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The independent contributions of cognitive impairment and neuropsychiatric symptoms to everyday function in older adults

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Abstract

The everyday functional capacities of older adults are determined by multiple factors. The primary goal of the present study was to evaluate whether apathy and depression have unique influences on degree of functional impairment, independent of the effects of specific cognitive impairments. Participants included 344 older adults (199 normals, 87 with MCI, 58 with dementia). The Everyday Cognition (ECog) scales were used to measure both global and domain-specific functional abilities. Neuropsychiatric symptoms of depression and apathy were measured by the Neuropsychiatric Inventory (NPI), and specific neuropsychological domains measured included episodic memory and executive functioning. Results indicated that worse memory and executive function, as well as greater depression and apathy, were all independent and additive determinants of poorer functional abilities. Apathy had a slightly more restricted effect than the other variables across the specific functional domains assessed. Secondary analysis suggested that neuropsychiatric symptoms may be more strongly associated with everyday function within cognitively normal and MCI groups, while cognitive impairment is more strongly associated with everyday function in dementia. Thus, a somewhat different set of factors may be associated with functional status across various clinical groups.

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Keywords

Everyday function; ADLs; Apathy; Depression; Dementia

Decline in the ability to perform everyday activities and the eventual loss of independence are major concerns for older adults. Functional impairments are associated with patient and caregiver distress, increased use of healthcare services, nursing home placement, and reduced quality of life (Hope, Keene, Gedling, Fairburn, & Jacoby, 1998; Severson et al., 1994; Vetter et al., 1999). Dementia, such as Alzheimer's disease (AD), is clearly associated with the loss of the ability to function independently in major areas of life, including the ability to manage finances and medications, drive, and so forth. More recently, Mild Cognitive Impairment (MCI), often a prodromal state leading to dementia, has been found to be associated with mild decrements in the ability to carry out high-level functional abilities (Brown, Devanand, Liu, & Caccappolo, 2011; Burton, Strauss, Bunce, Hunter, & Hultsch, 2009; Farias et al., 2006; Gold, 2012; Teng, Becker, Woo, Cummings, & Lu, 2010; Wadley et al., 2007). Even cognitively normal older adults have been shown to demonstrate poorer performance in everyday tasks when compared to younger adults (Royall, Palmer, Chiodo, & Polk, 2004; Schmitter-Edgecombe, McAlister, & Weakley, 2012; Vance, Wadley, Crowe, Raper, & Ball, 2011). Two major determinants of functional limitations are cognitive impairment and neuropsychiatric symptoms (Boyle et al., 2003; Cahn-Weiner et al., 2007). With regard to cognitive function, deficits in executive functioning (Bell-McGinty, Podell, Franzen, Baird, & Williams, 2002; Cahn-Weiner, Boyle, & Malloy, 2002; Grigsby, Kaye, Baxter, Shetterly, & Hamman, 1998) and episodic memory (Brown et al., 2011; Farias, Mungas, Reed, Haan, & Jagust, 2004; Goldstein, McCue, Rogers, & Nussbaum, 1992; Jefferson et al., 2008) have been most consistently and robustly associated with various functional capacities in older adults. However, recent reviews emphasize that even when taking into consideration the impact of multiple cognitive domains, much of the variability in everyday function remains unexplained (Gold, 2012; Royall et al., 2007). To this end, the contribution of a variety of neuropsychiatric symptoms to functional impairment also has been examined. Two of the neuropsychiatric symptoms most consistently associated with everyday functional abilities are depression and apathy (D'Onofrio et al., 2012; Hinton, Tomaszewski Farias, & Wegelin, 2008; Okura et al., 2010; Palmer et al., 2011; Tam et al., 2008).

Neuropsychiatric symptoms are common in older adults with MCI and dementia, and generally increase in prevalence with disease severity (Okura et al., 2010). Both clinical- and community-based studies suggest that depressive symptoms and apathy are among the most common neuropsychiatric symptoms in MCI and early/mild dementia (Apostolova & Cummings, 2008; Assal & Cummings, 2002; Ellison, Harper, Berlow, & Zeranski, 2008; Lyketsos et al., 2001; Starkstein, Dragovic, Jorge, Brockman, & Robinson, 2011; Starkstein, Jorge, Mizrahi, & Robinson, 2005; Van Winkel, Leentjens, & Verhey, 2006; Zubenko et al., 2003). Additionally, depressive symptoms in particular (Anstey, von Sanden, Sargent-Cox, & Luszcz, 2007; Goldney, Fisher, Dal Grande, & Taylor, 2004), but also apathy (Onyike et al., 2007), are not uncommon in older adults with normal cognitive function. Depression and apathy have substantial overlap in key characteristics, but can represent distinct symptom

