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Poor awareness of IADL deficits is associated with reduced regional brain volume in older adults with cognitive impairment

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ABSTRACT

Performance of instrumental activities of daily living (IADLs) can become compromised in older adults with mild cognitive impairment (MCI). Patients' level of insight into their everyday functioning varies both amongst individuals and across domains assessed, with some individuals exhibiting complete unawareness of deficits. The current cross-sectional study examined the neuroanatomical substrates of self-awareness in order to help explain the variability in this phenomenon in older adults across a continuum of cognitive impairment. Eighty-five participants (ages 54–88, mean age = 73 years, 57% female, 89% Caucasian) diagnosed with MCI or mild probable dementia underwent structural magnetic resonance imaging. Level of self-awareness was assessed by calculating the discrepancy between objective and subjective performance across six IADLs (Financial Management, Driving, Grocery Shopping, Nutrition Evaluation, Medication Management, and Telephone Use). Over-estimation of current abilities occurred in 13–31% of the sample depending on which IADL was evaluated. Poor awareness was significantly related to reduced volume in the bilateral medial prefrontal cortex, middle and posterior cingulate cortex, right insular cortex, and cerebellum. No associations were found with total white matter lesion load. These findings were broadly consistent across all functional domains assessed, supporting the theory that cortical midline and cerebellar structures are involved in self-referential processing across a variety of different cognitive and behavioral skills. Longitudinal studies are needed to confirm this association.

1. Introduction

Unawareness of deficits occurs in 50–80% of individuals with Alzheimer's disease (AD) (Reed et al., 1993; Starkstein et al., 2006; Vogel et al., 2005) and 10–60% of those with mild cognitive impairment (MCI) (Okonkwo et al., 2009; Okonkwo et al., 2010; Starkstein et al., 2006; Steward et al., 2019; Tabert et al., 2002). Patients' level of insight can range from a mild underreporting of symptoms to a complete lack of awareness of their disease process (Okonkwo et al., 2010; Reed et al., 1993) and may vary according to the specific domain that patients are asked to self-evaluate (Clare et al., 2011; Okonkwo et al., 2009; Steward et al., 2019). Poor self-awareness predicts conversion to dementia (Spalletta et al., 2014; Tabert et al., 2002) and thus has become an important clinical symptom to understand in those with MCI.

Thus far, few studies have examined the neuroanatomical substrates of unawareness during the MCI stage of disease progression. Structural magnetic resonance imaging (MRI) studies in this population have found that poor insight into memory deficits is associated with reduced gray matter (GM) volume in primarily right hemispheric lateral and medial frontal regions (e.g., pars triangularis of the inferior frontal gyrus, medial frontal gyrus, and anterior cingulate cortex [ACC]) (Ford et al., 2014; Spalletta et al., 2014; Yi et al., 2016); left hemispheric inferior, middle, and superior temporal gyri (Ries et al., 2012; Spalletta et al., 2014); and bilateral cerebellar regions (Ford et al., 2014; Spalletta et al., 2014). In contrast, another study found no relationship between GM volume and unawareness of memory deficits in those with MCI; however, it should be noted that this study had a particularly small sample size (Ries et al., 2007). In dementia populations, impaired self-awareness is consistently correlated with reduced volume in the orbitofrontal cortex (OFC), ventromedial prefrontal cortex (vmPFC), superior frontal gyri, ACC, middle cingulate cortex (MCC), anterior insula, and cerebellar vermis (Amanzio et al., 2016; Cosentino et al., 2015; Fujimoto et al., 2017; Guerrier et al., 2018; Rosen et al., 2010; Shany-Ur et al., 2014). Thus far no studies have examined the relationship between white matter lesions (WML) and self-awareness of deficits in those with neurodegenerative disease, despite a strong

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relationship between increased WML burden and cognitive/functional decline in older adults (Abraham et al., 2016; Smith et al., 2008; Wardlaw et al., 2015; Yoshita et al., 2006) and evidence of a relationship between white matter integrity and impaired self-awareness following stroke (Brookes et al., 2014; Lunven et al., 2015; Prigatano et al., 2011; Venneri, 2004).

