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Cognitive and Neuropsychiatric Correlates of Functional Impairment Across the Continuum of No Cognitive Impairment to Dementia

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Abstract

Objective: The ability to carry out instrumental activities (IADL) of daily living allows older adults to continue to live independently. Previous research suggested IADL were supported by multiple cognitive and neuropsychiatric factors. The primary goal of this study was to investigate whether immediate memory, executive functions, depression, and apathy, predicted unique variance in IADL over and above demographic variables (age and education) and general cognitive screening (Mini-Mental State Exam).

Method: Participants ($N = 403$) were recruited from the Rural and Remote Memory Clinic (75 no cognitive impairment; 75 mild cognitive impairment; 139 dementia due to Alzheimer's disease; 114 non-Alzheimer's dementia).

Results: Results of hierarchical regression analyses suggested immediate memory, executive functions, apathy, and depression each accounted for unique variance in IADL in the overall sample, but as a predictor only apathy predicted variance in IADLs above demographics and general cognitive status. Further analysis of the diagnostic subgroups suggested different variables were more strongly associated with IADL from group to group (apathy and depression for normal participants, apathy for MCI participants and for participants with dementia due to AD, but not for those with non-AD dementia).

Conclusions: The implications for developing cognitive rehabilitation interventions are discussed, with a recommendation for interventions for symptoms of apathy.

Keywords: Everyday functioning; Alzheimer's disease; Mild cognitive impairment; Rehabilitation

Instrumental activities of daily living (IADL) are the day-to-day functional activities that allow an individual to live independently. They include tasks such as cooking, shopping, financial management, traveling, and medication management (Sikkes, de Lange-de Klerk, Pijnenburg, Scheltens, & Uitdehaag, 2009). IADL are more complex than basic activities of daily living (BADL), which are focused on personal care and self-maintenance skills such as bathing, toileting, and eating (Sikkes et al., 2009). In the context of health, and neurodegenerative disease in particular, changes in functional status have significant diagnostic implications; decline in function and impairment at work or other usual activities are core features of a dementia diagnosis (McKhann et al., 2011; Robillard, 2007). When individuals with cognitive concerns participate in cognitive rehabilitation treatment goals are focused on improving function, increasing participation in meaningful activity, and managing day-to-day problems (Clare et al., 2010; Giebel & Challis, 2015; Kurz et al., 2012). This study aimed to inform the development of these interventions by exploring the cognitive and neuropsychiatric correlates of IADL.

Research on the trajectory of impairment in late life and in dementia has tended to focus on cognition rather than on IADL (Farias et al., 2013), but increasingly the focus of interventions, particularly cognitive rehabilitation is on function and personally relevant goals (Clare, 2008; Kurz, Leucht, & Lautenschlager, 2011). The gap in understanding the variables that underlie decreased function leads to the criticism that interventions are delivered without a strong theoretical framework (Giebel & Challis, 2015). A handful of meta-analyses and systematic reviews have worked to integrate the literature on the cognitive correlates of IADL in older adults, including studies that analyzed data from a broad range of clinically relevant populations

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(Overdorp, Kessels, Claassen, & Oosterman, 2016; Royall et al., 2007) and analyses focused on the MCI literature (Lindbergh, Dishman, & Miller, 2016; McAlister, Schmitter-Edgecombe & Lamb, 2016). These meta-analyses have consistently reported a great deal of heterogeneity in the literature (Lindbergh et al., 2016; Royall et al., 2007). For example, in Royall and colleagues (2007) meta-analysis the total variance in function accounted for by cognitive variables in the 68 studies included in the analysis ranged from 0% to 78.0%. The population sampled (e.g., clinical, community based), effects of clinical condition (e.g., healthy older adults, MCI, dementia due to AD, non-AD dementia), approach to IADL assessment (e.g. self-report questionnaire, informant questionnaire, performance based), cognitive and neuropsychological tests selected, and approach to prediction models all contribute to the variability in the literature examining neuropsychological function and IADL (see Gold, 2012 for a narrative review and discussion).

Despite the study-to-study variability some consistent findings are emerging. Globally, cognition seems to account for a relatively small proportion of the total variance in IADL (e.g., McAlister et al., 2016; Royall et al., 2007). Royall and colleagues (2007), whose meta-analysis included studies from the neuropsychiatric, geriatric and rehabilitation literature, reported that cognition explained an average of 21% of the total variance in function. Similarly, McAlister and colleagues (2016) who included only MCI samples in their meta-analysis, reported cognition accounted for an average of 23% of the variance in function. It has consistently been the case that broad, non-specific screening tests such as the Mini Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) are strongly associated with function (e.g., Gold, 2012). For example, Royall and colleagues (2007) were surprised to find that general screening tests explained the most variance in functional outcome versus tests in the specific cognitive domains of language, visual spatial, attention, executive, or memory.

