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# Neuroimaging Correlates of Everyday Action in Dementia

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## Abstract

The everyday, functional impairments associated with dementia remain poorly understood from a neuropsychological perspective. This study investigated relations between brain structure volumes and two measures of everyday action – caregiver questionnaire and direct assessment – in 57 participants with dementia. Results showed that caregiver ratings reflecting more functional impairment were strongly associated with smaller volumes of deep white matter. Direct assessment of everyday task performance in a subsample revealed relations between unique neurological substrates and discrete everyday action error types. Findings emphasize differences in functional assessment methods and highlight the role of white matter in functional deficits in dementia.

### Keywords

dementia; everyday action; executive control; episodic memory; white matter alterations

## Introduction

In dementia, impaired ability to perform daily activities is a primary diagnostic criterion (American Psychiatric Association, 2000), a determinant of healthcare services utilization, and highly associated with caregiver burden (Hope, Keene, Gedling, Fairburn, & Jacoby, 1998; Knopman, Kitto, Deinard, & Heiring, 1988; Noale et al., 2003; Severson et al., 1994). As the prevalence of dementia dramatically increases in the U.S., research on daily activities grows increasingly relevant (Green et al., 2004; Moore, Palmer, Patterson, & Jeste, 2007). Investigators have used the term everyday action to describe complex everyday behaviors (e.g., preparing a meal). Activities of daily living (ADL) is a related term to denote everyday activities that are necessary for independent living, which are subdivided into basic activities of daily living (BADL; e.g., bathing) and instrumental activities of daily living (IADL; e.g., money management). To advance the study of everyday action impairment in dementia, we investigated hypothesized associations between brain structure volumes and two measures of everyday action: ADL ratings by caregivers and a performance-based measure that allowed examination of specific errors made during completion of everyday tasks.

Current clinical characterizations of everyday action remain largely restricted to generic terms such as “problems in everyday activities” or “functional difficulties.” While such descriptions are useful broad indicators of an individual’s level of independence, they contrast with the more fine-grained characterizations of other cognitive domains. The most frequently used measures of everyday action are questionnaires that require caregivers to

rate a patient's level of independence in various BADLs and IADLs. The few studies of ADL measures that have included neuroimaging variables are all dependent on such measures. Some such studies have supported a relation between IADL ratings and measures of white matter (WM) integrity (Cahn et al., 1996; Boyle et al., 2003; Boyle, Paul, Moser, & Cohen, 2004; Farias, Mungas, Reed, Haan, & Jagust, 2004), whereas others have found associations with hippocampal volume (Cahn-Weiner et al., 2007). Researchers using positron emission tomography (PET) have demonstrated associations between functional performance ratings and a broad network of brain regions (Landau et al., 2009; Perneczky et al., 2008; Salmon et al., 2005). While the existing literature indicates possible relations between ADLs and multiple neuroimaging variables, their neuropsychological insights into everyday action may be greatly constrained by method. Although caregiver questionnaires offer brevity, efficiency, and low cost, they can be prone to bias (Arguelles, Loewenstein, Eisdorfer, & Arguelles, 2001; DeBettignies, Mahurin, & Pirozzolo, 1993; Rubenstein, Schairer, Wieland, & Kane, 1984). In addition, it is well known that complex tasks can be failed for a variety of reasons (see Kaplan, 1988, 1990), but data obtained from most caregiver questionnaires offer only a gross assessment of performance and provide no opportunity for detailed error analysis. If everyday action is multidimensional, as suggested by some authors (Giovannetti et al., 2008b; Hartmann, Goldenberg, Daumuller, & Hermsdorfer, 2005), global analysis of overall functioning may cloud meaningful associations between brain structures and specific functional deficits.

Another methodological approach to everyday action is the use of performance-based measures that provide direct assessment and detailed error analysis. Recent evidence using such measures has suggested that distinct patterns of everyday action impairment are associated with deficits in different cognitive processes (Bangen, 2010; Forde & Humphreys, 2002; Mioshi et al., 2007). Giovannetti and colleagues (2008) have suggested that errors of omission (i.e., failure to perform a task step) are distinct from those of commission (i.e., inaccurate execution of a step) (Giovannetti et al., 2008b), with omissions associated with reduced performance on tests of declarative memory (i.e., episodic and semantic) and commissions with executive dysfunction (Giovannetti et al., 2012; Giovannetti, Schwartz, & Buxbaum, 2007; Kessler, Giovannetti, & MacMullen, 2007). A third error category, off-task commissions[1], includes errors that involve the performance of an additional task step that is not pertinent to the task goal. This category has been identified as distinct from omissions and commissions, but its neuropsychological correlates are less clear (Giovannetti et al., 2008). A complete neuropsychological model of everyday action would ultimately be built upon an understanding of both cognitive processes and associated underlying neuropathology, but this has not yet been investigated.