Functional neuroimaging studies of individuals with MCI and AD have generally confirmed the role of the aforementioned regions in accurate self-appraisal. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies have reported a significant relationship between impaired self-awareness and hypometabolism or hypoperfusion in the prefrontal cortex (Perrotin et al., 2015; Salmon et al., 2006; Vogel et al., 2005; Yi et al., 2016), cingulate cortex (Guerrier et al., 2018; Hanyu et al., 2008; Nobili et al., 2010; Perrotin et al., 2015; Vannini et al., 2016), medial temporal cortex (Perrotin et al., 2015; Salmon et al., 2006), left parietal lobule (Nobili et al., 2010; Yi et al., 2016), and the hippocampus (Vannini et al., 2016). Functional MRI (fMRI) techniques have revealed that poor self-appraisal is associated with reduced hemodynamic response in the medial prefrontal cortex (mPFC) (Amanzio et al., 2011; Ries et al., 2007; Zamboni et al., 2013), left anterior temporal regions (Zamboni et al., 2013), posterior cingulate cortex (PCC) (Ries et al., 2007), right parietal regions, striatum, and cerebellum (Amanzio et al., 2011). In addition, those with poor insight have reduced connectivity between the mPFC and other regions of the PFC, cingulate cortex, striatum, hippocampus, and cerebellum (Ries et al., 2012). Similarly, reduced connectivity has also been found between the PCC and regions in the OFC and parietal lobule (Vannini et al., 2016).

Performance in instrumental activities of daily living (IADLs) may become subtly compromised in older adults with MCI (Jekel et al., 2015). Accordingly, discrepancy between objective and subjective assessment of performance across IADLs may be useful to detect and measure self-awareness. However, only one previous study specifically examined the neural basis of self-awareness of IADLs, and the sample in this study consisted solely of subjects with frontotemporal dementia (Amanzio et al., 2016). There is evidence that level of insight in individuals with neurodegenerative disease may vary across cognitive, emotional, behavioral, and functional domains (Banks and Weintraub, 2008; Clare et al., 2011; Okonkwo et al., 2009; Steward et al., 2019). Therefore, it is possible that self-awareness of memory or other cognitive domains may not necessarily share the same neural correlates as self-awareness of everyday functional abilities (e.g., financial management, driving, meal preparation, medication management, technology use). An additional limitation of prior work in this field is that awareness of deficits is often measured using a patient-caregiver report discrepancy score (with informant reports serving as the “true measure” of the patient's current abilities). This metric is problematic given that reports from informants are often biased by a number of factors, including the nature and duration of their relationship to the patient and their own emotional and cognitive status (Ready et al., 2004; Zanetti et al., 1999).

To the authors’ knowledge, this is the first study examining the neuroanatomical correlates of unawareness for IADL deficits in older adults across a continuum of cognitive impairment. Level of self-awareness was assessed through comparison of self-report to objective performance on a number of different tasks critical for independent daily functioning. We hypothesized that poor awareness would be associated with reduced volume in primarily right hemispheric (and to a lesser extent, left hemispheric) mPFC and temporo-parietal regions as well as in the hippocampi and cerebellum. In addition, we hypothesized that unawareness would be correlated with higher total WML burden.

2. Materials and methods

2.1. Subjects and procedure

Participants with working diagnoses of MCI due to suspected AD were recruited from memory disorders, geriatrics, and neurology clinics as part of the larger Applying Programs to Preserve Skills Study at the University of Alabama at Birmingham (UAB). Exclusionary criteria for the current analyses included history of other neurological illness, moderate to severe traumatic brain injury, clinical stroke in the last two years, significant psychiatric diagnoses aside from mild depression, or contraindications to having an MRI.

This study was granted approval by the UAB Institutional Review Board. We assessed competency to consent using the Competency Assessment Checklist for Informed Consent (Daniel Marson, J.D., Ph.D, University of Alabama at Birmingham, V.2 October 2002; MCI Study version 1 July 2004). All participants provided both verbal and written consent for undergoing study procedures.