Many authors have worked to identify the relationship between specific cognitive domains and IADL in late life (e.g., Bangen et al., 2010; Burton, Strauss, Hultsch, & Hunter, 2006; Chaytor, et al., 2015; Farias et al., 2009; Makizako et al., 2015; Marshall et al., 2011; Rog et al., 2014; Schmitter-Edgecombe & Parsey, 2014; Tuokko, Morris, & Ebert, 2005; Woods, Weinborn, Velnoweth, Rooney, & Bucks, 2012). Despite substantial heterogeneity from individual to study to individual study trends have emerged in recently published meta-analyses. Overdorp and colleagues (2016), who included a broad range of clinical conditions but only studies that examined both neuropsychological test performance and morphological brain changes, concluded memory and executive functions independently predict IADL. Similarly, in their meta-analysis of cognition and function in MCI, McAlister and colleagues (2016) concluded executive functions (particularly switching and particularly as measured by the Trail Making Test B), particularly immediate memory (described by authors as short delayed memory), visual memory, attention, and working memory were the strongest correlates of function in that order. Guided by this research, the current study focuses on immediate memory and executive function as neuropsychological variables.

Executive functions, in particular, have been a focus of the research on IADL and cognitive function (e.g., Gold, 2012; Vaughan & Giovanello, 2010). In Martyr and Clare's (2012) meta-analysis of individuals with dementia due to AD, they found a consistent moderate relationship between executive functions and activities of daily living. Importantly, the term "executive functions" does not refer to a single cognitive or neurophysiological process, but to a broad range of different cognitive processes that are sensitive to, but not specific to, impairment in circuits of the prefrontal cortex (Alvarez & Emory, 2006). Executive functions are top-down, effortful mental processes (Diamond, 2013). The core executive functions include inhibition and interference control, working memory, and cognitive flexibility (e.g., Diamond, 2013; Miyake et al., 2000). Rather than selecting a single neuropsychological test measuring executive functions, in the investigation of IADL and cognition presented here we included three tests of executive functions in our analyses: the Trail Making Test B (Reitan, 1992), the Stroop test (Trennery, Crosson, DeBoe, & Leber, 1989), and COWAT verbal fluency (Spreen & Benton, 1977). In this way, we hoped to better understand the heterogeneity in the results of studies examining the relationship between executive functions and IADL.

Cognitive rehabilitation endeavors to take a holistic, biopsychosocial approach to intervention (Clare, 2008), which includes working to address goals related to emotional well-being. Therefore, we wanted to consider variables outside the domain of cognition in this study. Depression and apathy are particularly relevant clinical variables when considering the determinants of decreased function across the continuum from normal aging to dementia (Okura et al., 2010; Rog et al., 2014). Definitions of apathy focus on impairment in goal-directed behavior and, depending on the author, conceptualize apathy as a disorder of motivation, interest, action, initiation and/or emotional reactivity (see Mortby, Maercker, & Forstmeier, 2012 for a critical review). Depression is characterized by depressed mood (feelings of sadness, emptiness, hopelessness) and/or anhedonia (loss of interest or pleasure in activity; American Psychiatric Association, 2013). Apathy and depression are overlapping constructs, and anhedonia and apathy in particular are closely tied conceptually. Nonetheless, the constructs can be differentiated and this distinction is particularly relevant for older adults (Mortby et al., 2012). For example, previous research found high apathy scores were not associated with elevated depression in individuals diagnosed with AD and in individuals with right hemisphere stroke (Marin, Firinciogullari, & Biedrzycki, 1994).

Depressive symptoms were associated with functional impairment and disability in community samples of older adults (Beekman, Deeg, Braam, Smit, & Van Tilburg, 1997; Patrick, Johnson, Goins, & Brown, 2004; Vanoh, Shahar, Yahya, & Hamid, 2016), a clinical sample of older adults with coronary heart disease (Sin, Yaffe, & Whooley, 2015), and mixed community/institutional samples of individuals with and without dementia (Forsell & Winbald, 1998). Apathy, which is generally found to be more common in dementia compared to MCI or cognitively normal samples (Okura et al., 2010), has also been associated with decreased function (Clarke et al., 2011; Lechowski et al., 2009). When depression and apathy are considered concurrently, which is important because of their conceptual overlap, findings have been mixed. For example, Lam, Tam, Chiu, and Liu (2007) found that both depression and apathy predicted function in their MCI subsample, but only apathy predicted function in their dementia subsample. Rog and colleagues (2014) built on this work by including neuropsychological predictors of function in a sample of individuals across the cognitive continuum from normal aging to dementia. In their overall sample they found that memory, executive functions, depression and apathy each made independent contributions to everyday function. In a secondary analysis, they suggested that the relationships between depression, apathy, cognition, and function varied by diagnostic category. Specifically, for cognitively normal participants' episodic memory, executive function, and depression were all significantly correlated with function. For individuals with MCI only depression and apathy were correlated with function, and in the dementia subsample only episodic memory and executive function were correlated function. The study presented here builds on this work.

The purpose of this study is to extend previous research that has examined the relationship between IADL, demographic/clinical variables, and cognitive variables including executive function. Despite substantial heterogeneity, executive function, immediate memory, depression, and apathy have consistently been associated with functional abilities, but because they have rarely been examined concurrently (see Rog et al., 2014 for an exception) it is unclear how much unique variance in IADL each account for. We hypothesized that adding these neuropsychological variables (immediate memory, executive functions) and neuropsychiatric variables (depression, apathy) in the second step of a hierarchical regression would account for significantly more variance than a model that included only age, education, and MMSE independent variables. We anticipated that immediate memory, depression, and apathy would each significantly predict unique variance in IADL. Regarding executive functions, based on McAlister and colleagues (2016) we hypothesized that Trails B would a strong predictor of IADL. A second purpose of this study was to explore whether diagnostic category (e.g., cognitively normal, MCI, AD, non-AD dementia) influenced the strength of the relationship between each of the independent variables (executive functions, immediate memory, depression, apathy) and IADL.