clusters (Starkstein, Petracca, Chmerinski, & Kremer, 2001; Tagariello, Girardi, & Amore, 2008). Apathy has been defined as a disorder of self-initiated, goal-directed behavior and a lack of motoric, emotional, and cognitive motivation (Marin, 1997). Shared symptoms among apathy and depression include loss of interest and reduced activity level (Marsh, McDonald, Cummings, & Ravina, 2006; Starkstein et al., 2005; Tagariello et al., 2008). Dysphoria (e.g., sadness, self-criticism, guilt, hopelessness) is present in depression, whereas a lack of emotional responsiveness is characteristic of apathy (Marin, 1997). There also is evidence that the two syndromes have distinct pathophysiologic underpinnings. Imaging studies suggest that depression is associated with dysregulation of left prefrontal and limbic areas, while apathy is driven primarily by dysfunction in medial frontal/anterior cingulate regions (Casanova, Starkstein, & Jellinger, 2011; Holthoff et al., 2005; Hirono et al., 1998; Kim et al., 2011; Migneco et al., 2001).

Studies have previously linked both major depression and the presence of mild or subthreshold depressive symptoms in the elderly with reduced functional capacity in everyday life (Beekman, Deeg, Braam, Smit, & Van Tilburg, 1997; Chopra et al., 2005; Forsell & Winblad, 1998; Lyketsos et al., 1997; Lyness et al., 2007; Pearson, Teri, Reifler, & Raskind, 1989). Similarly, apathy, when examined independently, also has been found to have a negative impact on everyday function (Boyle et al., 2003; Starkstein et al., 2005; Tam et al., 2008; Zawacki et al., 2002). Given that there are overlapping symptoms in both depression and apathy, it is important to consider whether both make independent contributions to predicting poorer function in everyday life, or whether it is their shared symptoms that primarily affect everyday function.

A limited number of studies have attempted to examine the relative impact of depression and apathy on everyday function with mixed results. For example, one study found that depression, but not apathy, made a unique contribution to worse everyday function (Okura et al., 2010); two studies found that only apathy was a unique predictor (Norton, Malloy, & Salloway, 2001; Senanarong et al., 2005); and two studies did not show clear evidence that either depression or apathy were differentially more important to everyday function (Benoit et al., 2008; Lam, Tam, Chiu, & Lui, 2007). One reason for the mixed findings may be that the population of older adults used in each study differed, with some using those with dementia or AD specifically (Benoit et al., 2008; Norton et al., 2001; Senanarong et al., 2005), and others including both MCI and AD groups (Lam et al., 2007; Okura et al., 2010). In fact, the results of at least one study suggested that the relative importance of apathy and depression to everyday function may differ depending on the particular type of older adult group studied, with both apathy and depression predicting everyday function in a MCI subsample, and apathy, but not depression, predicting function in a dementia subsample (Lam et al., 2007).

Previous studies often have not controlled for cognitive test performance when examining the effects of apathy and/or depression on everyday function. Global cognitive screening measures have been used most typically, though these provide limited assessment of specific cognitive functions (e.g., executive functions) and are insensitive to mild cognitive impairment (Ravaglia et al., 2005). Thus, it is not presently clear to what degree depression and apathy contribute to functional deficits above and beyond the contributions of specific

cognitive impairments. This point is particularly important, given that there is conceptual overlap between apathy and certain aspects of executive function, including initiation and goal setting (Duffy & Campbell, 1994; Fogel, 1994). While standardized cognitive tests are not always sensitive to apathy (Brodaty, Altendorf, Withall, & Sachdev, 2010), previous studies have shown that behavioral ratings of apathy tend to correlate with poor executive function in older adults with dementia (Esposito et al., 2010; Kuzis, Sabe, Tiberti, Dorrego, & Starkstein, 1999; McPherson, Fairbanks, Tiken, Cummings, & Back-Madruga, 2002; Tsoi, Baillon, & Lindesay, 2008) and even in cognitively normal older adults (Feil, Razani, Boone, & Lesser, 2003). There also is shared pathophysiology between apathy and executive dysfunction involving frontal lobe regions (Holthoff et al., 2005; Rosen et al., 2005). Additionally, apathy has been associated with other cognitive deficits, including aspects of memory (Esposito, Rochat, Juillerat Van der Linden, & Van der Linden, 2012), and frequently occurs in individuals with memory and other cognitive impairments (e.g., MCI and Alzheimer's disease; Geda et al., 2013). Similarly, previous studies have demonstrated associations between depression and cognitive impairment in older adults. There has been particular emphasis on the link between depressive symptoms and executive dysfunction (Alexopoulos, 2005; Kiosses, Klimstra, Murphy, & Alexopoulos, 2001; Lockwood, Alexopoulos, Kakuma, & van Gorp, 2000; Lockwood, Alexopoulos, & van Gorp, 2002), including some overlap in their neuroanatomical substrates (Aizenstein et al., 2009; Alexopoulos, 2003; Baldwin & O'Brien, 2002; Burton et al., 2004; Gunning-Dixon & Raz, 2003; Kramer, Reed, Mungas, Weiner, & Chui, 2002; Lamar, Charlton, Zhang, & Kumar, 2012; Marin, Butters, Mulsant, Pollock, & Reynolds, 2003; O'Brien et al., 2002; Tullberg et al., 2004). However, depressive symptoms in the elderly also have been shown to be associated with performance in other cognitive domains, including episodic memory (King, Cox, Lyness, Conwell, & Caine, 1998; Paradiso, Lambert, Garvey, & Robinson, 1997).

