

Comparing the relationship between subjective memory complaints, objective memory performance, and medial temporal lobe volumes in patients with mild cognitive impairment

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Abstract

Introduction: This study examined the relationship between subjective memory complaints (both self- and informant-report), objective memory performance, and medial temporal lobe (MTL) volume.

Methods: Mild cognitive impairment (MCI) patients (n = 58) and their informants (n = 51) completed the Memory Assessment Clinics self- (MAC-S) and family (MAC-F)-rating scales as a measure of subjective memory. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Immediate and Delayed Memory indices were used as objective measures of memory and a subset of MCI participants also underwent magnetic resonance imaging, which was used to measure MTL volume.

Results: Patients reported greater difficulty with semantically based information (e.g., word and name recall) relative to informant report. However, the severity of these self-reports was unrelated to objective memory performance and only a single MAC-S scale was related to amygdalar volume. Conversely, several MAC-F indices were related to the RBANS Delayed Memory index and to amygdalar and hippocampal volumes. Measures of executive functioning were associated with MAC-S frequency scales but not any MAC-F scale.

Discussion: The results of this study suggest that, in those who are cognitively symptomatic, the frequency of self-reported subjective memory difficulty may reflect executive dysfunction but holds little value for verifying memory impairment. Conversely, informant report provides meaningful information about actual memory deficits in those with MCI.

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Keywords:

Aging; Diagnosis; Memory complaints; Dementia; Alzheimer's disease

1. Introduction

Mild cognitive impairment (MCI) describes an intermediate state between normal aging and dementia and is characterized by significant cognitive deficits, especially in the areas of learning and memory. Specifically, MCI requires (1) subjective memory complaints, preferably corroborated by an informant, (2) objective memory decline, and (3) a

general preservation of everyday functioning [1,2]. Additionally, brain atrophy within the medial temporal lobes (MTL) has been associated with objective learning and memory deficits in MCI [3,4]. The current report addresses a knowledge gap about self- and informant-report of memory complaints and their relationship with objective memory performance and MTL volumes.

Subjective memory complaints help to establish a decline in functioning relative to premorbid status, and existing evidence suggests that the presence of such complaints may be a harbinger of subsequent cognitive decline [5-7]. In addition, studies have reported similar MTL volumes (and

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other brain regions) in patients with MCI and healthy older adults with subjective memory complaints [8]. An important caveat is that these relationships generally appear limited to “cognitively intact” older adults (i.e., those whose objective memory test performances fall within normal limits). A meta-analysis [9] and a review of longitudinal studies [5] revealed inconsistent evidence for the value of subjective memory complaints in those with objective memory impairment (i.e., MCI). Informant-reported memory impairment may hold diagnostic value as it has previously been shown to reflect objective memory test impairment [10–12]. Conversely, some studies have found a relationship between subjective memory complaints and objective test performance [5,13], whereas other studies have not [10,14]. Such discrepant results may arise from the presence or absence of anosognosia, which is a common feature of Alzheimer’s disease (AD) that has been variably reported in MCI [15–17]. It is important to note that such awareness of deficit requires the ability to monitor and evaluate one’s performance in the moment, which literature suggests requires intact executive abilities and associated prefrontal-parietal networks [e.g., 18,19]. Of course, being able to report the nature and/or severity of cognitive impairment requires an accurate memory for the episodes of failure, which certainly relies on the MTL memory system. Thus, MCI patients may experience difficulty due to one or both of these aspects of awareness.

Another reason for the discrepant findings about the value of self-reported complaints is that a range of measures have been used, most of which dichotomize participants based on a single question (i.e., present vs. absent) [5]. Recently, Buckley et al. [14] examined the relationship between subjective memory, affect, and biomarkers of AD in a large sample of healthy controls and MCI patients who were enrolled in the Australian Imaging Biomarkers and Lifestyle study of Aging. Importantly, this study used the memory assessment clinics questionnaire (MAC-Q [20]), which is a brief measure that rates the severity of subjective memory complaints along a continuum. The results demonstrated that complaint severity was unrelated to objective memory test performance or to any biomarkers of AD (gray matter, white matter, or hippocampal volumes; amyloid burden) in either group. Similarly, another recent study found that informant report of overall cognitive impairment in MCI patients was more related to biomarkers of AD than was self-report [12; though see 13 for positive findings]. It is possible that the brevity of the measures used in these studies limited the detection of meaningful relationships in the MCI patients, in which case a more comprehensive measure that assesses perceived difficulty across different situations/contexts will be more reflective of objective impairment.