This study has three strengths. First, the sample is clinical and closely related to the individuals with cognitive concerns who may be referred for cognitive rehabilitation. Second, we chose to consider three measures of executive functions (Trail Making Test B, Controlled Oral Word Association Test, and Stroop) separately. Third, cognition and mood are considered concurrently, and we have worked to differentiate low mood from apathy. The goal of this work is to inform the development of cognitive rehabilitation strategies for individuals across the continuum of normal aging, MCI and dementia. We believe better understanding the relationship between the strongest correlates of IADLs in this population will strengthen the theoretical basis for cognitive rehabilitation interventions.

Method

Participants

Participants were 403 consecutive referrals to an interdisciplinary memory clinic, the Rural and Remote Memory Clinic (RRMC; Data Release 6), who were found to have no cognitive impairment (n = 75), MCI (n = 75), dementia due to Alzheimer's disease (n = 139), or non-AD dementia (n = 114). The non-AD dementia subgroup included individuals who met the diagnostic criteria for dementia due to frontotemporal lobar degeneration, vascular dementia, mixed dementia, or Lewy body disease. See Morgan and colleagues 2009 for a complete description of the procedures at the RRMC. Diagnoses were based on consensus between the clinic's neurologist and neuropsychologist, and were consistent with the guidelines provided from the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD3; Robillard, 2007). The assessment included a clinical interview with the participants and a knowledgeable informant, a neuropsychological assessment, a neurological assessment, a physical therapy assessment, a CT head scan, and recent blood work. Table 1 provides descriptive statistics for the sample broken down by diagnostic category. Informal caregivers accompanied patients to their assessment appointment provided the collateral information and completed questionnaires. Most commonly caregivers were family members: 30% were wives, 18% were husbands, 24% were daughters, 8% were sons, and 10% had another relationship with the patient including nieces, nephews, grandchildren, or friends.

Table 1. Descriptive statistics for demographic and clinical variables for each of the diagnostic subgroups

	No CI *M* (*SD*) *n*	MCI *M* (*SD*) *n*	AD *M* (*SD*) *n*	Non-AD *M* (*SD*) *n*
Age	60.79 (12.97) 75	70.92 (11.25) 74	75.98 (7.44) 138	71.95 (10.54) 113
Gender (% female)	55%	55%	68%	56%
Education	12.49 (3.32) 59	10.92 (3.40) 65	10.10 (3.27) 119	10.88 (3.31) 93
FAQ	4.74 (5.66) 66	7.56 (5.71) 72	15.74 (7.75) 133	15.20 (8.21) 107
MMSE	28.41 (1.53) 59	27.03 (2.12) 64	21.66 (4.11) 120	23.04 (4.66) 91
Memory	95.98 (11.31) 58	78.78 (14.93) 64	57.62 (14.07) 109	64.95 (16.88) 79
Stroop (*z* score)	−.41 (1.18) 53	−1.43 (1.23) 54	−1.90 (1.23) 61	−2.23 (1.02) 47
Trails B (*z* score)	−.61 (1.25) 56	−1.37 (1.31) 52	−2.05 (1.28) 64	−2.35 (1.11) 49
COWAT (*z* score)	−.72 (1.25) 58	−1.28 (1.08) 64	−1.41 (.99) 107	−1.95 (1.03) 80
NPI Apathy Severity	.75 (.94) 65	.55 (.81) 69	1.02 (.98) 132	1.17 (1.01) 103
CESD	18.38 (11.09) 68	14.64 (9.0) 66	12.71 (10.0) 79	13.30 (8.71) 111

Note: FAQ = Functional Activities Questionnaire; Memory = Immediate Memory index from the Repeatable Battery for the Assessment of Neuropsychological Status; MMSE = Mini-Mental State Exam; NPI = Neuropsychiatric Inventory; CESD = Center for Epidemiologic Studies – Depression scale.

Measures

The complete list of measures administered to RRMC participants at the time of their initial assessment is described in Morgan and colleagues (2009). Here, the following measures were used to address the study's hypotheses.

Measure of IADL. The Functional Activities Questionnaire (FAQ; Pfeffer, Kurosaki, Harrah, Chace, & Filo, 1982) was used as the measure of function and IADL. The FAQ is an informant-completed measure that asks caregivers to rate the patient's ability to perform daily activities (e.g., pay bills, shop, work on a hobby, prepare a meal) from "normal" to "dependent." Scores range from 0 to 30 and higher scores indicate greater dependence. The FAQ discriminated between dementia and non-dementia samples (Juva et al., 1997), and between MCI and AD samples (Kaur, Belchior, Grelinas, & Bier, 2016; Teng, Becker, Woo, Cummings, & Lu, 2010).

