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Positive and negative affect, depression, and cognitive processes in the Cognition in the Study of Tamoxifen and Raloxifene (Co-STAR) Trial

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Abstract

Objectives—This study examined the relationship between positive and negative affect, depressive symptoms, and cognitive performance.

Methods—The sample consisted of 1,479 non-demented, postmenopausal women (mean age=67 years) at increased risk of breast cancer enrolled in the National Surgical Adjuvant Breast and Bowel Project's Study of Tamoxifen and Raloxifene (STAR). At each annual visit, women completed a standardized neuropsychological battery and self-report measures of affect and depression. Data from 3 visits were used in linear mixed models for repeated measures using likelihood ratio tests. Separate analyses were performed to relate positive/negative affect and depression to each cognitive measure.

Results—Higher positive affect was associated with better letter fluency ($p=0.006$) and category fluency ($p<0.0001$). Higher negative affect was associated with worse global cognitive function ($p<0.0001$), verbal memory (CVLT List B; $p=0.002$), and spatial ability ($p<0.0001$). Depressive symptoms were negatively associated with verbal knowledge ($p=0.004$), figural memory ($p<0.0001$), and verbal memory (p's≤ 0.0001).

Discussion—Findings are consistent with some prior research demonstrating a link between positive affect and increased verbal fluency and between depressive symptoms and decreased memory. The most novel finding shows that negative affect is related to decreased global cognition and visuospatial ability. Overall, this research in a large, longitudinal sample supports the notion that positive affect is related to increases and negative affect to decreases in performance on distinct cognitive measures.

Keywords

positive affect; negative affect; depression; cognition; women's health

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Introduction

Affect refers to one's emotional experience or mood. Positive affect reflects the extent of one's experience of positive emotions (e.g., feeling enthusiastic, excited, attentive, alert) while negative affect reflects distress and negative mood (e.g., feeling nervous, ashamed, scared, upset) (Watson, Clark, & Tellegen, 1988). It is generally accepted that positive and negative affect are not opposite ends of a unitary dimension. However, they are distinct dimensions that typically demonstrate low correlations with one another (Cacioppo & Berntson, 1999; Watson, Clark, & Tellegen, 1988). Affect presumably influences cognitive appraisals of the significance of stimuli and decisions regarding appropriate actions (Cacioppo & Bernston, 1999). In cross-sectional studies, older adults, compared to younger adults, tend to report a higher frequency of positive emotions and a lower frequency of negative emotions (e.g., Carstensen et al., 2011). Further, older adults are more likely than younger adults to describe the co-occurrence of positive and negative emotions (Löckenhoff, Costa, & Lane, 2008) and to demonstrate stable levels of both positive and negative affect over time (Kunzmann, 2008).

Given that positive and negative affect are two relatively independent constructs (Watson, Clark, & Tellegen, 1988), they may demonstrate differential associations with various aspects of cognition. The recently developed "broaden and build" theory of positive emotions suggests that positive affect broadens attention, cognition, and action and widens one's array of thoughts and actions. The related "narrowing" hypothesis suggests that negative affect may have the opposite effect (Fredrickson, 2001; Fredrickson, 2003). Overall, positive moods are typically associated with more general schematic and relational processing, whereas negative moods tend to be associated with item-specific, detail-oriented processing, in both younger and older adults. Research has demonstrated that people reporting positive affect show thought patterns that are flexible, creative, integrative, open to new information, and efficient (Fredrickson, 2001; Isen, 2000). In particular, a review of the psychological and biological bases of the mood-cognition relationship in younger adults provides evidence that positive affect is associated with improved performance on tasks of verbal fluency (Mitchell & Phillips, 2007). Letter fluency tasks, widely used to test executive function, require retrieval of words beginning with a specified letter in a short time period. Fluency tasks are thought to depend on strategic retrieval, initiation of action, inhibition of previously dominant responses, and ability to switch search strategies. In contrast, positive mood has also been found to impair aspects of executive functioning such as working memory, planning, and task-switching (Mitchell & Phillips, 2007). For example, positive mood states have been found to decrease working memory capacity (Martin & Kerns, 2011; Spies et al., 1996) and impair switching where the task requirements are to switch to previously activated stimuli in the environment (Phillips et al., 2002), but positive mood can facilitate switching to novel information (Dreisbach & Goschke, 2004).

While support for the influence of positive affect on cognitive processes is strong, null effects of negative mood are more common. Where detail-oriented processing favors the task, negative mood appears to have little or beneficial effects, and where gestalt-oriented processing favors the task, negative mood is detrimental. For example, no direct evidence of negative mood effects on fluency have been demonstrated (Phillips et al., 2002; Mitchell & Phillips, 2007). Similarly, compared to induced positive and neutral moods, negative mood does not seem to influence working memory capacity or task-switching (Martin & Kerns, 2011; Spies et al., 1996). Further, a recent cross-sectional analysis of a large sample (N=516) of German older adults found that combined scores for speed, memory, fluency, and knowledge demonstrated no association with negative affect (Kunzmann, 2008). In contrast, on visual-processing tasks such as the local-global task, induced negative mood facilitates processing of the features of a visual object, versus the whole object (Branigan &