The current study used the full MAC self-rating scale (MAC-S) and family-rating (MAC-F) questionnaires, which provide continuous measures of functioning across several ecologically relevant contexts, to assess subjective memory complaints in those previously diagnosed with MCI. These

subjective ratings were correlated with objective memory test performances (via the memory indices from the Repeatable Battery for the Assessment of Neuropsychological Status—RBANS), measures of executive functioning, and MTL volumes. Thus, this study allowed us to directly compare the utility of self- vs. informant-report of memory complaints while at the same time examining potential biological explanations for any observed differences.

2. Methods

2.1. Participants

A total of 58 participants, diagnosed with MCI according to Petersen’s criteria [2], were recruited from the Emory University Alzheimer’s Disease Research Center and surrounding community as part of a larger, multisession study on cognitive rehabilitation. Each patient had been diagnosed with MCI at a consensus conference using all relevant clinical data (e.g., laboratory findings, neuroimaging, neuropsychological testing). Participants were then referred to our study and, after providing written informed consent, completed a brief neuropsychological protocol that included both subjective and objective measures of memory functioning (see Table 1). This protocol was developed to minimize overlap with the tests used during the diagnostic process. For example, we used the RBANS as a brief, yet relatively comprehensive, measure of cognitive functioning (especially for learning and memory) given evidence of its sensitivity to MCI [21] and AD [22]. These results allowed us to ensure persistent cognitive (especially memory) deficits at the time of study enrolment. Informant-based information was obtained for 51 of these participants using the MAC-Family (MAC-F) questionnaire during this screening session. Informants were typically spouses or other family members and all lived and/or interacted with the patient multiple times per week. All neuropsychological and neuroimaging data (see later) included in this study were both independent of those used for the clinical diagnosis and obtained before cognitive rehabilitation was provided.

General exclusion criteria included a history of neurologic injury or disease (e.g., stroke, moderate or severe traumatic brain injury, and epilepsy), psychiatric disorders (e.g., severe depression, bipolar disorder schizophrenia), and current or past alcohol or drug abuse/dependence. The Institutional Review board of Emory University approved the study procedures.

2.2. MAC—self and family-rating scale

The MAC-S consists of 21 items that assess one’s perceived functioning (i.e., ability) and that are grouped into five memory areas (Remote, Numeric, Everyday, Semantic, and Spatial) [23]. It also includes another 24 items that assess the frequency of memory concerns and are also grouped into five scales (Semantic, Concentration, Everyday, Forgetfulness, and Facial). There are four global

Table 1
Demographics, neuropsychological measures, and brain volumes for patients with MCI

	MCI (n = 58)
Gender	Number of participants
Male	33
Female	25
Ethnicity	Number of participants
Caucasian	37
African American	19
Latino	2
	M (SD)
Age (years)	71.69 (8.28)
Education (years)	15.86 (2.79)
MMSE	27.47 (2.19)
WAIS-III Information Subtest	12.14 (2.52)
WTAR-Reading Standard Score	
VIQ	109.22 (13.05)
PIQ	106.17 (9.79)
FSIQ	108.10 (13.19)
Trails A (T-score)	47.43 (10.32)
Trails B (T-score)	48.36 (11.24)
Emory WCST [†]	
# Strategies identified	2.63 (0.59) (WNL)
# Sorts completed	3.37 (1.70) (-1 SD)
# Perseverative errors	5.93 (6.07) (WNL)
# Set loss errors	1.63 (1.72) (-1 SD)
WMS/KBNA (percent correct)	
Auto index—accuracy	98.25 (3.01)
Nonauto index—accuracy	84.44 (16.66)
GDS	1.69 (1.76)
FAQ	3.41 (4.64)
RBANS indices (std. score)	
Immediate memory	87.48 (14.55)
Delayed memory	80.09 (18.96)
Visuoconstructional	95.60 (16.74)
Language	92.72 (15.02)
Attention	96.48 (14.58)
Total score	87.52 (11.78)
Brain volumes (% of total ICV)*	
Inferior lateral ventricle	0.20 (0.09)
Hippocampus	0.47 (0.07)
Amygdala	0.21 (0.04)