Following referral and consent to this study, participants (n = 87) were administered a comprehensive neuropsychological testing battery (see Appendix) along with questionnaires obtaining information regarding current health and medications, sociodemographics, and depressive symptomology. Informants were interviewed separately about the participants' functional status. Each participant's case was randomly assigned to two members of a multidisciplinary panel, which included geropsychologists, neuropsychologists, and a behavioral neurologist. Panel members used all of this information to determine diagnoses in accordance with previously published guidelines (Winblad et al., 2004). Briefly, possible MCI was classified with existence of subjective cognitive complaints from subject or informant but limited evidence of objective impairment (n = 9). Generally, a participant was considered to have objective cognitive impairment in a particular cognitive domain (e.g., memory) if two or more tests within that domain fell greater than 1.5 standard deviations below expected performance based on demographically adjusted normative data. Those with objective evidence of MCI were further classified as: amnestic single domain MCI (n = 23), amnestic multi-domain MCI (n = 37), non-amnestic single domain MCI (n = 2), or non-amnestic multi-domain MCI (n = 1). Mild probable AD classification required cognitive and functional complaints with mild to moderate objective cognitive impairment (n = 13). Participants with evidence of objective cognitive impairment but unclear etiology were grouped as cognitive impairment-cannot classify (n = 2).

Eligible participants completed a second visit within two months of their diagnostic visit during which subjective and objective functional measures, including an on-road driving evaluation, and brain MRI were collected. All effort was taken to ensure that subjective functional measures were administered before objective assessments so that their study performance did not bias their self-ratings; however, in approximately 10% of cases the on-road driving evaluation needed to be scheduled earlier in the day or to a different day due to pending inclement weather or a conflict with the driving clinic's schedule.

Following this second visit, one individual with mild probable AD was excluded from analyses due to an MRI acquisition issue and one participant with amnestic multi-domain MCI was excluded after review of T2-weighted images revealed a large right-sided middle cerebral artery territory infarct. Table 1 displays demographic and clinical variables for the remaining participants who were included in analyses (n = 85). Sixteen individuals reported living alone and all but five participants were retired from working. Far visual acuity ranged from Snellen scores of 20/16 to 20/38 (M = 20/23, SD = 5.6).

2.2. Calculation of self-awareness for IADLs

Self-awareness was assessed for six IADLs (Financial Management, Driving, Telephone Use, Grocery Shopping, Nutrition Evaluation, and Medication Management) by calculating a discrepancy score between objective and subjective measures for each domain. Of note, all subjective measures used were designed to parallel the domains and items assessed in the respective objective measure.

Financial Management was objectively measured using the Financial Capacity Instrument-Short Form (FCI-SF) (Gerstenecker et al.,

Table 1
Demographic and clinical characteristics of study sample (n = 85).

Variable	N	%
Age (years)		
54-64	13	15
65-74	36	42
75-88	36	42
Gender (female)	48	57
Race		
Caucasian	76	89
African-American	7	8
Asian	2	2
Education (years)		
< 12	5	6
12	10	12
13-15	16	19
16	25	29
> 16	29	34
DRS-2 total score		
135-144	30	36
125-134	33	40
108-124	20	24
CES-D total score		
< 16	69	81
≥16	16	19
Takes medication(s) for memory loss		
Yes	47	55
No	29	34
Unknown	9	11

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; DRS-2, Dementia Rating Scale 2nd Edition.
Note. For DRS-2, higher score indicates better global cognition. For CES-D, higher score indicates more depressive symptomology.

2016), which provides a total score ranging from 0 to 74. Those who performed more than one standard deviation below expected performance based on age- and education-adjusted normative data (Gerstenecker et al., 2016) were classified as having objective impairment on this domain. Subjective financial management skill was assessed with a four-point Likert scale on the Past and Present Financial Capacity Form (PPFCF) (Wadley et al., 2003). This questionnaire parallels the FCI-SF and asks participants about their ability to manage their money and financial affairs. Those who did not endorse the highest rating (i.e., that they can do this independently and without difficulty) were classified as having subjective impairment.

Driving performance was assessed with a standardized 45–60 min on-road driving evaluation in an instrumented vehicle (Wadley et al., 2009). A Certified Driving Rehabilitation Specialist (CDRS) and a back seat rater, who were both masked to the participants' cognitive performance, rated subjects' global driving performance on a five-point Likert scale (rated one—drive terminated, two—unsafe, three—unsatisfactory but not unsafe, four—a few minor flaws but satisfactory, to five—optimal). These ratings were averaged due to strong inter-rater reliability ($\kappa = 0.857$, $p < .001$) (McHugh, 2012) and those whose averaged global driving rating fell below a four were classified as having objective impairment. Similarly, subjective driving performance was assessed using a five-point Likert scale on the Mobility/Driving Habits for Current Drivers Questionnaire (Owsley et al., 1999), and subjective impairment was determined using the same cut-off criteria as for the objective driving rating.