Fredrickson, 2005; Gasper & Clore, 2002). Another potential advantage of detail-oriented processing during negative affect is demonstrated in the literature on false memory in older adults, where negative mood actually decreases memory for false information (McCabe, Presmanes, Robertson, & Smith, 2004; Hess, Popham, Emery, & Elliott, 2012), although the effects of induced mood on memory are under-explored,

In addition to affect, it is important to examine the relationship between depressive symptomatology and cognition. Negative affect is a construct that is related to, yet different from, depression in that individuals may experience negative affect whether or not they are depressed. Further, those who are depressed tend to experience negative affect as well as additional non-mood (i.e., somatic, vegetative) depressive symptoms. Negative affect and depression may be correlated but are not interchangeable constructs. There is a large literature examining the relationship between depression and cognition. The inverse relationship between depressive symptoms and cognitive performance has been demonstrated in a variety of studies (Bierman et al., 2007; Ganguli et al., 2006; Godin et al., 2007; Han et al., 2006; Raji et al., 2007). One study that compared adults with mood disorders (depression) to age-matched normal controls found that cognitive decline was comparable between these two groups until age 45; age-related cognitive decline in the domains of memory, attention, processing speed, and executive function began to diverge between the groups after age 45 and diverged even more dramatically after age 65, with the depressed adults faring worse than the normal controls (Gualtieri & Johnson, 2008). Another recent study of 840 community-dwelling older adults in a primary care setting found that over 3.5 years, those participants with significant depressive symptoms were twice as likely to develop mild cognitive impairment than whose without depressive symptoms (Geda et al., 2006). Further, a recent meta-analysis found that a history of depression was positively associated with a higher risk of later developing Alzheimer's disease (Ownby et al., 2006). In older adults, depressive symptoms have been associated with a variety of cognitive deficits including measures of attention, visuospatial abilities, motor function, memory processing, accuracy on working memory tasks, concept formation, information processing speed, executive function, and general cognitive function (Baune et al., 2006; Baune et al., 2007; Boone et al., 1994; Comijs et al., 2001; Cui et al., 2007; Dotson et al., 2008; Ganguli et al., 2006; Lockwood et al., 2002; Paterniti et al., 2002; Rose & Ebmeier, 2006; Sheline et al., 2006).

In contrast to prior experimental studies of affect and cognition, Cognition in the Study of Tamoxifen and Raloxifene (Co-STAR) (Legault et al., 2009), an ancillary study of STAR (Study of Tamoxifene and Raloxifene), offers longitudinal measures of positive and negative affect, depression, and a broad range of cognitive tests in a large sample of healthy community-dwelling older women at increased risk of breast cancer. Additionally, much of the previous research examining emotion and cognition has controlled for affect rather than studying its association with cognitive function. The goal of these analyses was to evaluate the relationship between affect (positive and negative), depressive symptoms, and cognitive performance on tests of verbal knowledge, figural and verbal memory, working memory, spatial rotation, and speed. We hypothesized that: (1) Positive affect would be associated with higher concurrent scores on verbal fluency, a measure of executive function; (2) Negative affect would not be significantly related to cognitive function; and (3) Women who report greater depressive symptoms would have lower cognitive test scores, particularly in the areas of global cognitive function, memory, and processing speed than women who report fewer depressive symptoms.

Methods

Study of Tamoxifen and Raloxifene (STAR) Trial – Design

STAR was a multi-center, randomized clinical trial of oral tamoxifen 20 mg/day or oral raloxifene 60 mg/day for a maximum of 5 years, among 19,747 postmenopausal women 35 years of age or older at increased risk for breast cancer as determined by their age, family history of breast cancer, personal medical history, age at first menstrual period, and age at first live birth according to the modified Gail model (Gail et al., 1989; Gail & Constantino, 2001). STAR was coordinated by the National Surgical Adjuvant Breast and Bowel Project (NSABP) from July 1, 1999 to December 31, 2005 (Vogel et al, 2006). Eligible women were postmenopausal; not taking tamoxifen, raloxifene, hormone therapy, oral contraceptives, or androgens; not taking warfarin or cholestyramine; without history of stroke, pulmonary, or deep vein thrombosis; and no history of malignancy within the past 5 years, except basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix. Women with a history of lobular carcinoma in situ of the breast treated by local excision alone were eligible. Uncontrolled atrial fibrillation, diabetes, or hypertension; and/or psychiatric conditions that could interfere with trial adherence or normal activity for a significant portion of each day were exclusion factors. The mean age of STAR participants at randomization was 58.5 years and about 93% were white (Vogel et al., 2006).

Cognition in the Study of Tamoxifen and Raloxifene (Co-STAR) – Design

Co-STAR was an ancillary study to the STAR trial that focused on the cognitive effects of tamoxifen and raloxifene in a subset of women enrolled in the STAR trial. Co-STAR enrolled 1,498 women randomized in the STAR trial, age 65 and over, who had not been diagnosed with dementia. All participants were fluent in English and provided written Informed Consent for the Co-STAR study. Co-STAR was coordinated by the Wake Forest School of Medicine, approved by its Institutional Review Board, and sponsored by the National Institute on Aging.