Abbreviations: MCI, mild cognitive impairment; MMSE, Mini-Mental Status Examination; WAIS-III, Wechsler Adult Intelligence Scale-III; WTAR, Wechsler Test of Adult Reading; VQI, Verbal Intelligence Quotient; PIQ, Performance Intelligence Quotient; FSIQ, Full Scale Intelligence Quotient; Emory WCST, Emory version of the Wisconsin Card Sorting Test; SD, standard deviation; WMS/KBNA, Wechsler Memory Scale/Kaplan Baycrest Neurocognitive Assessment; GDS, Geriatric Depression Scale; FAQ, Functional Assessment Questionnaire; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; ICV, intracranial volume.

*Brain volumes provided by NeuroQuant[®].

[†]Emory WCST performance ranges are based on internally developed normative data (WNL = within normal limits).

rating items that measure the overall degree of cognitive concern and that form the Global Memory scale. The MAC-F uses the same format and number of items but is completed by an informant. Both the MAC-S and -F use a 5-point Likert scale to evaluate the severity of perceived impairment, where low scores represent difficulty (1 = very poor; 5 = very good). Ratings for each of the statements are summed for the five ability and five frequency

scales. Totals for each scale are added to provide the total ability and total frequency, all of which are then z-normalized [24]. Low z-scores indicate poor ability, frequent memory concerns, and a worse overall rating of their current memory, whereas a higher score indicates the opposite.

2.3. Structural magnetic resonance imaging and volumetric measurements

A total of 40 MCI patients underwent high-resolution anatomic magnetic resonance imaging (MRI) scanning as part of a recently completed cognitive rehabilitation study, the results of which will be reported elsewhere. Participants were scanned an average of 47 days (SD = 35.5) after completing the neuropsychological and subjective measures described previously. All scans were performed using a Siemens Trio 3T MRI Scanner (Siemens Medical Solutions, Malvern, PA) with a 12-channel head coil. High-resolution anatomic images were acquired using a three-dimensional magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence (repetition time [TR] 2300 ms, echo time [TE] 3.9 ms, flip angle [FA] 8°) with 176, 1 mm thick, sagittal slices (field of view [FOV] 256 mm, in-plane resolution 1 × 1 mm, in-plane matrix 256 × 256). All data in this report were collected before any cognitive rehabilitation. A senior MR technologist visually inspected all data at the time of acquisition; suboptimal scans were repeated to ensure usable data.

Volumetric data were obtained via NeuroQuant[®]. Details of the segmentation process can be found elsewhere [3,25]. Briefly, NeuroQuant[®] performs two quality control checks that (1) ensure that data adhere to the automatic segmentation specifications using a measurement index that quantifies the deviation between the target brain and a normalized anatomic atlas; (2) corrects for gradient nonlinearities and field inhomogeneities (using the same methods as the Alzheimer's Disease Neuroimaging Initiative [ADNI]). Skull stripping and nonlinear registration to a probabilistic atlas follow. During segmentation, each voxel is given a neuroanatomical label based on its location within the atlas and then iteratively checked to maximize the probability that it belongs to the labeled structure. A report is then generated that provides the volumes of brain structures as a percent of intracranial volume (ICV), which accounts for head size and allows for interindividual comparisons. NeuroQuant[®] provides the volumes of three MTL regions: the hippocampus, inferior lateral ventricles, and the amygdala. Total volumes for these structures were calculated by combining the left and right hemisphere volumes (all values are in percent of ICV).