Given the inter-relationships, and in some cases, conceptual overlap among neuropsychological functions and neuropsychiatric symptoms, the primary goal of the present study was to evaluate whether depression, apathy, executive function, and memory each make independent or unique contributions to predicting degree of functional impairment. The measurement of functional limitations used in the present study was based on the Everyday Cognition (ECog) scales (Farias et al., 2008). The ECog is an informant-based measure that provides a global index of the degree of functional impairment (i.e., Global ECog), as well as measurement of functional abilities across six specific cognitively relevant domains (i.e., Everyday Memory, Everyday Language, Everyday Visuospatial Functions, and three scales measuring everyday executive functions – Everyday Planning, Everyday Organization, and Everyday Divided Attention). We expected that depressive symptoms and apathy would have fairly widespread effects across the different functional ECog domains. However, given the literature linking both apathy and depressive symptoms particularly to executive functioning, we also anticipated that apathy and depression would be most strongly correlated with the everyday executive domains of the ECog. Finally, because previous work has suggested that the contribution of neuropsychiatric and cognitive performance to everyday function may vary by cognitive status (Lam et al., 2007), secondary analysis examined whether there were differential relations between the

neuropsychiatric and cognitive determinants of everyday function by diagnostic category (i.e., normal cognition, MCI, dementia).

METHOD

Participants

All participants in the present study were enrolled in an ongoing longitudinal research study on cognitive aging at the University of California at Davis (UCD) Alzheimer's Disease Center (ADC). Some participants had initially been seen for clinical evaluations due to concern about cognitive impairment, and others were recruited for research directly from the community. All participants who were part of the present study underwent the same multidisciplinary clinical assessment to establish syndromic diagnosis (i.e., normal cognition, MCI, or dementia) regardless of route of recruitment, as has been described in more detail elsewhere (Farias et al., 2013). This included physical and neurological exam, clinical exam, imaging, lab work, and neuropsychological testing from the Alzheimer's Disease Uniform Dataset Neuropsychological Battery (Weintraub et al., 2009). Each participant received a consensus diagnosis made by a team of clinicians that included neurologists, neuropsychologists, nurses, and social workers, and was based on all available information from the clinical assessment. Dementia was diagnosed using DSM-III-R criteria (American Psychiatric Association, 1987), modified such that dementia could be diagnosed in the absence of memory impairment if there was significant impairment in any two or more other cognitive domains. Additionally, for a diagnosis of dementia, significant functional impairment as evidenced by loss of independence in major instrumental or basic ADLs was required. Although no strict psychometric cut-off scores were used to define cognitive impairment, ADC neuropsychologists clinically identified cognitive impairment when a participant's performance fell at least 1.5 standard deviations below age-matched norms and in reference to his or her educational and socioeconomic background. MCI was diagnosed according to standard criteria (Petersen, 2004). Individuals with MCI could not have impairments in basic ADLs or be dependent in any instrumental ADL. For clinical diagnosis, functional impairment was assessed using a variety of standardized tests and a clinical interview with the patient and informant. Clinical diagnoses were made without knowledge of the ECog data or any of the primary predictors in this study.

All participants signed informed consent, and all human subject involvement was overseen by institutional review boards at the University of California at Davis, the Veterans Administration Northern California Health Care System, and San Joaquin General Hospital in Stockton, California.

Neuropsychiatric Symptoms

For the purposes of this study, apathy and depression were assessed with the Neuropsychiatric Inventory (NPI; Cummings, 1997; Cummings et al., 1994), which is administered as a structured clinical interview with the participant's informant. The NPI was originally designed to quantify 12 different behavioral disturbances that present in dementia; however, there are many studies supporting its ability to also detect symptoms in normal aging and in MCI (Geda et al., 2008; Hwang, Masterman, Ortiz, Fairbanks, & Cummings,

2004; Okura et al., 2010). In addition to apathy and depressive symptoms, the NPI also asks about other symptoms, including delusions, hallucinations, anxiety, agitation, aggression, euphoria, eating abnormalities, disinhibition, irritability/lability, and aberrant motor activity. However, we were only interested in the depression and apathy items of the NPI, and for the purposes of this study the NPI scores were dichotomized to indicate presence or absence of depressive symptoms and apathy.