Participants

Women enrolled in the STAR trial were eligible for Co-STAR if: they were 65 years of age or older, had not been diagnosed with dementia, and were enrolled at one of the participating Co-STAR sites. Previous diagnoses of chronic neurologic disease (Parkinson's disease, stroke, epilepsy, multiple sclerosis), history of head injury, depression, alcohol addiction, drug addiction, and other neurologic or psychiatric conditions were recorded but did not serve as exclusion factors for this study. Only 4% of Co-Star participants had GDS-SF scores ≥ 5 'suggestive' of depressive symptomatology. The Co-STAR trial was conducted at 153 (76%) STAR/Co-STAR Clinical Sites across the United States and Canada. The Co-STAR clinical centers were chosen based on their strong performances in the STAR Trial with respect to enrollment and retention and the age and ethnic distribution of participants.

Enrollment

Co-STAR enrollment began in October 2001, 18 months after STAR enrollment started and continued until the unmasking of STAR in June 2006. Visit 1 refers to the first assessment when a participant enrolled in Co-STAR, and visits 2 and 3 refer to the beginning of years 2 and 3 in Co-STAR, respectively, corresponding to one-year and two-year follow-up. Although some participants completed assessments at years 4 and 5, each participant has a maximum of 3 Co-STAR assessments included in this paper due to the low numbers of participants with more than 3 visits.

Co-STAR originally planned to recruit participants at their STAR randomization. However, due to a small number of women over 65 years of age at STAR randomization, the protocol

was amended to allow age eligible women to join Co-STAR any time during their first 4 years of STAR follow-up. Therefore, most participants did not receive cognitive assessments until after study drugs had been initiated.

Co-STAR Cognitive Battery Procedure

A standardized 80-minute neuropsychological test battery modeled after that used in the Women's Health Initiative Study of Cognitive Aging (WHISCA) (Resnick, 2004) was administered yearly (See Appendix 1 for all cognitive measures and scoring information). The battery included 14 tests from several domains that have been shown to be sensitive to subtle changes in cognitive function associated with aging and hormone therapy. The individual cognitive tests representing each of the cognitive domains in order of administration are the following (with abbreviations defined in the paragraphs that follow): (1) global cognitive function (3MSE); (2) verbal knowledge (PMA Vocabulary); (3) verbal fluency (letter fluency, category fluency); (4) figural memory (Benton Visual Retention Test); (5) verbal memory (CVLT List A, List B, Short-delay free recall, Long-delay free recall); (6) working memory (Digits Forward, Digits Backward); (7) spatial ability (Card Rotations); and (8) fine motor speed (Finger Tapping Dominant, Finger Tapping Non-Dominant). The following are the individual tests of interest that comprised the battery.

Modified Mini-Mental State Exam (3MSE; Teng & Chui, 1987)—The 3MSE consists of 15 items that sum to 0–100; higher scores reflect better cognitive functioning. Test items measure temporal and spatial orientation, immediate and delayed recall, executive function, naming, verbal fluency, abstract reasoning, praxis, writing, and visuo-constructional abilities. It has good reliability, sensitivity, and specificity for detecting cognitive impairment and dementia (Women's Health Initiative, 1998).

Primary Mental Abilities Vocabulary Test (PMA Vocabulary; DeFries et al., 1974)—The PMA-V assesses verbal knowledge and reasoning ability. For each of 50 target words, participants selected the one word out of four choices that is most similar in meaning to the target word. The score was the total number of correct words completed within 3 minutes minus 1/3 of the total number incorrect.

Letter Fluency Test and Category Fluency Test (Goodglass & Kaplan, 1983)—In the letter fluency test, the participant was given one minute to generate as many words as possible beginning with each letter (F, A, and S). In the semantic fluency test, the participant was given one minute to generate as many examples as possible of members of two categories of items (fruits and vegetables). The total number of unique words generated for letters and categories were the outcome measures.

Benton Visual Retention Test (BVRT; Benton, 1968; Benton, 1974)—The BVRT is a test of figural memory (e.g. the ability to remember line drawings). Participants viewed each of 10 line drawings for ten seconds before the figure was removed and participants were asked to draw it from memory. Drawings were progressively more complex and each trial was scored independently for errors by two trained examiners according to standard procedures (Benton, 1974). The score on the BVRT was the total number of figures with errors and ranged from 0 to 26.

Modified California Verbal Learning Test (CVLT A, CVLT B, CVLT Short and Long Delay Free Recall; Delis et al., 1987)—This test is a measure of learning and memory. A target list of 16 words, constituting a shopping list (List A) comprised of four words from each of four semantic categories, was presented three times. The participant was asked to recall as many words as possible after each presentation. The outcome measures

were the total number of words learned during the three immediate recall trials of List A, the number of words learned and immediately recalled from a second "interference" shopping list (List B), the number of words from List A produced by unprompted 'free recall' (short delay free recall), and the number of words from List A produced by free recall after a 20 minute delay (long delay free recall). Short-term increased exposure to the words can result in participants developing a strategy that could lead to better recall which in turn can limit the statistical power to detect cognitive changes. In order to minimize these practice effects, the test was modified from the original five immediate free recall trials to three immediate recalls, and extra category-cued recall trials were eliminated. In addition, forms with different shopping lists were used at the third and fourth evaluations to minimize test-re-test effects (Lamar et al., 2003; Legault et al., 2009; Resnick et al., 2004). Among all the tests in the battery, this test may be most sensitive to the effects of hormone therapy (Maki et al., 2001).

