactivation of the HIPP (Egan et al., 2003; Jacobs et al., 2016a; Meyer-Lindenberg et al., 2001; Wei et al., 2018). Thus, we would argue that increased BOLD activity in the HIPP suggests a failure to disengage. Some studies have hypothesized that failure to disengage is related to a failure to suppress the default mode network (DMN) during the task (Fernandez-Corcuera et al., 2013; Miskowiak et al., 2016). Thus, reproductive age and BDNF may potentially have an impact on overall DMN and not only the HIPP. Dysregulation in HIPP and DMN are often observed before the onset of cognitive symptoms in AD (Drzezga et al., 2011; O'Brien et al., 2010; Sheline et al., 2010), suggesting that functional brain changes may be an early indicator of future cognitive impairment for some individuals.

Alternatively, increased activity in the HIPP and DLPFC may be a compensatory mechanism to help maintain task performance in postmenopausal women. The relationship between task performance and fMRI BOLD activity was extensively reported and discussed in Jacobs et al. (2016a) in the same cohort. We found that the magnitude of regional activity and connectivity within WM circuitry were strongly related to task performance. Specifically, in postmenopausal women, task performance positively correlated with activity in the DLPFC and DLPFC-HIPP connectivity. In the current study, we extended these findings and examined this relationship in the context of BDNF. Interestingly, we found no significant associations between task performance and BDNF in the total sample and within each sex and reproductive group. Given the negative association between BDNF and DLPFC activity, these results suggest that higher fMRI activity in postmenopausal women with low levels of BDNF may help maintain task performance in a compensatory manner.

The current results should be viewed in light of certain limitations. The first is that the sample sizes when broken down by menopausal status were relatively small and thus future studies should aim to replicate these findings in larger populations. The study design is also a cross-sectional design, and as such, causality cannot be determined. We are unable, as yet, to establish whether maintaining high levels of BDNF over reproductive aging contributes to intact memory function postmenopause. In our future longitudinal study with this cohort, we will prospectively assess the neuroprotective effects of BDNF levels in individuals as they

transition through menopause. Lastly, BDNF levels were assessed from plasma, presenting limitations for the relationship with neuronal levels of BDNF. The cellular source of plasma BDNF is not clearly defined. Possible contributors are vascular endothelial and smooth muscle cells as well as activated macrophages, lymphocytes, and dendritic cells. BDNF is also produced in the brain and readily crosses the blood brain barrier (Pan et al., 1998). A possible contributor of plasma BDNF is hypothesized to be from neurons and glial cells. Several preclinical and clinical studies have shown direct correlations between cerebral and plasma levels of BDNF (Klein et al., 2011; Pillai et al., 2010; Rasmussen et al., 2009).

## 5. Conclusion

At a human population-level, these findings suggest that higher levels of BDNF in postmenopausal women is associated with better memory performance. BDNF is involved in many downstream cellular processes such as neuronal survival (Scharfman et al., 2005; Yoshii and Constantine-Paton, 2010), synaptic plasticity (Tyler and Pozzo-Miller, 2003), glutamate release (Zhang et al., 2013), and axonal and dendritic growth (Gonzalez et al., 2016). BDNF and its TrkB receptor are also synthesized in the heart and expressed in the endothelial cell lining of coronary arteries and are present in muscle (Donovan et al., 2000; Nakahashi et al., 2000). Disruptions in BDNF/TrkB signaling affect the physiology of cardiac muscles and are related to cardiovascular diseases (CVD) such as hypertension and myocardial infarction (Pius-Sadowska and Machalinski, 2017), well-known risk factors of AD (Justin et al., 2013). Given its widespread downstream effects, BDNF plays a major role in numerous psychiatric and neurological disorders and comorbidity with CVD. Examining the upstream regulation of BDNF expression in different disorders may help us understand the pathophysiological mechanisms that result in lower levels of BDNF. For example, given that glucocorticoids suppress BDNF expression (Kumamaru et al., 2011) and HPG function, dysfunction in the HPA axis may modulate BDNF levels and impact cognitive function. Further, major depressive disorder is associated with lower BDNF levels, an effect that is reversed with antidepressant treatment (Aydemir et al., 2005; Gonul et al., 2005; Piccinni et al., 2008; Tadic et al., 2011). Thus, understanding the mediating role of major depression on memory decline over the menopausal transition may be important for understanding the trajectory that leads to memory decline in some women. The current results provide evidence for potential sex-dependent avenues for and timing of attenuating risk of memory decline in early midlife.

## Disclosure statement

Authors have no conflicts of interest. JMG is a consultant/on the scientific advisory board for Cala Health, but this has no relation to the content in this study.

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