The remaining IADLs were objectively assessed with the Timed Instrumental Activities of Daily Living (TIADL) (Owsley et al., 2001): Nutrition Evaluation (3 items), Medication Management (2 items), Telephone Use (1 item), and Grocery Shopping (1 item). If subjects were not able to complete all items in the domain within the allotted time limit and without error, they were classified as having objective impairment with that particular IADL. These same IADL domains were subjectively measured using the MILES Self-Report Questionnaire (Okonkwo et al., 2009), which asks participants to rate the level of difficulty they have with each of these IADLs using a four-point Likert scale. Any participant who did not endorse the highest rating (i.e., that they can complete this IADL without any difficulty) was classified as having subjective impairment in that domain.

For each IADL, the dichotomized subjective rating (0 = no impairment, 1 = impairment) was subtracted from the dichotomized objective rating (0 = no impairment, 1 = impairment). Thus, a discrepancy score of +1 indicates overestimation of their ability, a 0 indicates accurate estimation, and a −1 indicates underestimation of performance. Similar dichotomization methods and calculation of discrepancy scores have been previously published as a data reduction step for ease of interpretation and to minimize experiment-wise error rate (Okonkwo et al., 2009; Okonkwo et al., 2008; Steward et al., 2019).

As the current analyses were focused on investigating brain regions associated with poor self-awareness of deficits, participants were classified as either overestimating performance or accurately/under-estimating performance for each instrumental activity.

2.3. Structural MRI acquisition and processing

Brain scans were performed at the UAB Philips 3 T MRI facility. MRI acquisition and processing methods have been previously described (Launer et al., 2015; Tamura et al., 2016). In summary, GM volume, total brain volume, and WML loads were derived from 1 mm isotropic sequences: 1) sagittal 3D T1-weighted sequence (matrix = 256 × 256, TR: 1900 ms, TE: 2.89 ms, flip angle: 9°, slick thickness: 1 mm, number of slices: 176); 2) sagittal 3D T2 Fluid Attenuated Inversion Recovery (FLAIR) (matrix = 258 × 221, TR: 6000 ms, TE: 160 ms, phase FOV: 0.85 [250 mm], slice thickness: 1 mm, number of slices: 160); and 3) sagittal 3D T2-weighted Fast Spin Echo (matrix = 258 × 256, TR: 3200 ms, TE: 409 ms, flip angle: 120°, phase FOV: 0.80 [250 mm], slice thickness: 1 mm, number of slices: 176). Imaging data were then transmitted to the MRI Reading Center at the University of Pennsylvania for quality control and processing using a DICOM image transfer software program (TRIAD, American College of Radiology).

T1 images were first pre-processed to correct for intensity inhomogeneity and a multi-atlas registration based method was used for removing the extra-cranial material (skull-stripping) (Doshi et al., 2013). The output brain masks were visually verified for quality, and the few with errors were manually corrected. A multi-atlas label fusion method was applied for segmenting the brain into a set of anatomical regions of interest (ROIs) (Doshi et al., 2016; Ou et al., 2011). After co-registration of T1, T2, and FLAIR scans, a supervised learning based multi-modal lesion segmentation technique, which uses a model trained on manually segmented lesions, was applied to segment WML (Zacharaki et al., 2008). A neuroradiologist (I.M.N.) reviewed all images for incidental findings prior to analysis.

To limit number of analyses, we focused on 16 ROIs: right and left mPFC, right and left inferior PFC, right insular cortex, ACC, MCC, PCC, left lateral temporal cortex, right and left medial limbic cortex, left and right hippocampi, left lateral parietal cortex, left medial parietal cortex, and the cerebellum. As summarized earlier and reviewed in Zamboni and Wilcock (2010), these regions have been previously implicated in the self-awareness literature. In addition, we assessed the relationship between unawareness and total WML burden.

2.4. Statistical analyses

Within each functional domain, separate linear models were created for each of the ROIs. Empirical Bayes shrinkage methods were used to moderate the t-statistics for individual linear models (Phipson et al., 2016). This approach shrinks the sample variances towards a common value and augments the degrees of freedom for the individual variances, which increases power as well as accounts for the correlation amongst brain regions within an individual. Age and intracranial volume (ICV) were included as covariates in the models. Statistical analyses were performed using the *limma* package (Ritchie et al., 2015) in R (R: A language and environment for statistical computing, 2018) and *p*-values were adjusted using a Holm step-down procedure for multiple comparisons. Significance was set at adjusted *p*-value < .05.