Assessment of Memory and Executive Functioning

Cognitive measures of memory and executive functioning were derived from the Spanish English Neuropsychological Assessment Scales (SENAS), a test battery that has undergone extensive development and validation (Mungas, Reed, Crane, Haan, & Gonzalez, 2004; Mungas, Reed, Farias, & DeCarli, 2005; Mungas, Reed, Marshall, & Gonzalez, 2000). Sophisticated psychometric methods based on Item Response Theory were used to create psychometrically matched subscales measuring different cognitive domains; this means that subscales all have comparable reliability and sensitivity to individual differences, which is critical when evaluating whether there are differential relationships between the specific neuropsychological predictors and functional abilities. Important for measurement precision, the subscales do not have appreciable floor or ceiling effects for participants in this sample, and have linear measurement properties across a broad ability range. In the present study we used a subset of SENAS tests to measure two cognitive domains: episodic memory and executive function. The Episodic Memory Index is a composite score derived from a multi-trial word list-learning test (Word List Learning I). The Executive Function Index is a composite measure constructed from component tasks of category fluency, phonemic (letter) fluency, and working memory (e.g., digit span). The SENAS indices were converted to z -scores for ease of presentation ($M = 100$, $SD = 15$) and are based on a subsample of cognitively normal older adults from whom data were collected at the UCD ADC.

Assessment of Everyday Function

Everyday function was assessed via the Everyday Cognition (ECog) scales (Farias et al., 2008). The ECog is a 39-item informant-based rating scale that measures different domains of everyday functioning. On each item, informants are asked to compare the participant's current level of everyday functioning with how he or she functioned 10 years earlier. In this way, participants serve as their own controls. Ratings are made on a four-point scale: 1 = better or no change compared to 10 years earlier; 2 = questionable or occasional problems; 3 = consistently a little worse; 4 = consistently much worse. There also is an 'I don't know' response option. Both the individual ECog domain scores and the Global ECog score are represented as an average. For example, the Global ECog score was calculated as a sum of all items completed (out of a possible 39 items) divided by the total number of items completed. Thus, the Global ECog and domain scores can range from 1 to 4. If more than half of the items were missing or marked as 'I don't know,' the score was not computed. In determining the sample for analysis, 66 individuals were omitted due to having incomplete ECog data related to a high number of 'I don't know' responses. The ECog has been shown to have excellent internal reliability (Cronbach's $\alpha = 0.97$) as well as good test re-test reliability ($r = 0.82$, $p < .001$; Farias et al., 2008). Confirmatory factor analysis supports the separable functional domains reflected in the ECog (Farias et al., 2008): Everyday Memory,

Everyday Language, Everyday Visuospatial Functions, Everyday Planning, Everyday Organization, and Everyday Divided Attention. The ECog has been shown to be sensitive to the early and subtle functional impairments in MCI as well as in dementia (Farias et al., 2006; Farias et al., 2008).

Statistical Analyses

Pearson correlation or Kendall's tau was used to assess collinearity of predictors, while Spearman correlation was used to assess the simple correlation between the ECog domains and the neuropsychiatric and neuropsychological predictors. Due to the restricted range of the ECog scores (1–4) and a high frequency of observations at the upper and lower ends of the range, Tobit regression models were used to assess the association between apathy, depressive symptoms, cognition, and everyday functioning. The natural logarithm ($\ln$) of the ECog was used as the outcome to better meet model assumptions, yielding a new range of zero to $\ln(4)$. We then set the lower and upper bounds for the Tobit model to correspond to the new range. Multivariate models were constructed for each ECog domain (and Global ECog) separately. Multivariate models included the following predictors: age, education, the two cognitive variables (episodic memory and executive function), presence or absence of apathy, and presence or absence of depressive symptoms. Because of the large number of models fit, False Discovery Rate (FDR) was used to determine which cognitive and neuropsychiatric variables were significantly associated with the outcomes. Secondary analyses considered differences in the association between everyday function and neuropsychiatric symptoms by cognitive diagnosis (normal, MCI, or dementia) by assessing Spearman correlations stratified by diagnosis, and adding an interaction term to the Tobit model between cognitive diagnosis and neuropsychiatric symptoms.

RESULTS

Sample characteristics

A total of 344 participants were available for analysis, having complete ECog data and all of the predictor variables, which were collected within six months of the ECog assessment. A total of 199 participants were cognitively normal, 87 participants had MCI, and 58 had dementia. For the sample as a whole, the average age was 75.67 ($SD = 7.01$), 61% were female, and average years of education was 13.26 ($SD = 3.99$). The ethnic/racial breakdown was 48% Caucasian, 23% Hispanic, 25% African American, and 4% other or unknown. Table 1 presents the demographic characteristics of the sample broken down by cognitive status/diagnostic group as well as mean scores for the predictor and outcome variables. The groups did not differ by educational level ($p = 0.25$) or gender ($p = 0.10$), but as expected, there were group differences on all of the cognitive, functional, and neuropsychiatric variables (all $ps < .001$), except that the MCI and dementia groups did not differ on apathy ($p = 0.15$) or depressive symptoms ($p = 0.43$).