The relations between specific everyday action errors and different cognitive processes in the Omission-Commission model suggest possible associations between error categories and brain structures. Considerable research has demonstrated the importance of hippocampus and cortical gray matter in the cognitive processes linked to omission errors, including information acquisition, storage, and retrieval (Squire, 1992; Mormino et al., 2009; Petersen et al., 2000; West, Coleman, Flood, & Troncoso, 1994; Querbes et al., 2009; Patterson et al., 2007). In contrast, the cognitive processes linked to commission errors – executive control – have been associated with WM variables. WM abnormalities seen on brain MRI are thought to disrupt the pathways connecting prefrontal cortex and subcortical structures (Alexander et al., 1986; Lamar et al., 2008), thereby impacting performance on executive cognitive measures (Price, Jefferson, Merino, Heilman, & Libon, 2005; Price et al., 2012; Seidel, Giovannetti, & Libon, 2012). Although WM has been structurally defined in the past only in

[1]The term "action addition errors" also has been used to refer to off-task commissions.

its core region (deep WM), the most peripheral WM areas bordering the cortex (surface WM) contain multiple short association fiber tracts connecting adjacent cortical gyri (U-fibers) (Oishi et al., 2008). Recent evidence (see Lee et al., 2009) supports a view of surface WM as serving functions distinct from deep and periventricular regions.

The relations between neuroimaging variables and everyday action performance remain unclear. This study analyzed relations between volumes of putatively intact regional WM, hippocampus, and cortical gray matter and two measures of everyday action: a frequently used ADL measure, caregiver ratings, and a direct assessment that allowed for quantification of discrete error categories. Regarding relations between specific structures and ADL ratings, we expected poorer ratings would be related to decreasing volumes of multiple brain structures. Hypotheses regarding performance-based tests were based on the Omission-Commission model. We hypothesized that greater numbers of omission errors would be related to decreasing volumes of hippocampus and cortical gray matter, and greater numbers of on-task commission errors would be related to decreasing volumes of deep and periventricular WM. We did not have explicit predictions regarding associations between neuroimaging variables and off-task commissions, because this error type remains incompletely understood.

## Method

### Participants

Participants were recruited from an outpatient dementia evaluation program at the University of Medicine and Dentistry in New Jersey (UMDNJ) between 2002 and 2007. Clinical assessment included evaluation by a geriatrician and a neuropsychologist, brain MRI, and laboratory studies to evaluate reversible causes of cognitive impairment. The dementia sample was diagnostically heterogeneous, with approximately 50% of participants carrying a clinical diagnoses of probable Alzheimer's disease (AD; NINCDS-ADRDA criteria) (McKhann et al., 1984), 40% possible ischemic vascular dementia (VaD; California Criteria) (Chui et al., 1992), and 10% mixed dementia. Participants with VaD presented with a slow, progressive course of cognitive decline and evidence of extensive white matter changes on MRI, suggestive of small-vessel disease; participants with large-vessel cortical strokes (i.e., multi-infarct dementia) were not included. Clinical diagnosis was not analyzed or used as a grouping variable because of growing evidence of gray matter/vascular pathology overlap (Fein et al., 2000; Salat et al., 2010) and the questionable validity of consensus panel diagnostic criteria for VaD (Wiederkehr, Simard, Fortin, & van Reekum, 2008). Participants were on a stable and maximum dose of acetylcholinesterase (AChE) inhibitors and/or memantine. Criteria for exclusion included cortical infarcts on MRI, cognitive changes with sudden onset or stepwise decline, chronic major depressive illness, current severe anxiety disorder or psychotic disorder, severe nervous system infections, metabolic disorders, tumors, major head trauma, recurrent sports-related concussion, seizure disorders, and English as a second language. All historical information regarding inclusion and exclusion criteria was gathered from a knowledgeable family member.

All participants ($N$ =57) underwent an MRI of the brain and had caregiver-ratings of ADL/IADL functioning (Lawton & Brody, 1969). Twenty-eight participants also completed a direct assessment of everyday action (Naturalistic Action Test, NAT; Schwartz et al., 2002; NAT subsample). Demographic characteristics of the total sample and NAT subsample did not differ significantly in terms of age, education, or scores on the Mini-Mental State Examination (Folstein, Folstein, & McHugh, 1975; MMSE) and Geriatric Depression Scale (GDS; Yesavage et al., 1982) (see Table 1). The participants were predominantly female (Total sample, 81%; NAT subsample, 71%), with mild to moderate dementia severity, and GDS scores within the normal range. Data from this sample have been reported in prior

publications (Price et al., 2012; Price et al., under review) and were collected in compliance with regulations of the UMDNJ Institutional Review Board.

## Caregiver ratings

BADL and IADL questionnaires (Lawton & Brody, 1969) were administered to caregivers as part of the clinical evaluation. Caregiver ratings were reviewed with an examiner prior to final score determination. The BADL questionnaire included 6 items: toileting, feeding, dressing, grooming, ambulation, and bathing. Items were assigned a score of 1 (complete independence) or 0 (requires assistance). The IADL questionnaire included 8 items: telephone use (0–3), shopping (0–1), food preparation (0–1), housekeeping (0–4), laundry (0–2), transportation use (0–3), medication management (0–1), and financial management (0–2). The highest score for each item indicated complete independence, with gradations of lower levels of independence varying by item.