MMSE. The Mini Mental State Exam (MMSE; Folstein et al., 1975) is a widely used cognitive screening measure. The items on the MMSE were designed to capture orientation, immediate and delayed recall, calculation, and language (Strauss, Sherman, & Spreen, 2006). The internal consistency of the MMSE ranges from .31 to .96, the test–retest reliability is adequate ranging between .80 and .95, and the inter-rater reliability is marginal .65 (Strauss et al. 2006). Regarding evidence for validity, the MMSE is moderately to highly correlated with other screening tools (e.g., the Dementia Rating Scale), and has been found to be sensitive to moderate to severe dementia, but generally does not differentiate individuals with less pronounced cognitive changes (e.g., MCI; Strauss et al. 2006).

Immediate memory. Memory was measured using the immediate memory index from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, Tierney, Mohr, & Chase, 1998). The immediate memory index is comprised of two subtests: list learning and story memory. The immediate memory index ($M = 100$, $SD = 15$) is based on the sum of the age-scaled subtest scores. Strauss and colleagues (2006) summarized the evidence for the reliability and validity of the RBANS subscales. The internal consistency coefficients were in the .80s, and test–retest reliability coefficients ranged from .55 to .78. There is evidence to support the use of the RBANS to differentiate individuals with a dementia

diagnosis from healthy individuals, and individuals with dementia due to a cortical etiology from individuals with dementia due to a subcortical etiology (Strauss et al., 2006).

Measures of executive functions. Three measures of executive function were used in the analyses reported below: the Trail Making Test B (TMT-B; Reitan, 1992), the Controlled Oral Word Association Test (COWAT; Spreen & Benton, 1977), and the Stroop Neuropsychological Screening Test (Trennery et al. 1989). For each of these measures standard age-corrected scores (i.e., *z*-scores) are always reported.

The TMT-B (Reitan, 1992) was administered as a measure of divided attention. In healthy adults and older adults, the reliability coefficients for TMT-B have been found to be adequate and range from 0.67 to 0.89 (Strauss et al., 2006). In clinical samples the results have not been as consistent, and although reliability can be high in clinical populations this has not uniformly been the case. Related to the population studied here, in sample of older adults with diffuse cerebrovascular disease reliability was on the TMT-B was 0.67 (Strauss et al., 2006).

The Controlled Oral Word Association Test (COWAT; Spreen & Benton, 1977) was used as a measure of verbal fluency. Verbal fluency evaluates the spontaneous production of words under restricted conditions (Strauss et al., 2006). In healthy adults test–retest reliability coefficients have consistently been reported to be above 0.70, and small but reliable practice effects have been found (Strauss et al., 2006).

The Stroop Neuropsychological Screening Test (Trennery et al.,1989) was administered as a measure of executive function. As summarized by Strauss and colleagues (2006) the reliability of the Stroop Test has been shown to be adequate with test–retest reliability coefficients ranging between 0.73 and 0.91. Here, we used the color-word interference scores only, which is a measure of the ability to inhibit an automatic response (Trennery et al., 1989).

Depression. Depression was measured by the Centre for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977), which is a self-report scale developed to identify depression in the general population. The CES-D has been found to have adequate internal consistency and test–retest reliability (Cronbach's alpha between 0.82 and 0.91, and test-retest reliability ranging from 0.52 to 0.57 depending on the sample and time interval; Lewinsohn, Seeley, Roberts, & Allen, 1997; Radloff, 1977; Ros et al., 2011). There is evidence for the validity of the CES-D in samples of community dwelling older adults and older adults with cognitive impairment (Lewinsohn et al., 1997; Ros et al., 2011).

Apathy. The Neuropsychiatric Inventory (NPI; Cummings et al., 1994; Cummings, 1997), which was designed specifically to assess psychopathology in individuals diagnosed with dementia, provided a measure of apathy. The NPI is a caregiver completed measure of patient behaviors associated with caregiver distress. The frequency and severity of twelve symptoms (delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, night-time behviour disturbances, and appetite and eating abnormalities) are rated and caregiver distress related to each symptom is measured (Cummings, 1997). In the standardization sample of individuals diagnosed with dementia test–retest reliability was 0.79 overall. In the analyses below, the apathy severity score, which was rated from 0 to 3 by caregivers (if apathy was absent, this was rated 0) was used in all analyses.

Results

All analyses were carried out using IBM SPSS 24. Prior to analysis, the assumptions of multiple regression were checked following the procedures outlined by Tabachnick and Fidell (2013). FAQ, MMSE, RBANS index scores (Immediate Memory, Visuospatial, Language, Attention, and Delayed Memory), Trails B, Stroop, COWAT, CES-D, and NPI apathy scores were examined for missing values, and the fit between their distributions and the assumptions of multivariate analysis. Specifically, the assumptions of normality, homoscedasticity, and multicollinearity were reviewed.

No univariate outliers were identified. Mahalanobis distance was used to examine multivariate outliers and no cases with $p < .001$ were identified. The distributions of FAQ ($Z = 3.62$), MMSE ($Z = –4.5$), and CES-D ($Z = 3.64$) were all significantly skewed. Delayed Memory had significant kurtosis ($Z = 3.04$). When a square root transformation was applied, FAQ, MMSE, and CES-D scores were no longer significantly skewed. Significant skewness remained for the Delayed Memory scores. The regression analyses reported below were run with and without transformation, and the results were not substantially different. This is consistent with Tabachnick and Fidell's (2013) assertion that statistically significant skewness does that make a substantial difference in regression analyses when sample sizes include more than 100 cases. For ease of interpretation, non-transformed variables and results are reported here.