2.4. Statistical analyses

All analyses were performed using IBM SPSS Statistics 21. Between group comparisons used independent t-tests. We performed correlational analyses (Pearson's r) to determine relationships between subjective complaints (MAC-S or -F as appropriate), objective memory test performances

(i.e., RBANS Immediate and Delayed Memory Indices), measures of executive functioning (Trails A, Trails B, and select aspects of the Emory version of the Wisconsin Card Sorting Test), and MTL volumes. Self- and informant-reports of subjective impairment were considered separately. For all analyses, we used the false discovery rate (FDR) to correct for multiple comparisons because it minimizes both type I and type II error [26].

3. Results

3.1. Self-report (MAC-S) versus informant-report (MAC-F)

Patients reported significantly more memory difficulty on the semantic ability (e.g., remembering the meaning of both familiar and rarely used words) and frequency indices and the facial frequency scale relative to informants (Table 2). Although it did not survive FDR correction, informants tended to rate everyday memory functioning worse than did patients. As seen in the table, however, mean ratings for nearly all scales fell within 1 standard deviation of the mean for both patients and informants.

3.2. Self-report (MAC-S) findings

There were no significant correlations between any subjective scale and objective memory index (Table 3). However, amygdalar volume was inversely related to the frequency of General Forgetfulness scale of the MAC-S. Regarding measures of executive functioning, the number of set loss errors on the Emory version of the WCST was inversely related to both the Frequency of Concentration and Forgetfulness scales. The relationship between MAC-S scales and several

other measures of the WCST was below the $P < .05$ level but failed to survive FDR correction.

3.3. Informant-report (MAC-F) findings

The MAC-F Semantic, Spatial, and Total ability scales were related to the RBANS Delayed Memory Index (Table 4). Amygdalar volumes were related to MAC-F Remote, Numeric, Everyday, Spatial, and Total ability scales, and, frequency of Semantic and Facial occurrence scales. Hippocampal volume was related to the ability to remember numeric information. Measures of executive functioning were unrelated to any of the MAC-F scales.

4. Discussion

This study examined the relationship between subjective memory complaints, as measured by the MAC-S and MAC-F, objective memory test performance, measures of executive functioning, and MTL volumes in patients diagnosed with MCI. Consistent with a common clinical presentation, we found that patients reported greater difficulty with aspects of semantic (e.g., meanings of words) and episodic memory (e.g., recall of recently learned information) and also noticed the frequency of such difficulty (e.g., tip of tongue recall of names or words) more often than did their informants. These findings mirror frequent clinical complaints and are notable because they can feasibly be thought to impede social interactions.

In contrast to these data, however, our results add to other studies in this area showing that self-reported memory complaints are unrelated to actual memory test performance (i.e., objective memory impairment) in MCI patients [10–12,14]. These findings are consonant with the expected effects of memory impairment and reduced MTL integrity: that patients cannot accurately remember the severity or extent of their memory troubles. Our data revealed an inverse relationship between the volume of the amygdala and the frequency of forgetful type errors. The role of the amygdala, as opposed to the hippocampus, was somewhat unexpected but may reflect an enhanced emotional component to the perceived deficits that facilitates their recollection, at least until its structural integrity surpasses some biological threshold. Conversely, subjective complaints were associated with several aspects of the WCST (albeit these often failed to surpass the FDR correction threshold), typically on the Frequency Scales of the MAC-S. Most notable were the findings that patients who more frequently lost mental set during the WCST reported greater impairment with the Concentration and Forgetfulness Scales and tended to report more difficulty with memory in general (i.e., Total Ability and Total Frequency Scales). These findings (1) reinforce the previously noted distinction between executive and memory contributions to awareness of deficit, (2) indicate that MCI patients are more sensitive to the frequency with which they have memory failures rather than their actual memory abilities, and (3) suggest that the validity of subjective memory complaints

Table 2

Between group differences in subjective memory functioning (z-scores) and effect sizes (Cohen's d)