## NAT procedures

Everyday action performance was directly assessed by the Naturalistic Action Test (NAT) (Schwartz et al., 2002), which requires participants to perform everyday tasks with little guidance from the examiner. The NAT is a standardized and published measure of everyday action with sound psychometric properties (Buxbaum, Schwartz, & Montgomery, 1998; Schwartz et al., 2003; Schwartz et al., 1999; Schwartz et al., 1998; Schwartz et al., 2002). Several studies have reported strong validity and reliability for adults over age 60 (Buxbaum et al., 1998; Giovannetti et al., 2007; Schwartz et al., 1999; Sestito, Schmidt, Gallo, Giovannetti, & Libon, 2005; T.G., unpublished data). Inter-rater reliability for NAT scoring is excellent for error scores (median kappa = .95) (Kessler, 2010; Schwartz et al., 2003).

NAT instructions and scoring are systematized and described in detail in the test manual (Schwartz et al., 2003). Participants sit at a U-shaped table upon which all task-necessary items are placed in standardized positions. The NAT involves three independent trials of increasing complexity: 1) prepare toast with butter and jelly and coffee with cream and sugar; 2) wrap a gift with related distracter objects present in the array (e.g., stapler); and 3) pack a lunchbox with a sandwich, snack, and a drink and a schoolbag with supplies for school, while several of the necessary objects (e.g., knife) are stored out of view in a drawer that contains additional, potentially distracting objects (e.g., spatula).

## NAT scoring procedures

NAT performance was videotaped for subsequent error coding by 2 independent raters who had undergone reliability evaluations. This method demonstrated 98.77% agreement in coding NAT errors (Cohen's $\kappa = .88$, almost perfect agreement) (Kessler, 2010). Occasional disagreements between coders were resolved following discussion and review of videotape with a third, senior coder (TG). Coders were blind to neuroimaging data.

In accordance with guidelines for comprehensive error score determination (CES; Schwartz et al., 2003; Schwartz et al., 1998), errors of the following types were recorded: omission, sequence (anticipation-omission and reversal), perseveration, substitution, and off-task errors (addition). Errors of gesture substitution, tool omission, spatial mis-estimation, and quality, which occurred infrequently in this and prior studies (Giovannetti et al., 2008b), were grouped under the error type "other." See Table 2 for details of each error type.

Two approaches to grouping NAT error types into categories for analysis have been used in past published work. Studies by Schwartz and colleagues (e.g., Schwartz, 1998) dichotomized errors into two categories: omissions and commissions, with the commission category including all non-omission error types. However, principal component analyses

reported by Giovannetti et al. (2008b) suggested further dividing the commission category according to the task-relevance of the error. Under this approach, those commissions that remain within task parameters (sequence, perseveration, substitution, and other errors) represent a separate category from off-task errors (additions), which represent behavior outside of task parameters. Both approaches to grouping NAT errors were used in the present study.

## Neuroimaging Variables

MRI brain scans were acquired using 1.5 Telsa GE, Signa, and Genesis systems. Anatomic volumetrics were acquired from T1-weighted three-dimensional sequences, reconfigured to 112 to 120 gapless, 2.4 mm images allowing for image reconstruction into any plane. Volumetrics for WM hyperintensities were acquired using clinical 2D Fluid Attenuated Inversion Recovery (FLAIR) protocols. Neuroimaging procedures also are described in prior publications (Price et al., 2012; Price et al., under review).

Reliability of structural volumetrics was calculated with the FMRIB Software Library (FSL, http://www.fmrib.ox.ac.uk/fsl/). FSL was used to overlap two rater masks, calculate their volumes, and determine volume of overlap, percentage difference, and the Dice Similarity Coefficient (DSC; Smith et al., 2004; Woolrich et al., 2009). The DSC takes into account the 3D spatial orientation of the segmented mask by analyzing the percentage of volume overlap between masks. DSC values greater than 0.7 indicate excellent agreement between two raters (Zijdenbos, Dawant, Margolin, & Palmer, 1994). Rater agreement was evaluated before proceeding with full database measurement.

**Intracranial Volume—**Supervised processing using the Brain Extraction Tool (BET) from FSL (Smith, 2002) was used to create a volume measure of the dural brain compartment (including brain stem and cerebellum) and cerebral CSF, which was used to determine intracranial volume. Intracranial volumes were obtained to adjust structure volumes for variations in head size.

**Cortical Gray Matter—**Cortical gray matter volume was calculated by subtracting WM in the surface region (detailed below) from a volume measure of surface tissue (i.e., gray matter and WM) and CSF.