3. Results

In terms of specific IADLs, three participants self-identified as non-drivers and two participants did not complete the TIADL Medication Management task; thus, they were excluded from the Driving and Medication Management domains, respectively. Similarly, one participant was excluded from the Grocery Shopping domain and four were excluded from the Nutrition Evaluation domain because they did not complete self-reported data. The percentages of individuals who were rated as over-estimating their abilities (i.e., poor self-awareness of their deficits) in each domain are as follows: Nutrition Evaluation (31%), Driving (23%), Financial Management (22%), Telephone Use (18%), Medication Management (16%), and Grocery Shopping (13%). Within each of the IADL domains, those who over-estimated their abilities did not differ from the under/accurate estimators in terms of gender, education, or depressive symptoms (CES-D total score [Radloff, 1977]) as measured using chi-square (gender) and independent samples t-tests (education, CES-D) (all $p > .05$).

Table 2 presents the results of the separate linear models for each instrumental activity after controlling for age and ICV. For Driving and Nutrition Evaluation domains, poor self-awareness of deficits was associated with significantly reduced volume in bilateral mPFC, MCC, and the cerebellum. In the Financial Management domain, these same regions were implicated along with significantly reduced volume in the right insular cortex. All aforementioned regions with the addition of the PCC were significantly smaller in individuals with impaired self-awareness in Grocery Shopping, Medication Management, and Telephone Use domains. Broadly, statistical significance was found bilaterally and there was no strong evidence of association only with right hemispheric regions. Total cerebral WML volume was not associated with self-awareness on any IADL.

To ensure that findings were not driven entirely by the participants with probable AD (n = 12), analyses were re-run with these participants excluded, leaving only those with MCI. Results remained the same with only two notable changes: 1) the right insular cortex was no longer significantly related to self-awareness of performance on any IADL, and 2) the left mPFC was no longer related to self-awareness of performance on the Nutrition Evaluation domain.

4. Discussion

The current cross-sectional study found that older adults with diagnoses ranging from possible MCI to probable AD have variable insight into their everyday functioning. Impaired self-awareness was associated with reduced volume in the cerebellum, bilateral medial prefrontal cortex, middle and posterior cingulate cortex, and right insular cortex. Moreover, this study generally found consistency in neuroanatomical correlates of unawareness across a spectrum of functional domains. Contrary to our hypotheses, we did not find strong evidence of right hemispheric laterality in this higher-order cognitive skill or evidence that impaired self-awareness of IADL performance is associated with temporal, parietal, or hippocampal volume. Similarly, we did not find evidence of an association between insight and total white matter lesion load.

Interestingly, unawareness for certain IADLs, such as grocery shopping, medication management, and telephone use, was associated with more brain regions (e.g., the right insular cortex and PCC) than other IADLs examined, such as driving and nutrition evaluation. It is possible that analyses in these functional domains were more prone to false-positive errors given that there was a lower frequency of individuals with impaired insight in these areas. Alternatively, these results could suggest that self-awareness across domains of daily function is differentially sensitive to brain damage, such that self-awareness for abilities like grocery shopping, medication management, and using the telephone can be compensated for by other brain regions up to a certain

Table 2
Separate linear models comparing regional volumes between individuals who did or did not have impaired self-awareness of abilities on each instrumental activity of daily living.