The assumptions of linearity homoscedasticity were examined using bivariate scatterplots, and no clear deviations from either of these assumptions were observed. Finally, the correlation matrix revealed no correlations greater than 0.90, indicating that multicollinearity was not problematic. The correlation between Immediate Memory and Delayed Memory from the RBANS, $r = .767$, $p < .0001$, was high enough that we considered including both measures of memory redundant, and only Immediate Memory was included in subsequent analyses. This decision was based on the recommendations of Tabachnick and Fidell (2013), the skewed distribution of Delayed Memory, and previous research demonstrating the stronger relationship between immediate memory and function versus delayed memory and function (e.g., Martyr et al., 2014).

Hierarchical regression (also known as sequential regression) was used to determine if executive function, delayed memory, depression and apathy improve prediction of IADLS beyond differences in age, education, and global cognitive function as screened by the MMSE. Given the complexities and challenges surrounding measures of executive functions reviewed in the introduction the decision to use three separate measures of executive was used, and the hierarchical regression was run three separate times using the Stroop test, COWAT, and TMT-B as measures of executive function. Due to multiple comparisons, p was set to .01, nevertheless the focus for interpretation remained on variance accounted for rather than mere p-value.

Hierarchical regression results with the Stroop test as the measure of executive functions

Table 2 displays the unstandardized regression coefficients (B), the standardized regression coefficients (β), the t values, and the squared semipartial correlations (si^2), after each step of the analysis. R was significantly different from zero at the end of each step. In Step 1, age, education and MMSE were entered into the equation, $R^2 = 0.17$, F_{inc} (3, 178) = 12.40, $p < .001$, 95% CI [.08, .27]. In Step 2, immediate memory, COWAT, NPI apathy, and CESD were entered, $R^2 = .36$, $\Delta R^2 = .19$, F_{inc} (4, 178) = 12.77, $p < .001$, 95% CI [.25, .47]. The addition of Stroop, delayed memory, depression and apathy lead to a significant increase in R^2, and an additional 19% of the variance in FAQ was accounted for. With all IVs included in the equation, the adjusted R^2 value of .36 indicates the complete model accounts for approximately one-third of the variability in FAQ. The demographic/screening variables accounted for one-tenth of the variance in FAQ, and executive functions (measured by the Stroop test in this case), delayed memory, depression, and apathy accounted for an additional fifth of the variability in predicting FAQ scores.

Hierarchical regression results with Trails B as the measure of executive functions

Table 3 displays the unstandardized regression coefficients (B), the standardized regression coefficients (β), the t values, and the squared semipartial correlations (si^2), after each step of the analysis. As in the previous analyses R was significantly different from zero after each step in the analysis. In Step 1, age, education and MMSE were entered into the equation, $R^2 = 0.23$, F_{inc} (3, 184) = 18.80, $p < .001$, 95% CI [.12, .32]. In Step 2, immediate memory, Trails B, depression and apathy added to the prediction of FAQ, $R^2 = 0.36$, $\Delta R^2 = .14$, F_{inc} (4, 184) = 9.71, $p < .001$ 95% CI [.26, .47]. The addition of Trails B, immediate memory, depression and apathy lead to a significant increment in R^2, and an additional 14% of variance accounted for in FAQ. With all IVs included in the equation, the adjusted R^2 value of .34 indicates over a third of the variability in FAQ

Table 2. Hierarchical regression analyses predicting IADL function with the Stroop test as the measure of executive function

Variable	B	β	t	sr_i^2
Step 1				
Age	0.14	.22	2.90**	.20
Education	0.07	.004	0.06	.004
MMSE	−0.63	−.27	−3.43**	−.23
Step 2				
Age	0.14	.23	3.13**	.19
Education	0.10	.04	0.64	.04
MMSE	−0.40	−.17	−2.04	−.12
Memory	−0.02	−.05	−0.56	−.03
Stroop	−0.83	−.15	−2.09	−.13
NPI apathy	3.04	.39	6.38***	.38
CESD	0.001	.002	0.03	.002

Note: Memory = Immediate Memory index from the Repeatable Battery for the Assessment of Neuropsychological Status; MMSE = Mini-Mental State Exam; NPI = Neuropsychiatric Inventory; CESD = Center for Epidemiologic Studies – Depression scale.
*$p < .05$. **$p < .01$. ***$p < .001$.

Table 3. Hierarchical regression analyses predicting IADL function with Trails B as the measure of executive function

Variable	*B*	*β*	*t*	sr_i^2
Step 1				
Age	0.12	.19	2.62**	.17
Education	0.14	.06	0.89	.06
MMSE	−0.82	−.37	−4.95***	−.32
Step 2				
Age	0.14	.22	3.08*	.18
Education	0.13	.06	0.86	.05
MMSE	−0.51	−.23	−2.69*	−.16
Memory	−0.01	−.02	−0.17	−.01
Trails B	−0.79	−.14	−2.04*	−.12
NPI apathy	2.82	.35	5.81***	.34
CESD	−0.02	−.02	−0.37	−.02

Note: Memory = Immediate Memory index from the Repeatable Battery for the Assessment of Neuropsychological Status; MMSE = Mini-Mental State Exam; NPI = Neuropsychiatric Inventory; CESD = Center for Epidemiologic Studies – Depression scale.
*$p < .05$. **$p < .01$. ***$p < .001$.