**Hippocampus—**Hippocampal volumes were manually segmented by two trained tracers using ITK-SNAP (Paul et al., 2006; Yushkevich et al., 2006; http://www.itksnap.org), which allows the target structures to be visualized in all three planes and saved as 3D binary masks. Hippocampal volumes were traced using guidelines from Duvernoy (1997) and showed excellent inter- and intra-rater spatial overlap and good volume reliability during training (inter-rater, $n = 10$: grand DSC = 80 ± .02; intra-rater, n = 22: grand DSC = .81 ±.05; all $p < .001$).

**Lateral Ventricles—**Lateral ventricular volumes were not specifically analyzed in the present study, but were essential for determination of the periventricular WM region. Lateral ventricular volumes were calculated by trained raters using a semi-automated segmentation method in ITK-SNAP (Yushkevich et al., 2006). Intra- and inter-rater spatial overlap and reliability were excellent (inter-rater grand DSC, $n = 10$: .92 ± .04; intra-rater grand DSC, $n = 20$: .96 ± .03; all $p < .001$).

**White Matter—**Total WM volume was determined with The Brain Extraction Tool (BET) from FSL, which aided extraction of brains from T1-weighted brain MRIs with brain center of gravity and fractional intensity revised by raters to achieve best extraction. BrainSuite9

and rater reviews for quality provided prosencephalon masks (minus cerebellum and brainstem). Re-extraction was completed if regions of subcortical gray matter were included in the final white matter mask. Estimated total white matter volume in $mm^3$ was adjusted for white matter lesions as described below.

**White Matter Lesions—**WM hyperintensities, indicating abnormalities (i.e., leukoaraiosis, LA), were measured using Image J (Abramoff, Magelhaes, & Ram, 2004; http://rsbweb.nih.gov/ij/docs/index.html) and a locally developed ImageJ macro (Towler, 2011). Reliability was demonstrated on an initial set of 15 MRIs. Spatial overlap was high in all inter- and intra-rater reliability comparisons of WM hyperintensity segmentations (Inter-rater range: DSC = .84–.93; Intra-rater range = .80–.83; DSC mean = .84 ± .12). Volumes of repeated WM hyperintensity segmentations demonstrated reliability (ICC = .96, $p < 0.001$). Analyses used a variable reflecting intact WM determined by subtracting the volume of hyperintensities from total WM volume.

**Regional Delineation of White Matter—**WM and WM hyperintensity volume were obtained for three separate regions defined as follows: periventricular – 5 mm out from the lateral ventricles; surface – 5 mm in from the cortex; and, deep – the region left in between. Regional delineation of WM was created using WM binary masks acquired from ImageJ, ventricle masks from ITK-SNAP, a prosencephalon mask from BrainSuite-9 (Shattuck & Leahy, 2000), and a locally developed script using fslmaths. The three separate regions served as individual binary masks that were multiplied by the WM volume mask to compartmentalize WM and WM hyperintensities in those regions. Although it is more common to analyze measures of WM hyperintensities (i.e., LA), we constructed variables reflecting putatively intact WM volume in deep and periventricular regions by subtracting the volume of hyperintensities from total WM volume. We chose this strategy for our analysis, because we were interested in comparing white versus gray matter structures in relation to measures of everyday functioning and wanted measures of all brain regions on the same metric.

### Data management

Neuroimaging variables were evaluated for consistency with the literature (Cosgrove, Mazure, & Staley, 2007; Courchesne et al., 2000). No implausible values or extreme outliers were identified in brain structure volume, ADL, or NAT error variables. Substantial skewness in NAT omission and NAT off-task commission error variables was corrected using a log transformation. Six participants who performed the NAT were not videotaped; therefore, detailed errors in performance could not be coded and these participants were excluded from analyses.

### Analyses

Pearson correlations were performed to examine the relations between brain structure volumes adjusted for intracranial volume, caregiver ratings of BADL and IADLs, and NAT errors by category. When simple, bivariate analyses showed multiple significant correlations, hierarchical multiple regression analyses were performed to evaluate the study hypotheses by examining the combined effects of multiple imaging predictors of performance.

## Results

### Summary Statistics

Summary statistics for everyday action variables (Table 3) and neuroimaging variables (Table 4) are presented below. ADL ratings and neuroimaging variables did not differ

between participants who performed the NAT and the rest of the sample ($t < |1.80|$, $p > .05$ for all), with the exception of slightly larger hippocampi in the sample that performed the NAT ($t = -2.02$, $p = .05$).

### Relations between neuroimaging variables and caregiver ratings

A significant positive correlation was observed between deep WM volumes (WM-Deep) and IADL ratings, suggesting greater volumes of WM-Deep are associated with better IADL ratings (Table 5). Relations of IADL ratings to volumes of periventricular WM (WM-Pven), cortical gray matter, and hippocampus were weak or near zero. Correlations between brain structure volumes and BADL ratings were generally weaker and not significant.