Digit Span Forward & Digit Span Backward (Wechsler D, 1955)—The participant was asked to provide immediate recall of a series of digits in the same order as presented initially (forward) or in the reverse order (backward). The outcome measure was the total correct trials for digit span forward and digit span backward.

Card Rotations Test (Ekstrom et al., 1976)—On each of 28 trials, participants viewed sample line drawings of a geometric figure and eight alterations representing two- or three-dimensional rotations of the drawing. Participants were asked to identify alternatives that showed the sample in two, but not in three, dimensions. The outcome measure was the total correct minus the total incorrect trials.

Finger Tapping Test Dominant, Finger Tapping Test Non-Dominant (Reitan & Davidson, 1974)—In this test of motor speed and dexterity, participants were asked to depress a lever as many times as possible in each of seven 10-second trials, first with the right hand and next with the left hand. The highest and lowest scores were dropped; the score was the average of the remaining five trials for each hand.

Affect and Depression Measures

The following affect and depression self-report measures were administered yearly:

Positive and Negative Affect Schedule (PANAS; Watson et al., 1988)—Positive and negative affect were assessed with the PANAS, a list of ten pleasant affective states (e.g., interested, proud, inspired) and ten unpleasant affective states (e.g., irritable, guilty, jittery). Respondents were asked to rate on a five-point scale the extent to which they have experienced each mood during the past two weeks. Ratings for each item can range from 0 to 4, with total scores for positive affect and negative affect subscales ranging from 0 to 40. Internal consistency reliability is high for the PANAS, .89 for PA and .85 for NA (Crawford & Henry, 2004).

Geriatric Depression Scale-Short Form (GDS-SF; Sheikh & Yesavage, 1986)—Depressive symptom severity was assessed with the 15-item short form of the Geriatric Depression Scale which measures non-somatic features of depression. Participants indicated the presence or absence of each symptom (range: 0–15). The GDS-SF has comparable sensitivity and specificity to the Center for Epidemiologic Studies Depression Scale (CES-D) for detecting late life syndromal depression in a non-psychiatric population (Lyness et al., 1977). Internal consistency reliability is high for the GDS-SF, .81 (Almeida & Almeida, 1999). Scores ≥ 5 suggest depressive symptomatology and further evaluation, and scores ≥ 10 are indicative of clinical depression.

Quality Assurance of the Cognitive Measures

Administration of the Co-STAR cognitive battery followed a rigorous training, certification, and quality assurance program. Central training sessions on the Co-STAR neuropsychological battery was provided for prospective Co-STAR technicians. Training included a presentation on each test, detailed instructions on the administration and scoring of each test, discussion of challenges to data fidelity, direct observation of a criterion administration, and practice administrations with feedback.

Following centralized training, technicians were required to practice administering the battery at their study site. An audiotaped administration of the entire battery was then reviewed by the training staff at the Co-STAR Coordinating Center at Wake Forest University. Technicians failing to meet criteria were required to submit additional audiotaped administrations until they met criteria. Once certified, technicians were required to submit recertification tapes every six months for the first year and annually thereafter to prevent decay of their skills (Resnick et al., 2004).

Statistical Analysis

All statistical analyses were performed using SAS (version 9.3, SAS institute Inc., Cary, NC, USA). The distribution of individual test scores was assessed at the first Co-STAR visit by treatment group and for the entire Co-STAR population. Means and standard deviations for continuous variables and frequency distributions for categorical variables were calculated. Simple t-tests were used to compare the means for variables measured on a continuous scale and a chi-square test was applied to the categorical covariates. A Spearman correlation coefficient was used as an additional measure of association.

Linear mixed models for repeated measures using likelihood ratio tests were used for the analysis. The first 3 Co-STAR visits were included in the analysis. Years 4 and 5 were excluded, because data were available only for 243 and 84 participants, respectively. Time since randomization was added because women did not all enter Co-STAR at the same time as randomization in STAR. Separate analyses were performed for each outcome measure. It was decided a priori that the analyses would be adjusted for treatment (Raloxifene/Tamoxifen), visit (1–3), time between STAR randomization and first Co-STAR assessment ("time between"), age at baseline, race, and education. To account for the fact that CVLT tests were administered using different shopping lists at times 3 and 4, the analyses of CVLT A, CVLT B, CVLT Short and Long Delay were adjusted for CVLT version. The joint effect of two interaction terms of treatment with annual visit index and "time between" was tested first. After the univariate significance of positive affect, negative affect, and depression score were assessed separately, a stepwise procedure was performed, adding them into the model in order of their univariate p-values. After the main effects model was constructed, separate tests for interactions were performed. A significance level of 0.01 was adopted a priori for all outcomes to control for multiple testing; a Bonferroni adjustment would have been too strict, given the correlation among these outcomes.

Results

Sample Characteristics

The distribution of the 1479 participants is presented in Table 1 for each visit. About 70% of participants enrolled in Co-STAR had a second visit, and 40% had a third visit. As Co-STAR was initiated after STAR opened, not all participants could complete 3 Co-STAR visits before STAR ended. In addition, 69 participants withdrew from each arm during the Co-STAR trial for reasons including a dislike of cognitive testing; family, personal, or physical problems; and rarely, death.