Bivariate relationships between the ECog and neuropsychiatric and cognitive predictors

Spearman correlations or Kendall's tau were used to assess the bivariate relationships between age, education, episodic memory, executive functioning, depressive symptoms, and apathy. Age was moderately correlated with memory performance, $r = -0.35$, $p < .01$, and

weakly to moderately correlated with executive functioning performance, $r = -0.27, p < .01$. Education had a negligible correlation with memory, $r = 0.13, p = .01$, but was moderately correlated with executive functioning, $r = 0.32, p < 0.01$. Memory and executive functioning composite scores were moderately to strongly correlated with one another, $r = 0.62, p < .01$, and were negligibly correlated with depressive symptoms (memory: $\tau = -0.16, p < .001$; executive function: $\tau = -0.17, p < .001$) and apathy scores (memory: $\tau = -0.18, p < .001$; executive function: $\tau = -0.17, p < .001$). Apathy and depressive symptoms were moderately correlated with one another, $\tau = 0.33, p < .001$. The degree of relationships between the predictor variables (moderately strong at most) supports their inclusion as predictors in the multivariate regression analyses.

Examining correlations (Table 2) between model variables revealed that memory, executive functioning, depressive symptoms, and apathy were all correlated with each ECog domain score and the Global ECog score. In all cases, greater functional impairment was associated with worse cognitive functioning and higher levels of apathy and depressive symptoms. Contrary to our expectations, we did not observe a clear pattern in which depression and/or apathy was more strongly associated with the everyday executive domains (Everyday Planning, Organization, and Divided Attention) as compared to the other ECog domains.

Neuropsychiatric and cognitive predictors of everyday function

Table 3 presents multivariate models (all models have been adjusted for age and education) examining the neuropsychiatric and cognitive predictors of each ECog domain and the Global ECog score for the participant sample as a whole (including cognitively normal older adults, those with MCI, and those with dementia). In reference to the cognitive predictors, episodic memory was a significant independent predictor of all ECog domains and the Global ECog score, and executive function was independently associated with the Global ECog and all ECog domains except Everyday Memory. In all cases, worse neuropsychological function (lower scores) was associated with worse everyday function (higher scores). Of primary interest was the potential additional impact of the neuropsychiatric variables on everyday function. Results showed that while simultaneously accounting for the effects of memory and executive functioning, presence of depressive symptoms made a further independent contribution to predicting greater functional impairment across all of the ECog domains and Global ECog. Additionally, independent of both cognition and depressive symptoms, the presence of apathy led to even worse everyday function across all of the ECog domains and Global ECog. These results remained significant after adjusting for multiple comparisons using FDR.

Neuropsychiatric and cognitive predictors of everyday function by diagnostic group

Next, we sought to examine whether the effect of presence of depressive symptoms and apathy on everyday function differed by clinical group. In this secondary analysis we focused only on global functional status (Global ECog), although the pattern of associations between predictors and the individual ECog domains were essentially the same as when using the global functional outcome. We first examined bivariate correlations between the Global ECog and neuropsychiatric and cognitive variables by diagnostic group (i.e., normal cognition, MCI, and dementia), as seen in Table 4. In all cases, the general direction of the

correlations indicated that worse cognition and greater degree of neuropsychiatric symptoms were associated with worse everyday function. Within the cognitively normal subgroup, the strength of the associations between the Global ECog and the cognitive variables and depressive symptoms was fairly similar; apathy was not significantly related to the Global ECog in this group. Within the MCI subgroup, both depression and apathy had significant relationships with the Global ECog score (the latter was slightly stronger) whereas neither of the cognitive variables were statistically significantly associated with Global ECog. When examining the dementia subgroup, the opposite pattern emerged - the cognitive variables were significantly correlated with the Global ECog score, whereas the neuropsychiatric variables were not. Finally, using the multivariate modeling approach as in the above section, we added an interaction term to the models to more formally evaluate possible diagnostic differences in the relationship between the neuropsychiatric variables, cognition, and everyday function. In this case, the addition of the interaction did not reach statistical significance, $p > 0.2$; however, due to the relatively small group sizes in each diagnostic category, there was limited power to detect interaction effects.