We considered running partial correlation analyses with BADL/IADLs and neuroimaging variables, controlling for MMSE, but we did not think that it made conceptual sense given that functional abilities and dementia are highly overlapping constructs. In fact, relations between MMSE and BADL/IADLs were moderate in strength (MMSE x BADL: $r = .46$; MMSE x IADL: $r = .43$). Correlation analyses between neuroimaging variables and MMSE suggested another reason against partial correlations – the pattern of relations between neuroimaging variables and MMSE was quite different than the pattern of relations between neuroimaging variables and BADL/IADL ratings reported in Table 5 (MMSE x WM-Deep: $r = .18$, $p = .17$; MMSE x WM-Peri: $r = -.12$, $p = .40$; MMSE x Cortical Gray: $r = 0.03$, $p = .81$; MMSE x Hippocampus: $r = .25$, $p = .06$). Therefore, the correlations reported in Table 5 appear to be specific to functional abilities and should not be interpreted as simply reflecting relations between brain volumes and gross dementia severity.

### Relations between neuroimaging variables and NAT error categories

Correlation analyses were performed first with NAT error categories as most commonly dichotomized (omissions vs. total commissions). Total commission errors showed a significant strong relation to deep WM volume (WM-Deep), such that more commissions were associated with smaller volumes of WM-Deep (Table 6). Commission errors also showed a moderate relation to gray matter structures, with more commissions significantly associated with smaller hippocampal volumes. A different pattern of relations was noted for omission errors. Omission errors were most strongly related to hippocampal volume in the expected direction, but the association was not statistically significant. A significant positive correlation was observed between periventricular WM volumes (WM-Pven) and omissions, suggesting that more errors were associated with greater volumes of WM-Pven[2].

Commission errors were significantly associated with multiple neuroimaging variables. Consequently, we performed a hierarchical regression model to evaluate the hypothesis that commissions would be most strongly associated with deep white matter. Gray matter structures (cortical gray matter and hippocampus) were entered into the model first; then, WM-Deep volume was entered in a separate block to determine whether deep WM explained significantly more variance. As shown in Table 7, deep WM volume explained 31% of the variance in total commission errors above and beyond cortical gray matter and hippocampal volume. In a full model predicting 50% of the variance in total commission errors, both deep WM and cortical gray matter emerged as significant predictors, with hippocampal volume trending towards significance.

[2]MMSE was comparably associated with both omission errors ($r = -.41$, $p < .05$) and commission errors ($r = -.48$, $p < .05$); therefore, the different pattern of relations to neuroimaging variables between these error types cannot be explained by the possibility that one error type is more or less strongly associated with gross dementia severity.

Correlation analyses with neuroimaging variables were also performed after dividing commission errors into on-task and off-task commission error categories (see Table 8). On-task commission errors were moderately associated with volumes of WM-Deep, such that more on-task commissions were related to smaller volumes of WM-Deep, although this relation did not reach statistical significance ($p < .10$). An association of comparable strength ($p < .10$) also was observed between WM-Pven and on-task commission errors; however, in contrast to expectations, more on-task errors were associated with greater volumes of WM-Pven. Off-task commission errors showed a moderate but nonsignificant ($p < .10$) relation to deep WM as well as stronger and significant relations to volumes of gray matter structures (cortical gray and hippocampus).

Off-task commissions were associated with more than one neuroimaging variable in the expected direction. Consequently, a hierarchical regression model was performed to evaluate the relative contribution of white and gray matter structures. Gray matter structures (cortical gray matter and hippocampus) were entered into the model first; then, WM-Deep volume was entered in a separate block. As shown in Table 9, deep WM volume explained 14% of the variance in off-task commission errors above and beyond cortical gray matter and hippocampal volume. In a full model predicting 46% of the variance in off-task commissions, both cortical gray matter and deep WM reached significance, with hippocampal volume showing a trend towards significance[3].

## Discussion

To improve our understanding of the neuropsychology of everyday action impairment in dementia, we examined the relation of everyday functioning to neuroimaging variables in older adults with dementia, considering associations between regional WM, hippocampus, and cortical gray matter volume and both caregiver ratings on a commonly used ADL questionnaire and distinct error categories on a performance-based measure. We expected poorer IADL ratings by caregivers would be related to decreasing volumes of multiple brain structures, but our results showed that better ratings were strongly related to larger volumes of deep WM. In a subsample of participants, analyses of error categories partially supported our predictions that increasing omission errors would be related to decreasing volumes of hippocampus and cortical gray matter, and increasing on-task commission errors would be related to decreasing volumes of deep and periventricular WM. Greater numbers of omission errors were associated with smaller hippocampal volume ($r = -.20$), although this relation was not statistically significant. Consistent with our prediction, a greater total number of commission errors (inaccurate step execution) was related to deep WM, but, contrary to prediction commissions also were positively associated with cortical gray matter and hippocampal volumes. Analyses of commission errors by subtype according to task-relevance showed that greater numbers of on-task commission errors (inaccurate execution of steps that are within task parameters) were associated in the expected direction only to smaller deep WM volume ($p < .10$), which in a prior study on the same sample was differentially associated with mental control/working memory (Price et al., under review). By contrast, off-task commissions (performance of steps inconsistent with task parameters) were related to more structures, including cortical gray matter ($r = -.49$), hippocampal ($r = -.39$), and deep WM ($r = -.33$) volumes. These findings extend our understanding of everyday action impairment in dementia in several important ways.