Demographic information is provided in Table 2. On average, women entered Co-STAR 27.7 (SD=18.5) months after randomization in STAR at a mean age of 67.1 (SD=4.3) years. In the Co-STAR sample, 94.7% of women were White and 95% had completed at least a high school education. There were no significant differences between treatment groups for any of these demographic variables. Means and standard deviations for cognitive tests, affect, and depression for each treatment group and study visit are presented in Table 3. Although mean cognitive scores tended to be slightly higher in the raloxifene group than in the tamoxifen group, there were no statistically significant differences between treatment groups on any of these variables.

At each visit, correlations between PANAS positive affect and GDS were moderate (-0.43 to −0.60), as were the correlations between PANAS negative affect and GDS (0.42 to 0.61). Correlations between positive and negative affect by visit were modest (−0.19 to −0.35).

Longitudinal Analyses

In the repeated measures models, interactions between treatment and annual visit index and treatment with time between STAR randomization and first Co-STAR visit were not significant in any of the univariate assessments and therefore were not included in any multivariate modeling. Depression, positive affect, and negative affect were each assessed in separate “base” models for each cognitive test, which included treatment, annual visit index, time between STAR randomization and first Co-STAR assessment, age, race, and education (results not shown). From these models, positive affect was significantly associated with better performance on the CVLT short delay, letter fluency and category fluency but not with any other cognitive measures. Negative affect was significantly associated with worse performance on the 3MSE, BVRT, CVLT Lists A and B, and short and long delay, card rotations and PMA vocabulary. Depression was significantly associated with worse performance on the 3MSE, BVRT, CVLT List A, short delay and long delays, category fluency, card rotations, digits forward, and PMA vocabulary.

The coefficient estimates and the p-values of the variables included in the final multivariate models are presented in Table 4. There were no statistically significant interactions between treatment and any of the cognitive test results. After controlling for CVLT version in the step-wise analysis, results for all CVLT outcomes (Form A, Form B, Short-Delay, Long-Delay) remained significant (all p’s< .0001). The version of the shopping list used did not alter the results. Depression was associated with worse cognitive performance on the BVRT (p<0.0001), CVLT List A (p<0.0001), CVLT Long Delay (p=0.0002), CVLT Short Delay (p<0.0001), and PMA Vocabulary (p=0.0004). A one point increase in GDS-SF is associated with a .13 increase in errors on the BVRT, a .22 decrease in words remembered on CVLT List A, a .09 decrease in words remembered on CVLT Long-Delay and a .11 decrease in words remembered on CVLT Short-Delay. For example, a clinically meaningful increase of 5 points on the GDS-SF would result in a memory decrease of one word on CVLT List A. Negative affect was associated with worse cognitive performance on the 3MSE (p<0.0001), CVLT B (p=0.003), and Card Rotations (p<0.0001). A one point increase in negative affect is associated with a .73 decrease in 3MSE, a .19 decrease in CVLT List B, and a 3.30 decrease in Card Rotations. For example, a 5 point increase in negative affect would result in a 3.65 point decrease in 3MSE. Positive affect was strongly associated with better cognitive performance on Letter Fluency (p=0.006) and Category Fluency (p<0.0001). A one point increase in positive affect is associated with a .80 increase in Letter Fluency and a .85 increase in Category Fluency. For example, a 5 point increase in positive affect would result in an increase in letter fluency of four letters.

Discussion

All three variables of interest in this multivariate analysis (positive affect, negative affect, depressive symptoms) showed a significant relationship with cognitive performance in multiple domains, after adjustment for treatment, visit, time between STAR randomization and first Co-STAR assessment, age at baseline, race, and education. In addition, positive affect, negative affect, and depressive symptoms each demonstrated a unique pattern of significant relations with multiple cognitive domains.

In Co-STAR, higher depressive symptom severity was robustly and significantly associated with decreased performance on memory measures (both figural and verbal) and vocabulary. Thus, our findings are consistent with some prior studies which demonstrate that greater depression is associated with decreased cognitive performance in the memory domain (Baune et al., 2006; Baune et al., 2007; Boone et al., 1994; Comijs et al., 2001; Ganguli et al., 2006; Gualtieri & Johnson, 2008; Godin et al., 2007; Han et al., 2006; Paterniti et al., 2002; Raji et al., 2007; Sheline et al., 2006). For example, Sheline et al. (2006) administered a comprehensive neuropsychological battery of tasks grouped into episodic memory, language, working memory, executive function, and processing speed domains to 155 participants who met DSM-IV criteria for major depression. Although processing speed and executive function accounted for a large amount of the variance in depression, episodic memory was also a significant predictor, after accounting for age, education, race and vascular risk factors. Our findings related to memory are particularly interesting in light of the fact that the study sample overall was not a sample with clinical depression; rather, rates of depressive symptoms in the Co-STAR sample were quite low (4%). Unlike some prior studies that have found a relationship between indicators of executive function such as working memory and task-set switching and depression (Cui et al., 2007; Lockwood et al., 2002; Rose & Ebmeier, 2006; Dotson et al., 2008), depressive symptomatology was not related to decreases in working memory capacity (digits forward and backwards) in this study. Executive function deficits in depression vary according to age and severity, but are most consistently observed in moderate and severe depression, often in the presence of processing speed deficits.