DISCUSSION

Previous work has shown that cognitive performance (particularly memory and executive functioning) and the neuropsychiatric symptoms of depression and apathy are associated with worse functional status in older adult populations. However, the unique contribution of these factors to everyday function when considering them simultaneously has not been well studied. Depressive symptoms and apathy are two of the most common neuropsychiatric disturbances in older adult populations, and both can be present throughout the cognitive spectrum ranging from normal cognitive aging through MCI and dementia (e.g., Apostolova & Cummings, 2008; Ellison et al., 2008; Hinton et al., 2008; Okura et al., 2010; Starkstein et al., 2005; Tam et al., 2008; Van Winkel et al., 2006). A primary finding of the present study was that cognitive performance, as well as ratings of depressive symptoms and apathy, all make largely independent contributions to informant-based ratings of functional capacities in older adults.

Not surprisingly, for the sample as a whole, both episodic memory and executive function were independent predictors across all of the functional domain ratings except for Everyday Memory (in which case episodic memory was the only independent cognitive predictor). Such findings are consistent with the rather extensive body of literature suggesting that memory and executive functions are associated with worse everyday function (Bell-McGinty et al., 2002; Brown et al., 2011; Cahn-Weiner et al., 2002; Farias et al., 2004; Goldstein et al., 1992; Grigsby et al., 1998; Jefferson et al., 2008). While accounting for the impact of cognitive performance on functional ratings, we further found that the presence of depressive symptoms also was associated with worse everyday abilities across all of the ECog domains and Global ECog. Finally, even when accounting for cognitive performance and depressive symptoms, the presence of apathy also made an independent contribution to worse everyday function across all ECog domains and Global ECog ratings. There was some evidence that apathy and depression were most robustly associated with limitations in some of the everyday executive domains (e.g. Everyday Divided Attention), consistent with our hypothesis. However, overall, the findings most clearly indicate that apathy and

depression have rather global effects across a broad array of cognitively-based functional ratings.

Previous work examining the relative importance of apathy, depressive symptoms, and cognition to everyday function in older adults has produced somewhat mixed results. While a host of methodological explanations may help account for discrepancies in findings across studies (e.g., differences in the instruments used to measure the various constructs), another potential reason could relate to the specific older adult populations studied. Most studies have focused on individuals with Alzheimer's disease, although some have included normal elderly and/or individuals with MCI. Lam and colleagues (2007) found that apathy, but not depressive symptoms, predicted functional impairment in Alzheimer's disease patients, while both apathy and depressive symptoms predicted functioning in a more mildly impaired group. Additionally, a previous study by our group showed that when examining the relative strength of cognitive impairment and depressive symptoms to everyday function in individuals with MCI, depressive symptoms were more strongly associated with everyday function than was global cognition (Hinton et al., 2008), although among the participants with dementia, cognitive impairment and depressive symptoms were about equally associated with everyday function. In an attempt to address this issue in the present study, we explored the possibility that the relationship between cognition, neuropsychiatric symptoms, and everyday function differed by cognitive status (i.e., normal, MCI, or dementia). Possibly limited by inadequate statistical power, we were not able to detect an interaction effect in a multivariate model, indicative of predictor-outcome differences by diagnosis. However, some interesting patterns emerged when examining individual correlations between the cognitive and neuropsychiatric variables and functional capacity (as measured by the Global ECog) in each subgroup. Among the participants who were cognitively normal, both memory and executive function as well as depressive symptoms were correlated with global functional ratings. Alternatively, apathy was not significantly correlated with functional ratings in the group with normal cognition, but the presence of apathy (7.5%) also was relatively uncommon in this subgroup, particularly in comparison to rate of depressive symptoms in this subgroup (19.1%). While one might question the clinical relevance of examining cognitive and neuropsychiatric correlates of everyday function in older adults who are considered cognitively normal, there is evidence that older adults with normal cognition perform more poorly than younger adults on functional tasks (Royall, Palmer, Chiodo, & Polk, 2004; Schmitter-Edgecombe, McAlister, & Weakley, 2012; Vance, Wadley, Crowe, Raper, & Ball, 2011). Additionally, a number of studies have now demonstrated subtle changes in cognition prior to a diagnosis of MCI (e.g., Howieson et al., 2008; Wilson, Leurgans, Boyle, & Bennett, 2011). Similarly, our group has recently demonstrated that there are subtle differences in functional capacities among cognitively normal elders who later go on to develop MCI or dementia over follow-up, as compared to those who remain cognitively normal (Farias et al., in press in *Psychology of Aging*). Longitudinal follow-up on our sample would be necessary to elucidate whether there are meaningful differences in the associations between the neuropsychological, neuropsychiatric, and functional variables in cognitively normal older adults who convert to MCI versus those who remain cognitively stable. With regard to the MCI group, we found stronger associations among depressive symptoms, apathy, and the Global ECog score than