Table 4. Hierarchical regression analyses predicting IADL function with COWAT as the measure of executive function

Variable	*B*	*β*	*t*	sr_i^2
Step 1				
Age	0.16	.23	3.83**	.21
Education	0.07	.03	0.47	.03
MMSE	−0.73	−.36	−5.77***	−.32
Step 2				
Age	0.19	.28	4.49***	.23
Education	0.11	.05	0.78	.04
MMSE	−0.54	−.27	−3.45**	−.18
Memory	−0.02	−.04	−0.51**	−.03
COWAT	−0.72	−.11	−1.86	−.10
NPI apathy	2.43	.30	5.72***	.29
CESD	0.04	.05	0.81	.04

Note: Memory = Immediate Memory index from the Repeatable Battery for the Assessment of Neuropsychological Status; MMSE = Mini-Mental State Exam; NPI = Neuropsychiatric Inventory; CESD = Center for Epidemiologic Studies – Depression scale.
*$p < .05$. **$p < .01$. ***$p < .001$.

is accounted for by the demographic, cognitive, and neuropsychiatric variables. These results are consisted with the pattern of the hierarchical regressions reported above. Again, when added to the model, executive functions, depression, and apathy predict additional variability in FAQ.

Hierarchical regression results with COWAT as the measure of executive functions

The unstandardized regression coefficients (*B*), the standardized regression coefficients (β), *t* values, and the squared semi-partial correlations (si^2) after each step of the analysis are shown in Table 4. *R* was significantly different from zero after each step. In Step 1, age, education and MMSE were entered into the equation, $R^2 = .25$, F_{inc} (3, 247) = 24.47, $p < .001$, 95% CI [.17, .35]. In Step 2, delayed memory, COWAT, depression, and apathy added to the prediction of IADL, $R^2 = .35$, $\Delta R^2 = .11$, F_{inc} (4, 247) = 10.13, $p < .001$, 95% CI [.26, .45]. The addition of COWAT, delayed memory, depression, and apathy lead to a significant increment in R^2 and an additional 11% of variance accounted for in FAQ. With all IVs included in the equation, the adjusted R^2 value of .35 indicates more than a third of the variability in FAQ is accounted for by the demographic, cognitive, and neuropsychiatric variables selected here. This pattern of results suggests that a quarter of the variability in FAQ is accounted for by demographic variables (age, education) and general cognitive function (MMSE). Consistent with the previous regression analyses, executive functions as measured by COWAT, delayed memory, depression, and apathy account for additional variability in predicting FAQ over and above these demographic/screening variables.

Correlations with function by diagnostic subgroup

The Pearson product–moment correlations between the independent variables of interest (MMSE, immediate memory, COWAT, Stroop, Trails B, depression, and apathy) and function as measured by the FAQ were examined within each diagnostic group (no CI, MCI, dementia due to AD, non-AD dementia). These correlations are provided in Table 5. As shown there, for those with no cognitive impairment there was a moderate relationship between apathy and FAQ, and depression and FAQ. In individuals diagnosed with MCI, there was moderate relationship between apathy and FAQ. In individuals diagnosed with dementia due to AD there was a moderate relationship between apathy and FAQ, but no substantial association between apathy and FAQ for non-AD dementia. The association between the general cognitive status screen, MMSE and the FAQ was only moderate for the groups diagnosed with dementia (AD and non-AD dementia).

Discussion

First, we found that for the sample as a whole, immediate memory, executive functions, depression, and apathy accounted for variance in IADL above and beyond the variance accounted for by age, education, and general cognitive function. This pattern was repeated regardless of the specific measure of executive function used: Stroop, Trails B, and COWAT independently predicted a small, but significant proportion of the total variance (squared semipartial correlations ranging from –.13 to –.10). Our finding is consistent with previous researchers, such as Marshall and colleagues (2011), who found executive functions were related to informant reported IADL impairment even after accounting for diagnosis, global cognitive impairment, memory performance, depression and apathy in a sample of cognitively normal older adults, individuals with MCI, and individuals with dementia due to AD. The hierarchical regression analyses are also consistent with Gold's (2012) argument that IADL are multidimensional and rely on multiple cognitive systems, which means that the strength of the relationship between IADL and any particular cognitive variable depends on whether or not demographic variables and general cognitive function are included in the prediction model. Consistent with this hypothesis, the models reported here suggest executive functions, as measured by Stroop, Trails B, and COWAT, and immediate memory account for a modest amount of unique variance in function.