Contrary to our hypotheses, negative affect was associated with worse performance on global cognitive function, verbal memory, and spatial ability. In contrast to depressive symptomatology and verbal memory, negative affect was associated with a measure of verbal memory ‘interference’ (CVLT List B), not CVLT List A, CVLT Long-Delay, or CVLT Short-Delay, suggesting that participants with negative affect were unable to discriminate between the two lists and were more susceptible to interference. To address the potential for test-retest effects on the CVLT (Lamar et al., 2003; Legault et al., 2009; Resnick et al., 2004), we used different shopping lists at times 3 and 4. In the analyses, we did not find evidence that using alternative word lists significantly impacted the results. The finding that negative affect is associated with decreased spatial ability is novel. Although normal aging is associated with decreases in visuospatial ability (Salthouse, in press), to our knowledge, no studies of affect and aging have examined this relationship specifically. One study of depressive symptoms and cognition found decreases in visuospatial ability in middle-aged men as measured by Matrix Reasoning from the Wechsler Adult Intelligence Scales (WAIS) and Card Rotations (Franz et al., 2011). This was attributed to possible executive function deficits due to the nature of the task. The result that negative affect was associated with different cognitive measures than positive affect or depression lends credence to the idea that separate constructs are being measured here. The differing pattern of associations between depressive symptoms and cognitive performance and negative affect and cognitive performance may reflect differences in complexity of these two states. By definition, ‘depression’ involves multiple changes in functional domains including thinking

(more negative in tone), affect (sad, irritable), behavior (lower activity, social withdrawal), and physical and physiological functioning (decreased sustained attention, low energy, anhedonia, appetite/weight changes, sleep changes, neurochemistry dysregulation). In contrast, 'negative affect' refers to solely to unpleasant mood states. Thus, negative affect is a separate construct and might be expected to correlate more selectively with cognitive functioning than depression.

A key finding from this study is the strong relationship between positive affect and verbal fluency found in older adult women. In a recent study, trait positive affect was associated prospectively with verbal fluency such that higher dispositional positive affect (extraversion) was associated with greater verbal fluency while higher trait negative affect (neuroticism) was associated with lower verbal fluency (Sutin et al., 2011), but this association was not moderated by age. Our results partially corroborate that study with positive but not negative affect related to verbal fluency. Similarly, our findings are consistent with a review of the mood-cognition relationship in younger adults that found positive affect can enhance performance on tasks of fluency, but no relationship for negative affect (Mitchell & Phillips, 2007). The association of positive affect with verbal fluency lends support to the "broaden and build" theory of positive emotions (Fredrickson, 2001) in which positive affect may serve to broaden one's ability to think creatively and flexibly, widening the array of thoughts that come to mind in response to the fluency tasks where one is more successful by generating longer lists of words that begin with a specific letter or fit within a particular category. Consistent with a proposed broadening function of positive affect, positive mood has been associated with an increased capacity to generate remote associates for familiar words (Rowe, Hirsh, & Anderson, 2007). Evidence for enhanced semantic search under these conditions is thought to reflect decreased inhibitory control (Stickgold, Rittenhouse, & Hobson, 1999; Friedman & Miyake, 2004). A more diffuse attentional focus results in increased priming for weak associates, including the activation of more semantically remote associations. Thus, one cognitive mechanism that has been proposed to explain the broadening effect is decreased inhibition, beneficial on tasks that require less focal attention. Support, however, for the corresponding 'narrowing hypothesis' in this study, as in others, is sparse.

This study has several limitations. First, Co-STAR included older adult women who were predominantly white, well-educated, at higher risk for developing breast cancer, and participating in a clinical trial. Therefore, the generalizability of these findings to older adult women in the general population may be limited. Second, as mentioned in the Introduction, most participants did not receive cognitive assessments until after study drugs had been initiated because Co-STAR started 18 months after STAR. Finally, this sample had lower numbers of participants with depressive symptoms and negative affect scores and higher numbers of participants with positive affect scores, similar to studies of healthy aging (Carstensen et al., 2011). Consequently, these analyses could underestimate relationships between negative affect, depressive symptoms, and cognition found in a more affectively diverse sample. In fact, only 4% of study participants reported depressive symptoms scores that would fall in the clinically significant range (GDS-SF ≥ 5). Finally, changes in affective states and cognitive processes could both be caused by another factor altogether such as changes in brain structure and function, and more research should be completed in this area.

This study makes a valuable contribution to the literature on affect, depression and cognition by prospectively using a standardized and well-validated cognitive battery on a large sample of community-dwelling, geographically diverse older adult women. The findings show that positive and negative affect and depression have selective and differing associations with cognition. In particular, positive affect is related to higher verbal fluency, and negative affect is related to decreased global cognition and visuospatial ability. Depressive symptoms

are related to decreased memory, but not executive function. Future research might examine these relationships in samples with a greater prevalence of affective variability and depressive symptoms. Based on our study findings, further exploration of the relationships between both positive and negative affect and cognitive function are warranted to develop theoretical models of these relationships in multiple cognitive domains.