was observed between the neuropsychological variables and the ECog (the latter correlations were not statistically significant). Such findings suggest that neuropsychiatric symptoms may play a more significant role in functional capacities in MCI than cognitive performance does at this stage of disease. In some respects, this may not be very surprising given that MCI was originally described as consisting of cognitive impairment in the absence of functional impairment. While more recent work has shown demonstrable but subtle functional changes often occur in MCI, other studies have failed to find an association between memory and/or executive function and everyday capacities in those with MCI (Bangen et al., 2010), with evidence that this association may differ based on specific MCI subtype (Bombin et al., 2012) and method of assessing everyday capacities (Farias, Mungas, & Jagust, 2005; Schmitter-Edgecombe et al., 2012). Finally, in the dementia group, the two cognitive variables were associated with functional ratings, though neither apathy nor depressive symptoms were significantly related to Global ECog. As such, this study further highlights the idea that there may be a different set of factors associated with everyday functional ratings in different clinical groups, which also has been suggested by other researchers (Lam et al., 2007). The results suggest that early in a neurodegenerative disease process, neuropsychiatric symptoms may be more strongly associated with everyday function than cognitive performance, but as the disease progresses and a full dementia syndrome is reached, cognitive impairment may be a more important contributor to functional impairment than the neuropsychiatric manifestations of the disease. Importantly, however, the subgroup analysis should be considered only preliminary, given the relatively small number of participants in each diagnostic category, particularly the dementia group.

It is important to acknowledge that the strength of the relationship between the neuropsychological and neuropsychiatric variables and the functional ratings were fairly modest (the highest correlation values were in the moderate range), and this is consistent with previous literature and recent reviews (see Gold, 2012; Royall et al., 2007). In part, this may be related to the limits of our instruments. Although commonly done (Clarke et al., 2011), apathy and depressive symptoms were measured using a single item from the NPI. This may be more of a limitation for the construct of apathy; as noted by Clarke et al., the lack of consensus for a clinical definition of apathy may limit the interpretability of research data using apathy measures. Additionally, developing cognitive tests explicitly designed to more closely mirror real-world abilities remains an important goal in the field, and may result in stronger associations with functional outcome measures. Further, while informant ratings of everyday function offer an efficient means of assessment and have been shown to be useful in differentiating demented from non-demented individuals (DeBettignies, Mahurin, & Pirozzolo, 1990; Isella et al., 2006; Jorm & Jacomb, 1986; Jorm & Korten, 1988; Kemp, Brodaty, Pond, & Luscombe, 2002; Seltzer, Vasterling, Mathias, & Brennan, 2001), and in predicting increased risk of disease progression (Daly et al., 2000; Harwood, Hope, & Jacoby, 1997; Jorm, Christensen, Jacomb, Korten, & Mackinnon, 2001), informant report also can be associated with problems in reporting accuracy (Demers, Oremus, Perrault, Champoux, & Wolfson, 2000; Ready, Ott, & Grace, 2004). Finally, the identification of additional factors that relate to everyday function is important. For example, use of compensatory strategies and the influence of environmental demands are

likely factors that may lessen the association between neuropsychological test performance and real-world functioning (Chaytor & Schmitter-Edgecombe, 2003).

Overall, our findings indicate that functional capacities in older adults are determined by multiple factors. Cognitive performance, as well as depressive symptoms and apathy, all make independent contributions to predicting functional abilities among older adults. For the most part, these cognitive and neuropsychiatric factors have widespread effects across a variety of functional abilities. This highlights the importance of assessing symptoms of depression and apathy in older adult populations presenting with cognitive and/or functional difficulties, given that they are common in older adults with MCI and depression (i.e., we found apathy in approximately 21% of the MCI and 33% of the dementia sample; depressive symptoms in 40% of the MCI and 48% of the dementia sample). This can serve to improve family and caregiver education with regard to the commonality of these symptoms in accompanying cognitive changes, as well as the potential impact of these neuropsychiatric symptoms on everyday functioning, including how this relationship could possibly differ depending on the person's cognitive status (though the latter finding is preliminary). Along these lines, one potential implication of our findings may be that treatments aimed at each of these factors could have incremental effects on lessening functional disability, although more research is needed to confirm this possibility. Preliminary findings also suggest that the relative impact of cognitive performance versus apathy and depressive symptoms on everyday function may vary by the specific older adult population, with depressive symptoms and apathy potentially having a greater impact on everyday function than cognitive performance in individuals with MCI, and cognition being a more primary correlate of functional status in dementia.

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Table 1

Demographic Characteristics and Everyday Cognition Scales, Spanish English Neuropsychological Assessment Scales, and Neuropsychiatric Inventory Scores Across Each Diagnostic Group.