	Financial Management (n = 85)		Driving (n = 82)		Nutrition Evaluation (n = 81)		Grocery Shopping (n = 84)		Medication Management (n = 83)		Telephone Use (n = 85)	
	t	Adj. *p*-value	t	Adj. *p*-value	t	Adj. *p*-value	t	Adj. *p*-value	t	Adj. *p*-value	t	Adj. *p*-value
R Medial Prefrontal	5.44	**< .001**	4.96	**< .001**	4.43	**< .001**	5.20	**< .001**	5.17	**< .001**	5.46	**< .001**
L Medial Prefrontal	3.98	**.002**	3.55	**.009**	3.25	**.024**	4.07	**.002**	4.08	**.001**	4.53	**< .001**
R Inferior Prefrontal	1.57	.598	1.14	1.00	1.28	1.00	1.47	.733	1.54	.634	1.37	.864
L Inferior Prefrontal	2.11	.227	1.58	.712	1.62	.894	1.99	.328	1.96	.365	1.89	.372
R Insular	3.32	**.017**	2.85	.072	2.43	.208	3.06	**.039**	3.05	**.037**	3.16	**.028**
Anterior Cingulate	2.32	.200	1.68	.685	1.71	.819	2.26	.267	2.03	.365	2.33	.212
Middle Cingulate	4.80	**< .001**	4.39	**< .001**	4.44	**< .001**	4.75	**< .001**	4.80	**< .001**	5.01	**< .001**
Posterior Cingulate	2.90	.057	2.80	.078	2.62	.137	3.04	**.039**	3.11	**.034**	3.05	**.037**
L Lateral Temporal	2.54	.129	1.74	.685	1.33	1.00	2.25	.267	2.00	.365	2.35	.212
R Limbic Medial Temporal	0.69	.952	0.51	1.00	0.50	1.00	0.63	1.00	0.34	1.00	0.56	1.00
L Limbic Medial Temporal	1.01	.952	0.71	1.00	0.85	1.00	0.79	1.00	0.53	1.00	0.80	1.00
R Hippocampus	−2.33	.200	−2.00	.494	−1.54	.894	−2.02	.328	−2.13	.328	−2.24	.223
L Hippocampus	−0.85	.952	−0.54	1.00	−0.45	1.00	−0.65	1.00	−0.95	1.00	−0.87	1.00
L Lateral Parietal	2.64	.108	2.34	.239	2.03	.504	2.77	.076	2.64	.109	2.79	.071
L Medial Parietal	1.26	.839	0.62	1.00	0.68	1.00	1.04	1.00	0.90	1.00	1.01	1.00
Cerebellum	6.91	**< .001**	6.62	**< .001**	5.85	**< .001**	6.55	**< .001**	6.32	**< .001**	6.43	**< .001**
Total WML	−2.23	.200	−1.93	.512	−1.79	.775	−2.12	.294	−2.46	.162	−2.18	.226

Abbreviations: L, left; R, right; WML, white matter lesions.
Note. T statistics are moderated using Empirical Bayes shrinkage methods. Positive t-values indicate that those with intact self-awareness had larger volume than those with impaired self-awareness of deficits after controlling for age and intracranial volume differences. *p*-values were adjusted using a Holm step-down procedure for multiple comparisons.
Bold indicates Holm-adjusted *p*-values are significant at threshold of .05.

extent of atrophy— a concept often referred to as cognitive reserve (Stern, 2002). Given that this is the first study to find such results, interpretation of findings is cautioned until replication studies can be performed.

Results of the supplementary sensitivity analyses including only those with MCI suggest that smaller volume of the right insular cortex and, to a lesser extent, the left mPFC, may only relate to unawareness after MCI progresses to dementia. Longitudinal studies would be beneficial for tracking the relationship between regional volumetric loss and decline in self-awareness over the course of disease progression.

In healthy adults, the cortical midline structures, such as the mPFC and cingulate cortex (Amodio and Frith, 2006; Northoff and Bermpohl, 2004), and right insula (Ullsperger et al., 2010) are commonly associated with performance monitoring, error detection, and making self-referential judgments. Our cross-sectional study found that a reduction in volume in these regions is related to an overestimation of ability to accurately and quickly perform a variety of IADLs. Other studies have similarly found a relationship between unawareness of cognitive (primarily memory) disturbance and reduced volume and/or functionality in the cingulate cortex (Amanzio et al., 2016; Guerrier et al., 2018; Hanyu et al., 2008; Nobili et al., 2010; Perrotin et al., 2015; Ries et al., 2007; Spalletta et al., 2014; Vannini et al., 2016), mPFC (Amanzio et al., 2011; Ford et al., 2014; Ries et al., 2007; Ries et al., 2012; Rosen et al., 2010; Shany-Ur et al., 2014; Zamboni et al., 2013), and insula (Cosentino et al., 2015; Shany-Ur et al., 2014) in older adults with MCI and dementia. Our findings, in combination with the imaging literature, support the theoretical Conscious Awareness Model (CAM)(Agnew and Morris, 1998; Amanzio et al., 2013; Palermo et al., 2013), which proposes that unawareness of functional deficits may stem from a breakdown in the central executive system, whereby individuals can no longer detect performance errors or use their ‘comparator mechanism’ to assess whether current task performance is consistent with past behavior. This leads to an inability to successfully update their ‘personal database’ with current information about themselves—sometimes referred to as developing a ‘petrified-self’ (Mograbi et al., 2009). Future research examining the neuropsychological correlates of impaired self-awareness of functional deficits in older adults with cognitive impairment is critical for supporting this hypothesis.