Immediate memory was not substantially correlated with function, but general cognitive status was moderately associated with function for both the AD and non-AD subgroups. Memory impairment is the hallmark of dementia due to Alzheimer's disease and cognitive rehabilitation interventions focus on this domain (e.g., Clare, 2008; Kurz et al., 2011); consequently, the lack of association was surprising. In addition, we were surprised by the non-significant correlations between the measures of executive functions and IADL across all three clinical groups. Previous meta-analyses reported a moderate association between IADL and executive functions in AD (Martyr & Clare, 2012) and between Trails B in particular and IADL in MCI (McAlister et al., 2016). For the non-AD subsample, it may be the case that the strongest correlates of function for non-AD dementia were not included here. For example, in dementia due to Lewy Bodies (DLB) motor dysfunction accounted for more variance in IADL than either cognitive changes or behavioral changes (Hamilton et al., 2014). Future studies, reviews, and meta-analyses should continue to divide heterogeneous samples into diagnostic subgroups as there do appear to be clear differences in cognitive correlates of function from MCI to AD to non-AD dementia.

Considering the relation between depression, apathy, and function, the hierarchical regression analyses suggested apathy predicted the most unique variance in FAQ with medium squared semipartial correlations (ranging from .29 to .38). In contrast to the predictive strength of apathy, we were surprised to find that depression was not a substantial predictor of function.

Table 5. Correlations with function (FAQ) for each diagnostic group

	No CI *r, n*	MCI *r, n*	AD *r, n*	Non-AD *r, n*
MMSE	−.07, 55	.04, 61	−.35, 117***	−.33, 88*
Memory	.07, 54	.08, 61	−.10, 108	−.08, 78
Stroop	−.10, 54	−.04, 51	−.09, 60	−.07, 46
Trails B	−.25, 52	.14, 50	−.01, 63	−.05, 49
COWAT	−.10, 54	.02, 61	.09, 105	−.16, 79
NPI Apathy	.47, 65***	.30, 68*	−.37, 131***	.18, 102
CESD	.34, 61**	.05, 64	.12, 110	.10, 79

Note: Memory = Immediate Memory index from the Repeatable Battery for the Assessment of Neuropsychological Status; MMSE = Mini-Mental State Exam; NPI = Neuropsychiatric Inventory; CESD = Center for Epidemiologic Studies – Depression scale.
*$p < .05$. **$p < .01$. ***$p < .001$.

These results are in contrast to Okura and colleagues (2010) who found those with clinically significant depression, but not apathy, had higher odds of having IADL limitations. However, our results are consistent with Norton, Malloy, and Salloway (2001) and Senanarong and colleagues (2005) who both reported apathy, but not depression, was associated with function. Previous researchers (Lam et al., 2007; Rog et al., 2014) have suggested that the relative importance of depression and apathy may depend on the diagnostic subsample.

In the subsample diagnosed with no cognitive impairment, our results suggested that both depression and apathy were moderately associated with IADL. Rog and colleagues (2014) found depression, but not apathy, correlated with everyday function in their cognitively normal subsample. The cognitively normal sample in this study was referred for a specialized dementia assessment whereas Rog and colleagues (2014) used a community sample, which could account for these discrepant findings. We did not find any association between depression and IADL in our clinical subsamples (MCI, AD, non-AD dementia). A recent meta-analysis (Lindbergh et al., 2016) of function in MCI reported depression was not an effect size moderator, which is consistent with the lack of relationship we found between depression and IADL in this study. Our data suggest for individuals diagnosed with MCI or AD there was a moderate relationship between apathy scores and FAQ scores. In the non-AD subsample, there was no relationship between function and either depression or apathy. Most other researchers have used either a heterogeneous dementia subsample (i.e., AD is not differentiated from other aetiologies of dementia), or an AD only subsample (i.e., individuals diagnosed with non-AD dementia were not included). Norton and colleagues (2001), in a mixed dementia sample (majority dementia due to AD), found apathy accounted for variance in function, but depression did not. Similarly, Lam and colleagues (2007) and Senanarong and colleagues (2005) reported apathy was associated with decreased function in their AD sample. Lam and colleagues (2007) also included a "questionable dementia subscale" (similar to MCI) and for this group both depression and apathy were associated with decreased function. Our results further support concluding that in MCI and AD apathy, but not depression, is associated with decreased function.

It is important to acknowledge the limitations of this study. First, there has been substantial discussion in the literature about the evidence for the validity of IADL questionnaires (Marcotte, Scott, Kamat, & Heaton, 2010). At present, there is no agreed upon gold standard for assessing IADL but self-reported questionnaires, informant reported questionnaires, and performance based measures do seem to produce different estimates of function (e.g., Loewenstein & Acevedo, 2009) and are not always strongly correlated with each other (Schmitter-Edgecombe, Parsey, & Cook, 2011; Vaughan & Giovanello, 2010). The FAQ is a widely used measure of IADL and although there is good evidence of its discriminability (Juva et al., 1997; Teng et al., 2010) its other psychometric properties (e.g., test-retest reliability, internal consistency) have been inadequately studied (Kaur et al., 2016).