[3]MMSE was significantly and strongly associated with on-task commissions ($r = .52$, $p < .05$), but was not significantly associated with off-task commissions ($r = -.11$). As mentioned earlier in the paper, MMSE was associated with only one of the neuroimaging variables – hippocampus ($r = .25$, $p = .06$). Therefore, to examine whether the different relations between on-task/off-task commissions and the hippocampus may be explained by gross dementia severity, partial correlations (controlling for MMSE) were performed. These results did not meaningfully change the pattern of findings reported in Table 8 (on-task commissions x hippocampus: $r_p = -.03$; off-task commissions x hippocampus: $r_p = -.37$, $p = .05$).

That both a questionnaire measure and performance-based measure (i.e., on-task commissions) were associated with WM is consistent with the literature suggesting the special importance of executive functions in everyday functioning. Several studies have reported relations between WM abnormalities and concurrent and future performance ratings in depression, VaD, and community samples (Cahn et al., 1996; Cahn-Weiner et al., 2007; Boyle et al., 2004, 2003; Farias et al., 2004; Pantoni et al., 2006). To our knowledge, this is the first study to identify a relation between performance-based functional assessment and integrity of a *specific* region of WM. DeCarli, Fletcher, Ramney, Harvey, and Jagust (2005) found WM pathologies in different regions to be highly related and therefore consideration by subregion to be of little value. Our data indicating differential associations between regional WM changes and everyday action suggest this approach is still worth considering, and that deep WM, which allows for reciprocal and downwardly projecting pathways linking the dorsolateral prefrontal cortex, basal ganglia, and thalamus, may be essential for the specific executive processes that are crucial for everyday functioning (also see Price et al., under review).

Our findings are consistent with past studies showing discrepancies between caregiver ratings and performance-based methods of assessing everyday functioning (DeBettignies et al., 1990; Zannetti et al., 1999). Our analyses of caregiver ratings support the broad notion that specific brain regions are related to the performance of everyday tasks, and they emphasize regions that support executive functions. These analyses also reveal the limitations of gross measures of dependence/independence derived from questionnaires to elucidate the assemblage of brain regions associated with the breakdown of everyday action. These gross measures simply are unable to map specific action difficulties or errors to distinct brain systems.

Performance-based methods support the importance of executive dysfunction and WM changes but suggest they do not account for all aspects of everyday functional impairment. Omission errors, the most frequent error type among dementia patients, were most strongly associated with hippocampal volumes (although not statistically significant) and off-task commission errors were associated with both hippocampal and cortical volumes. Thus, episodic memory (hippocampus) and representation of semantic knowledge (cerebral cortex) likely play a critical role in everyday action impairment among people with dementia, yet relative to executive deficits, these processes have been understudied in the everyday action literature. Taken together, these results support the proposed model of everyday action that distinguishes omissions from commissions and formed the basis for our hypotheses (Giovannetti et al., 2008b; Giovannetti et al., 2007; Giovannetti et al., 2012; Giovannetti et al., 2006; Kessler et al., 2007). These findings are also consistent with the results of a recent paper on performance-based action errors that was published after completion of this study. Bailey, Kurby, Giovannetti, and Zacks (in press) showed specific relations between omissions and medial temporal lobe volumes and between on-task commissions and dorsolateral prefrontal cortex volumes; off-task commissions were significantly associated with both volumes of the anterior cingulate cortex and posterior cortex. Bailey et al. did not examine relations between errors and white matter in the brain.

Our findings, along with the results of Bailey et al. (in press), refine the Omission-Commission model by suggesting that off-task errors should be examined separately from other commission errors in future action research. Off-task commission errors have not been related to specific cognitive tests in past studies. Evidence from this study that they are associated with multiple brain structures, including both white and gray matter structures, suggests they may be best explained in terms of multiple cognitive processes. Such errors may reflect diminished inhibition and pull to tangential environmental stimuli (executive deficits), loss of set (executive deficits), and/or degraded knowledge of task steps

(declarative memory deficits; Giovannetti et al., 2008b). Given the role of the hippocampus in episodic memory, the present findings suggest episodic memory may, in combination with executive functions, be important in the production of off-task errors. Failure to recall the task goal or premature decay of the action plan could allow stimulus-driven behavior to emerge, a behavior which is most often associated with impaired executive control. More broadly, the finding underscores the profit that can be realized with an analysis of process and errors whether in everyday action or any other neuropsychological test.

This study was not without limitations. While the main sample in which BADL/IADL ratings were examined was sufficiently powered to detect small to moderate effects, the smaller sample size used in analyses of NAT errors ($n$ = 28) sacrificed significant power and was able to capture only moderate to large effects. Small sample size and restricted range could have contributed to spurious correlations observed between periventricular WM and NAT error categories. Also, although our measures of WM were quite sophisticated relative to the existing literature on neuroimaging correlates of everyday action, they do not capture the non-volumetric abnormalities revealed by factional anisotropy (FA) measured using DTI. Studies have demonstrated that FA in normal appearing WM is variable and predicted by vascular risk factors (Lee et al., 2009). Future studies may also benefit from consideration of frontal lobe thickness as well as WM abnormalities when examining relations between everyday action and brain structures associated with executive functions.