	Diagnostic Groups		
	Normal	MCI	Dementia
Age (years)	74.6 (6.7)	76.0 (7.2)	78.7 (7.0)
Education (years)	13.1 (4.0)	13.9 (4.4)	12.97 (3.1)
Gender (% female)	66%	53%	59%
MMSE	27.8 (2.0)	25.3 (3.3)	21.6 (11.6)
SENAS ^a			
Episodic Memory	0.05 (0.81)	-0.87 (0.61)	-1.53 (0.56)
Executive Functioning	0.03 (0.64)	-0.42 (0.61)	-0.97 (0.75)
NPI ^b			
Depression (%)	19.1%	40.2%	48.3%
Apathy (%)	7.5%	20.7%	32.8%
ECog Domains ^c			
Everyday Memory	1.58 (0.59)	2.31 (0.96)	3.41 (0.70)
Everyday Language	1.38 (0.54)	1.62 (0.62)	2.69 (0.87)
Everyday Visuospatial	1.27 (0.46)	1.59 (0.75)	2.81 (1.00)
Everyday Planning	1.28 (0.47)	1.68 (0.78)	2.98 (0.99)
Everyday Organization	1.37 (0.56)	1.85 (0.87)	3.27 (0.86)
Everyday Divided Attention	1.48 (0.62)	2.01 (0.98)	3.21 (0.90)
Global ECog	1.40 (0.46)	1.84 (0.69)	3.04 (0.77)

Note. ECog = Everyday Cognition, MCI = Mild Cognitive Impairment, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory, SENAS = Spanish English Neuropsychological Assessment Scales. Except for education and gender, variables differed by group ($p < .001$). All pairwise differences for age, MMSE, SENAS, NPI, and ECog were significant after adjustment for multiple comparisons ($p < .001$) except for age between Normal and MCI ($p = 0.13$), and age ($p = 0.04$), apathy ($p = 0.15$), and depression ($p = 0.43$), between MCI and demented individuals.

^a SENAS z-score.

^b Presence of the symptom.

^c ECog averages.

Spearman Correlations (Cognitive) or Kendall's Tau (Neuropsychiatric) Between the Everyday Cognition Scales and Predictor Variables.

Table 2

	ECog Memory	ECog Language	ECog Spatial	ECog Planning	ECog Organization	ECog Div Attn	Global ECog
EF	−0.34	−0.44	−0.37	−0.39	−0.43	−0.39	−0.43
Memory	−0.51	−0.45	−0.42	−0.49	−0.48	−0.48	−0.52
Apathy	0.24	0.24	0.22	0.29	0.25	0.29	0.26
Depression	0.31	0.30	0.22	0.30	0.30	0.31	0.31

Note. ECog = Everyday Cognition, EF = Executive function, Div Attn = Divided Attention. All correlations are significant at $p < .001$.

Table 3
Tobit Model Estimates Showing the Associations Between Cognitive Function and Neuropsychiatric Symptoms with Everyday Cognition Scales.

Variable	Memory β (SE)	Language β (SE)	Spatial β (SE)	Planning β (SE)	Organization β (SE)	Divided Attention β (SE)	Global ECog β (SE)
EF	-0.07 (0.04)***	-0.19 (0.05)***	-0.19 (0.06)**	-0.20 (0.06)**	-0.25 (0.06)***	-0.17 (0.06)**	-0.12 (0.03)***
Memory	-0.22 (0.03)***	-0.12 (0.03)***	-0.16 (0.05)**	-0.25 (0.05)***	-0.18 (0.05)***	-0.23 (0.05)***	-0.15 (0.03)***
Apathy	0.18 (0.07)*	0.17 (0.07)*	0.25 (0.10)**	0.33 (0.10)**	0.21 (0.09)*	0.36 (0.10)***	0.18 (0.06)**
Depression	0.29 (0.06)***	0.26 (0.06)***	0.21 (0.08)**	0.32 (0.08)***	0.31 (0.07)***	0.36 (0.08)***	0.23 (0.04)***

Note. ECog = Everyday Cognition, EF = Executive functioning. All models were adjusted for age and education.

* $p < .05$,
** $p < .01$,
*** $p < .001$.

Spearman Correlation or Kendall's Tau Between Global Everyday Cognition Scale and Predictors by Diagnostic Group.

Table 4

Diagnosis	Neuropsychological Domain (SENAS scores)			NPI Behavioral Domain	
	Episodic Memory	Executive Functioning	Depression	Apathy	
Global ECog	Normal	-0.21	-0.27	0.26	0.10
	MCI	-0.15	-0.06	0.25	0.31
	Dementia	-0.28	-0.30	0.12	0.13

Note. ECog = Everyday Cognition, MCI = Mild Cognitive Impairment, NPI = Neuropsychiatric Inventory, SENAS = Spanish English Neuropsychological Assessment Scales. Spearman correlations are presented for SENAS while Kendall's taus are presented for the NPI Behavioral Domains. Bolded values denote $p < .05$.