Interestingly, both our research and several prior studies using dementia spectrum populations (Amanzio et al., 2016; Amanzio et al., 2011; Ford et al., 2014; Guerrier et al., 2018; Spalletta et al., 2014) have found a relationship between cerebellar volume/function and lack of insight into cognitive and functional deficits. The cerebellum has vast interconnections with the PFC and has been suggested to play a role in several cognitive domains such as attention, working memory, executive function, and emotional processing (Strick et al., 2009). There are limited studies in healthy adults that have examined a specific role for the cerebellum in self-referential processing and insight; therefore, this structure's exact role is unclear at this time. One suggestion is that reduced cerebellar volume may be related to increased apathy, which subsequently affects individuals' attention to performance errors (Guerrier et al., 2018). Another study suggested that impaired cerebellar function might affect semantic processing of self-information (Spalletta et al., 2014). However, additional evidence is needed to substantiate these hypotheses.

There are a few limitations to the current study. First, this study employed ROI analysis rather than a whole-brain voxel-based approach (Astrakas and Argyropoulou, 2010). Therefore, interpretation of our findings is restricted to regions selected *a priori* to be of significance. Second, since examination of WML differences was primarily exploratory, we examined total WML volume. Regional differences in WML, including lesion burden within defined white matter tracts, may be more sensitive to effects of WML on self-awareness. In addition, future studies should employ longitudinal designs and additional imaging modalities such as fMRI or diffusion tensor imaging (DTI) to support the role of the aforementioned brain regions in awareness of functional abilities. An additional limitation is that we conceptualized self-awareness categorically rather than continuously. This method was in part chosen due to comparability of our objective and subjective measures and also as a way to maintain consistency across the functional domains, which used different psychometric instruments. While this dichotomous classification is commonly used in the literature to aid in interpretation and clinical usefulness of findings (Ford et al., 2014; Marshall et al., 2004; Nobili et al., 2010; Okonkwo et al., 2009), we acknowledge that this is a simplification of the individual variability in level of awareness. Despite this limitation, the current findings are consistent with prior studies that conceptualized self-awareness as a continuous variable via calculation of the discrepancy between informant- and self-reported cognitive abilities (Fujimoto et al., 2017; Guerrier et al., 2018; Spalletta et al., 2014). It is recommended that future studies include samples with increased racial, socioeconomic, and cognitive heterogeneity to improve generalizability of findings since our sample consisted primarily of well-educated, clinic-referred, Caucasian adults with MCI. Finally, future studies should seek to reduce any possible influence of depression on IADL performance and self-awareness in MCI and exclude participants with diagnosed mood disorders, as the current study included a small percentage of those with possible mild depression.

The current study is the first to examine the neural correlates of unawareness for functional deficits in older adults across a continuum of cognitive impairment using an objective versus self-report methodology for measuring level of insight. Moreover, this study examined correlates across a number of instrumental activities of daily living and found consistency in brain regions associated with self-awareness of function. An additional strength of this study is that we incorporated a relatively large sample size in comparison to previous work in this area and our results were generally confirmatory of previous findings, supporting the idea of an extensive self-awareness network in the brain that becomes compromised within this population.

Impaired self-awareness of functional deficits has a number of negative implications for patients. Across a number of neuropsychiatric disorders, those who underreport problems in daily living my delay seeking treatment (Rosen, 2011), be less likely to comply with treatment and recommendations (Rusch and Corrigan, 2002), and have greater risk for engaging in dangerous behaviors (Starkstein et al., 2007) such as continuing to drive or manage their own medications despite a decline in their performance on these tasks. Moreover, there is a strong relationship between level of patient awareness and extent of caregiver burden and distress (Turro-Garriga et al., 2013). When possible, clinicians should regularly obtain objective IADL measures along with collateral interviews from close family members or friends in order to make diagnostic and capacity-related decisions. This information might also aid in determining the most effective interventions for both patients and caregivers. Given the importance of self-awareness, we hope that pinpointing its neural substrates will ultimately improve clinical care and quality of life for older adults with cognitive impairment.

Disclosures of interest

The authors have no financial, personal, or other potential conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropsychologia.2019.04.023.

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