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Appendix 1

Summary of test measures and outcome variables.

Measure	Outcome Variable	Maximum Possible Score
Global Cognitive Functioning: 3MSE	Total Score	100
Verbal Knowledge: PMA Vocabulary	Total correct – 1/3 number incorrect	50
Verbal Fluency:		
Letter Fluency (F,A,S)	Total correct	N/a
Semantic Fluency (vegetables, fruits)	Total correct	N/a
Figural Memory: BVRT®	Total figures with errors[a]	26[a]
Verbal Memory: CVLT	Total of 3 A learning trials	48
	Total for B trial	16
	Total for short-delay trial	16
	Total for long-delay trial	16
Attention and Working Memory:		
Digits Forward	Total correct trials	14
Digits Backward	Total correct trials	14

Measure	Outcome Variable	Maximum Possible Score
Spatial Ability: Card Rotations	Total correct – total incorrect	160
Fine Motor Speed:		
Finger Tapping Dominant	Total score	N/a
Finger Tapping Non-Dominant	Total score	N/a
Affect: PANAS		
PANAS Positive	Mean score	5
PANAS Negative	Mean score	5
Geriatric Depression Scale Short Form	Total score	15

Note. 3MSE= Modified Mini-Mental State Exam, PMA=Primary Mental Abilities, CVLT= California Verbal Learning Test; BVRT=Benton Visual Retention Test; PANAS= Positive and Negative Affect Schedule;

®Higher scores reflect poorer performance;

[a]Plus additions of designs.

Table 1

Distribution of participants present at each annual visit by treatment group

	Tamoxifen (N=727)		Raloxifene (N=752)	
Visit	**N**	**Percent**	**N**	**Percent**
1	727	-	752	-
2	490	67.4	531	70.6
3	280	38.5	308	41.0

Table 2

Characteristics of the Co-STAR population at first Co-STAR visit

Characteristic	Tamoxifen		Raloxifene		All population		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p-value***
Time between (months)							
Age	28.48	18.43	27.02	18.55	27.74	18.50	0.13
	67.21	4.36	67.01	4.30	67.11	4.33	0.39
	N	%	N	%	N	%	p-value*
Race							
Other	40	5.50	38	5.05	78	5.27	0.70
White	687	94.50	714	94.95	1401	94.73	
Education							
< High School	34	4.68	40	5.32	74	5.00	0.57
≥ High School	693	95.32	712	94.68	1405	95.00	

*Note: T-test is used to test for difference between treatment groups for characteristics measured on continuous scale and chi-square test for categorical covariates.

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Table 3

Means (standard deviations) of measures of cognition, affect and depression by Co-STAR visit and treatment

Characteristic	Visit 1		Visit 2		Visit 3	
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene
3MSE	95.07 (4.72)	95.12 (4.59)	95.85 (4.42)	95.92 (4.42)	96.00 (4.40)	95.85 (4.24)
PMA Vocabulary	36.08 (10.06)	36.07 (9.88)	37.30 (9.99)	37.44 (9.73)	38.37 (9.64)	37.95 (10.08)
Letter Fluency	38.76 (12.11)	38.86 (12.18)	39.93 (12.53)	40.53 (13.26)	40.59 (12.82)	40.85 (13.25)
Category Fluency	29.05 (6.37)	29.22 (6.17)	29.09 (6.30)	29.49 (6.25)	29.43 (6.63)	29.20 (6.43)
BVRT[1]	6.74 (4.12)	6.81 (4.16)	6.30 (3.99)	6.12 (3.82)	5.84 (3.54)	6.13 (3.93)
CVLT List A	28.04 (6.37)	28.41 (6.17)	29.35 (6.52)	29.89 (6.37)	26.76 (5.63)	27.23 (7.03)
CVLT List B	6.34 (2.12)	6.50 (2.13)	6.54 (2.09)	6.82 (2.24)	4.85 (1.80)	4.84 (1.87)
CVLT Short-Delay	8.36 (3.17)	8.32 (3.09)	8.99 (3.11)	8.92 (3.18)	8.45 (2.97)	8.27 (3.40)
CVLT Long-Delay	8.95 (3.12)	8.92 (2.96)	9.63 (3.18)	9.59 (3.13)	9.70 (2.93)	9.39 (3.48)
Digits Forward	7.81 (2.15)	7.61 (2.07)	7.82 (2.20)	7.70 (2.16)	7.93 (2.26)	7.67 (2.17)
Digits Backward	6.80 (2.14)	6.65 (2.03)	6.95 (2.15)	6.67 (1.99)	6.89 (2.14)	6.71 (2.11)
Card Rotations	57.68 (29.08)	57.93 (28.01)	62.87 (29.46)	64.98 (27.82)	67.43 (29.51)	66.16 (29.66)
Finger Tapping Dominant	40.78 (8.14)	41.18 (8.15)	41.23 (7.63)	41.42 (7.82)	41.76 (6.83)	41.84 (7.77)
Finger Tapping Non-dominant	38.20 (6.83)	38.58 (6.93)	38.42 (6.39)	38.61 (6.75)	37.99 (5.71)	38.75 (6.68)
GDS-SF Total Score	1.37 (2.02)	1.37 (2.00)	1.40 (2.06)	1.37 (1.93)	1.55 (2.20)	1.57 (2.28)
PANAS Positive Affect	3.64 (0.66)	3.65 (0.69)	3.59 (0.68)	3.67 (0.71)	3.57 (0.63)	3.60 (0.78)
PANAS Negative Affect	1.53 (0.58)	1.58 (0.62)	1.52 (0.56)	1.53 (0.57)	1.54 (0.58)	1.53 (0.57)

Note: There were no statistically significant group differences in cognitive, depression, or affect measures at baseline.