This study also had numerous strengths. WM in our study was examined using a volumetric variable, in contrast to studies of IADLs that have relied on visual ratings of hyperintensities (e.g., Farias, Mungas, Reed, Haan, & Jagust, 2004), a method that often produces categorical data and demonstrates variable inter-rater reliability (Enziner, Fazekas, Ropele, & Schmidt, 2007). WM was examined regionally, using a variable that reflected abnormalities while also accounting for the volume of normal-appearing WM. In contrast to prior investigations of IADL-brain relations, this study included a performance-based measure of everyday action that facilitated the examination of associations with specific error categories. Another important feature of our study was the inclusion of a heterogeneous dementia sample, including both patients diagnosed with AD, VaD, and mixed (AD/VaD) clinical features. This sample afforded a greater range of neuroimaging findings with which to examine patterns of performance and is in line with recent trends showing a greater appreciation of the neuropathologic heterogeneity of dementia (see van Norden et al., 2012). Given the finding that both gray and WM structures contribute to everyday action performance in a dementia sample, this study supports consideration of the full range of neuropathologic heterogeneity in studies examining behavior in this population.

This study sought to contribute to an understanding of brain-behavior relations in the performance of everyday tasks. By investigating relations of brain structure volumes to both caregiver ratings and a direct assessment of everyday action, we have added to the literature showing the relevance of WM integrity to functional abilities in a heterogeneous dementia sample. We also have provided information regarding the role of gray matter structures in everyday functioning. Our findings support a model of everyday action describing the cognitive processes and substrates underlying different patterns of performance, with on-task commission errors associated with WM integrity and omission errors and off-task commissions related to a different neural substrate – gray matter structures. These findings underscore the importance of a multi-method approach to clinical functional assessment and highlight the potential for performance-based assessments to identify specific functional deficit patterns that may be effectively treated with targeted intervention strategies in the future.

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## Table 1

Demographic Characteristics of the Total Sample and NAT Subsample

| | Mean (SD) | | Range | |
|---|---|---|---|---|
| | **Total Sample (*N* = 57)** | **NAT Subsample (*n* = 28)** | **Total Sample (*N* = 57)** | **NAT Subsample (*n* = 28)** |
| Age | 80.01 (6.01) | 80.39 (5.31) | 65–91 | 72–91 |
| MMSE | 22.07 (3.13) | 22.68 (3.30) | 14–28 | 16–28 |
| Education | 11.84 (2.04) | 12.36 (2.23) | 6–16 | 8–16 |
| GDS | 2.98 (2.98) | 2.71 (3.14) | 0–12 | 0–12 |

*Note*. NAT Subsample includes 28 participants from the total sample who were administered the Naturalistic Action Test, a performance-based measure of everyday action. MMSE = Mini-Mental State Examination; GDS = Geriatric Depression Scale.

**Table 2**

NAT Error Categories

| Error Category | | Definition | Examples From Toast and Coffee and Present-Wrapping Tasks |
|---|---|---|---|
| Omission | | a step or subtask is not performed | does not add sugar to coffee |
| On-task Commission | Substitution | semantically related or perceptually similar alternate object used in place of target object | spreads butter on toast with spoon instead of knife |
| | Sequence | a task step is performed out of order, such that the performance of an earlier task step is omitted (anticipation-omission); two steps are performed in reverse order (reversal) | applies butter on bread, without first toasting bread; applies jelly on bread, then applies butter |
| | Perseveration | a step or subtask is performed more than once, performed repetitively, or for an excessive amount of time | spreads butter on bread repeatedly or for an extended period of time (>19 seconds) |
| | Other | gesture substitution, tool omission, spatial misestimation, and quality errors | misorients wrapping paper with respect to the gift |
| Off-task Commission (Additions) | | behavior outside of task parameters | eats toast; uses school supplies |

## Table 3

Summary Statistics for Everyday Action Variables: Caregiver Ratings and NAT Errors

| | Mean (SD) | Range |
|---|---|---|
| **Caregiver Rating Variables (Total Sample *N* = 57)** | | |
| BADL | 4.70 (1.58) | 1–6 |
| IADL | 10.07 (4.76) | 1–17 |
| **NAT Error Variables (NAT Subsample *n* = 28)** | | |
| Omissions | 5.61 (5.70) | 0–20 |
| Commissions | 11.18 (7.47) | 2–29 |
| On-task Commissions | 6.71 (4.28) | 2–15 |
| Off-task Commissions | 2.68 (3.03) | 0–12 |

*Note*. BADL = basic activities of daily living; IADL = instrumental activities of daily living. NAT Subsample includes 28 participants from the total sample who were administered the Naturalistic Action Test, a performance-based measure of everyday action.