The FAQ approach to measuring IADL is problematic because of its reliance on an informant report, as was done in the current study. Informant state of mind, particularly distress and depression can affect their informant ratings of function (Mangone, et al., 1993; Martyr & Clare, 2017; Martyr, Nelis, & Clare, 2014). In fact, in 37 persons with early stage dementia due to AD or mixed vascular/AD (MMSE > 18), patient self-report of function was more associated with objectively measured function than was informant reports (Martyr & Clare, 2017). Informant burden and distress are related with informant rated IADs, but their relation is complicated. Longitudinal studies demonstrate that changes in caregiver burden are related to patient changes such as increasing functional (Berger et al., 2005) and neuropsychiatric symptoms (Berger et al., 2005; Mohamed, Rosenbeck, Lyketsos, & Schneider, 2010; van der Lee, Bakker, Duivenvoorden & Droes, 2017). Moreover, increasing caregiver distress, over time, is related to increasing neuropsychiatric symptoms of persons with dementia (van der Lee et al., 2017). Dementia severity, caregiver distress, and caregiver rated FAQ accounted for a large proportion of variance in caregiver burden (38%), but disinhibition and apathy accounted for an additional 21.8% of the variance in caregiver burden (Branger, Enright, O'Connell, & Morgan, 2017). Although approaching the limitation of caregiver distress/burden influencing caregiver reported IADL by partialling out the variance due to burden is conceptually problematic, we repeated the hierarchical regressions with burden partialled out and the results did not change: apathy remained the sole robust predictor of IADL above age and general cognitive status. Nevertheless, there is likely a bidirectional relationship between burden and informant rating of the IADLs of their loved one with dementia that cannot be ignored and is a limitation of these data and their conclusions. Ideally, studies investigating predictors of function would use multiple methods to evaluate function (McAlister et al., 2016).

Another limitation to the current analyses is the restricted sample used for the executive function analyses, particularly for the Stroop and Trails B because a large proportion of the sample with dementia was unable to complete these tests. We have demonstrated that inability to complete the Stroop and Trails B is not necessarily due to impaired executive function per se, but rather impairments in memory, language, visuospatial abilities, and attention (Enright, O'Connell, McKinnon, & Morgan, 2015). Consequently, the EF analyses are restricted only to those whose cognitive abilities were sufficiently strong to allow their completion of the Stroop and the TMTB, which could have restricted the range of possible Stroop and Trails B performance, possibility obfuscating their relation with IADL in persons with dementia.

This study is also limited by the decision to use a single item from the NPI to assess apathy. Again, although is approach has been used in previous research (e.g., Rog et al., 2014) it is not the most robust approach to measurement. Single item measures are problematic because their internal consistency cannot be evaluated (Gardner, Cummings, Dunham, & Pierce, 1998). Apathy emerged as a strong predictor of function in the hierarchical regression analyses reported here, and future studies should continue to examine the relationship between apathy and function. However, apathy is a challenging construct to assess because there is a lack of consensus about the clinical definition of apathy (Clarke et al., 2011).

A final limitation pertains to the group we have labeled as cognitively normal, which was based on their neuropsychological performance and clinical history. This group sought specialist consultation and agreed to be assessed after waiting a considerable length of time (the clinic's waitlist is typically around 11–12 months). Clearly, they were initially concerned about their cognition, despite their neuropsychological performance within normal limits. Worry about subjective cognitive complaints without evidence for objective cognitive impairments, also referred to as subjective memory impairments or subjective cognitive impairment, is a heterogeneous group whose symptoms might be related to mood or anxiety (Burmester, Leathem, & Merrick, 2016). Moreover, epidemiological data prospective over 6 years suggests those with subjective memory impairment might be at risk for subsequent diagnoses of dementia (Jessen et al., 2014), but part of the heterogeneity in this new area of literature are the methods used to categorize within normal limits on objective testing (Burmester et al., 2016) and more research is required.

Despite these limitations, the results of this study can help inform cognitive rehabilitation in a number of ways. First, these results support efforts to approach cognitive rehabilitation from a holistic perspective (e.g., Clare, 2008). This study added further support to the hypothesis that function is supported by both cognitive and neuropsychiatric variables, and here we found that memory, executive functions, depression, and apathy all predicted variance in IADL performance over and above demographic variables and general cognitive function in the overall sample. Of these predictors, however, apathy accounted for the most variance. Memory based interventions have been the central focus of the majority of cognitive rehabilitation interventions (e.g., Clare, 2008), and the results presented here support that approach particularly for individuals with MCI or dementia due to AD, which is where the majority of the cognitive rehabilitation studies have focused. As clinicians work to expand and develop these interventions the results reported here suggest that symptoms of apathy are an important domain to consider. First, we suggest focusing on working to differentiate apathy from depression during the assessment and treatment-planning phase of interventions. Non-pharmacological treatments for apathy are an active area of study (see Goris, Ansel, & Schutte, 2016 for a systematic review; O'Connell, Mateer, & Kerns, 2003 for a discussion of practical considerations) and some, such as music based interventions and external cuing appear promising. As discussed, apathy needs to be differentiated from depression and our results suggest the subgroup of individuals where depression focused interventions are most likely to support function are those who present for assessment with subjective concerns, but who are cognitively normal. These individuals should be screened for depression and depressive symptoms should be treated in any cognitive rehabilitation interventions that are provided. Finally, although the literature examining predictors of IADL is full of mixed results, due to differences in methodologies and limits in assessment measure, this area has the potential to further develop the theoretical basis upon which interventions are being developed.

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Conflict of interest

None declared.

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