[1]BVRT score is the mean number of figures with errors, thus higher scores indicate poorer performance.

3MSE=Modified Mini-Mental State Exam; PMA=Primary Mental Abilities; BVRT= Benton Visual Retention Test; CVLT=California Verbal Learning Test; GDS-SF=Geriatric Depression Scale Short Form; PANAS = Positive and Negative Affect Schedule.

Table 4

The results of the stepwise model building process for each cognitive test, after controlling for treatment, visit, time between STAR randomization and first CoSTAR assessment, age, race, and education[1]

Cognitive Test	Intercept	Treatment (Raloxifene)	Annual Visit	Time between	Age	Race (non-white)	Education (High school or greater)	GDS-SF	PANAS negative	PANAS positive	CVLT version
3MSE	105.73	0.09 (0.6579)	0.38 (<0.0001)	−0.01 (0.1618)	−0.20 (<0.0001)	−5.16 (<0.0001)	4.35 (<0.0001)		−0.73 (<0.0001)		
BVRT[2]	−3.82	0.01 (0.9442)	−0.38 (<0.0001)	0.01 (0.2584)	0.20 (<0.0001)	2.83 (<0.0001)	−3.32 (<0.0001)	0.13 (<0.0001)			
CVLT List A	41.71	0.43 (0.1357)	1.32 (<0.0001)	−0.02 (0.0183)	−0.32 (<0.0001)	−2.28 (0.0004)	3.22 (<0.0001)	−0.22 (<0.0001)			4.51 (<0.0001)
CVLT List B	8.33	0.17 (0.0557)	0.26 (0.0001)	−0.003 (0.2296)	−0.07 (<0.0001)	−0.75 (0.0002)	1.06 (<0.0001)		−0.19 (0.0028)		2.20 (<0.0001)
CVLT Long-Delay	15.76	−0.02 (0.8840)	0.59 (<0.0001)	−0.01 (0.0185)	−0.14 (<0.0001)	−1.36 (<0.0001)	1.36 (<0.0001)	−0.09 (0.0002)			0.88 (<0.0001)
CVLT Short-Delay	15.58	−0.04 (0.7880)	0.58 (<0.0001)	−0.01 (0.0236)	−0.15 (<0.0001)	−1.19 (0.0002)	1.66 (<0.0001)	−0.11 (<0.0001)			1.46 (<0.0001)
Letter Fluency	43.70	0.21 (0.7302)	0.86 (<0.0001)	0.01 (0.6614)	−0.25 (0.0007)	−5.22 (0.0001)	8.38 (<0.0001)			0.80 (0.0056)	
Category Fluency	43.96	0.17 (0.5692)	−0.02 (0.8051)	−0.02 (0.0302)	−0.32 (<0.0001)	−3.04 (<0.0001)	4.04 (<0.0001)			0.85 (<0.0001)	
Card Rotations	166.40	0.03 (0.9796)	3.92 (<0.0001)	−0.13 (0.0008)	−1.66 (<0.0001)	−15.81 (<0.0001)	9.23 (0.0033)		−3.30 (<0.0001)		
Digits Forward	10.49	−0.19 (0.0600)	0.06 (0.0679)	0.003 (0.3187)	−0.06 (<0.0001)	−0.96 (<0.0001)	1.00 (<0.0001)				
Digits Backward	8.09	−0.20 (0.0395)	0.01 (0.7712)	0.001 (0.6813)	−0.04 (0.0011)	−0.98 (<0.0001)	1.37 (<0.0001)				
Finger Tapping Dominant	54.32	0.17 (0.6488)	0.21 (0.0866)	−0.03 (0.0138)	−0.25 (<0.0001)	−1.51 (0.0728)	4.04 (<0.0001)				
Finger Tapping Non-dominant	52.87	0.23 (0.4696)	−0.07 (0.4639)	−0.02 (0.0313)	−0.25 (<0.0001)	−1.24 (0.0866)	3.30 (<0.0001)				
PMA Vocabulary	34.88	0.04 (0.9399)	0.92 (<0.0001)	0.02 (0.1831)	−0.16 (0.0055)	−8.04 (<0.0001)	11.66 (<0.0001)	−0.19 (0.0004)			

Note.

[1] Beta coefficient (p-value).

[2] BVRT score is total number of figures with errors, thus higher scores indicate poorer performance.

3MSE=Modified Mini-Mental State Exam; BVRT= Benton Visual Retention Test; CVLT=California Verbal Learning Test; PMA=Primary Mental Abilities GDS-SF=Geriatric Depression Scale Short Form; PANAS = Positive and Negative Affect Schedule.