## Table 4

Summary Statistics for Neuroimaging Variables: Total Sample and NAT Subsample

| | Mean (SD) | | Range | |
|---|---|---|---|---|
| | **Total Sample (*N* = 57)** | **NAT Subsample (*n* = 28)** | **Total Sample (*N* = 57)** | **NAT Subsample (*n* = 28)** |
| Intracranial | 1,333,508 (115,918) | 1,325,002 (113,128) | 990,262–1,604,863 | 990,262–1,465,182 |
| Cortical Gray | 455,927 (30,634) | 462,642 (27,083) | 392,346–511,969 | 408,252–497,849 |
| Hippocampus | 3,735 (1,071) | 3,994 (985) | 1,464–6,643 | 1,697–5,792 |
| WM | 322,171 (39,869) | 319,725 (42,106) | 201,220–431,440 | 201,220–382,057 |
| LA % of Deep WM | 5.50 (0.82) | 4.63 (0.93) | 0.67–26.36 | 0.74–17.97 |
| LA % of Pven WM | 25.20 (2.18) | 21.23 (2.23) | 1.74–72.11 | 1.74–53.34 |

*Note*. NAT Subsample includes 28 participants from the total sample who were administered the Naturalistic Action Test, a performance-based measure of everyday action. Brain structure volumes are in $mm^3$ unless otherwise noted. WM = white matter; LA = leukoaraiosis; Pven = periventricular.

**Table 5**

Correlations (r values) Between Neuroimaging Variables and Caregiver Ratings (N = 57).

| | BADL | IADL |
|---|---|---|
| WM-Deep | .19 | .30* |
| WM-Pven | −.03 | .05 |
| Cortical gray | −.01 | −.13 |
| Hippocampus | .07 | −.07 |

*Note*. Brain structure volumes were adjusted for intracranial volume. WM = white matter; Pven = periventricular.

* $p < .05$.

## Table 6

Correlations (r values) Between Neuroimaging Variables and Omission and Total Commission Errors in the NAT Subsample (n =28).

| | Omissions | Total Commissions |
|---|---|---|
| WM-Deep | −.04 | −.52** |
| WM-Pven | .40* | .25 |
| Cortical gray | −.01 | −.34† |
| Hippocampus | −.20 | −.37* |

*Note*. Brain structure volumes were adjusted for intracranial volume. WM = white matter; Pven = periventricular.

** $p < .01$.

* $p \leq .05$.

† $p < .10$.

## Table 7

Hierarchical Regression Models for Brain Structures Predicting Total Commission Errors in the NAT Subsample (n = 28).

| | *B* | *SE B* | β |
|---|---|---|---|
| Step 1 | | | |
| Constant | 57.25 | 25.59 | |
| Cortical gray | −104.43 | 75.74 | −.26 |
| Hippocampus | −3143.65 | 1940.82 | −.30 |
| Step 2 | | | |
| Constant | 98.98 | 23.26 | |
| Cortical gray | −125.69 | 61.10 | −.31* |
| Hippocampus | −3100.84 | 1559.15 | −.30† |
| WM - Deep | −237.49 | 61.86 | −.55** |

*Note*. Brain structure volumes were adjusted for intracranial volume. WM = white matter. $R^2$ = .20 for Step 1 ($p$ = .06); $\Delta R^2$ = .31 for Step 2 ($p$ < .01); $F$ (3, 27) = 8.12 for overall model, $p$ < .01.

** $p$ < .01.

* $p \leq .05$.

† $p$ < .10.

**Table 8**

Correlations Between Brain Structure Volumes and NAT Commission Error Subtypes (n =28).

| | On-Task Commission | Off-task Commission |
|---|---|---|
| WM-Deep | −.36† | −.33† |
| WM-Pven | .33† | −.04 |
| Cortical Gray | −06 | −.49** |
| Hippocampus | −.14 | −.39* |

*Note*. Brain structure volumes were adjusted for intracranial volume. WM = white matter; Pven = periventricular.

** $p < .01$.

* $p < .05$.

† $p < .10$.

## Table 9

Multiple Regression Models for Brain Structures Predicting Off-Task Commission Errors

| | *B* | *SE B* | β |
|---|---|---|---|
| Step 1 | | | |
| Constant | 3.39 | 1.03 | |
| Cortical gray | −7.33 | 3.04 | −.42* |
| Hippocampus | −124.07 | 77.91 | −.28 |
| Step 2 | | | |
| Constant | 4.63 | 1.06 | |
| Cortical gray | −7.97 | 2.77 | −.45** |
| Hippocampus | −122.80 | 70.76 | −.27† |
| WM - Deep | −7.05 | 2.80 | −.38* |

*Note*. Brain structure volumes were adjusted for intracranial volume. WM = white matter. $R^2$ = .31 for Step 1 ($p$ = .01); $\delta R^2$ = .14 for Step 2 ($p$ = .02). $F$ (3, 27) = 6.67 for overall model, $p$ < .01.

** $p$ < .01.

* $p$ < .05.

† $p$ < .10.