	MAC-S (z-scores) (n = 58), M (SD)	MAC-F (z-scores) (n = 51), M (SD)	t(107)	P	Cohen's d
Ability					
Remote	0.13 (0.79)	0.08 (1.03)	0.27	.786	0.054
Numeric	0.17 (0.97)	0.41 (1.20)	1.17	.244	0.220
Everyday	0.25 (0.84)	-0.38 (2.08)	2.11	.038	0.397
Semantic	-0.03 (0.67)	0.35 (0.97)	2.41	.018*	0.456
Spatial	-0.09 (0.94)	-0.03 (1.24)	0.30	.769	0.055
Total	-0.64 (0.74)	-0.61 (1.09)	0.20	.843	0.032
Frequency					
Semantic	-0.80 (0.80)	-0.36 (0.85)	2.76	.007*	0.533
Concentration	-0.02 (0.93)	0.37 (1.20)	1.95	.053	0.363
Everyday	0.28 (0.94)	0.24 (1.03)	0.23	.818	0.041
Forgetfulness	-0.18 (0.92)	-0.10 (1.02)	0.46	.650	0.082
Facial	0.18 (0.83)	0.63 (1.01)	2.55	.012*	0.487
Total	-1.22 (0.76)	-0.91 (0.89)	2.01	.047	0.375

Abbreviations: MAC-S, Memory Assessment Clinics self-rating scale; MAC-F, Memory Assessment Clinics family-rating scale; SD, standard deviation.

*Survives false discovery rate correction threshold of $P \leq .027$.

Table 3

Pearson correlations (*P*-value) between MAC-S scores, MTL volumes (in percent of total ICV), RBANS memory indices, and measures of executive functioning

MAC-S	Percent ICV (n = 40)			RBANS indices (n = 58)				Emory WCST (n = 57)			
	HP	ILV	AMY	IMI	DMI	Trails A	Trails B	# ID'd	Sorts	Persv	Set loss
Ability to remember scales											
Remote	0.088 (0.589)	0.093 (0.569)	-0.097 (0.550)	-0.097 (0.467)	0.079 (0.557)	0.033 (0.804)	-0.203 (0.138)	0.054 (0.691)	0.161 (0.232)	0.003 (0.982)	-0.248 (0.062)
Numeric	-0.005 (0.977)	0.234 (0.146)	-0.085 (0.602)	0.000 (0.998)	-0.128 (0.339)	0.006 (0.966)	-0.044 (0.749)	0.224 (0.094)	0.287 (0.030)	-0.069 (0.609)	-0.221 (0.099)
Everyday	-0.071 (0.663)	0.236 (0.142)	-0.298 (0.062)	-0.106 (0.431)	-0.006 (0.965)	0.009 (0.948)	-0.002 (0.989)	0.185 (0.168)	0.090 (0.507)	0.124 (0.360)	-0.251 (0.059)
Semantic	-0.173 (0.286)	0.205 (0.204)	-0.290 (0.070)	0.070 (0.601)	-0.106 (0.428)	0.054 (0.688)	-0.138 (0.316)	0.226 (0.090)	0.101 (0.454)	0.171 (0.205)	-0.163 (0.224)
Spatial	0.173 (0.287)	0.037 (0.821)	-0.068 (0.678)	-0.024 (0.859)	0.062 (0.645)	0.146 (0.273)	0.183 (0.180)	-0.040 (0.768)	0.107 (0.430)	0.043 (0.750)	-0.123 (0.363)
Total	0.016 (0.921)	0.220 (0.173)	-0.211 (0.192)	-0.051 (0.705)	-0.023 (0.865)	0.064 (0.635)	-0.045 (0.744)	0.171 (0.204)	0.215 (0.108)	0.053 (0.694)	-0.277 (0.037)
Frequency of occurrence scales											
Semantic	-0.146 (0.369)	0.296 (0.063)	-0.199 (0.218)	-0.056 (0.676)	-0.245 (0.064)	-0.006 (0.967)	-0.152 (0.268)	0.170 (0.205)	0.105 (0.435)	0.103 (0.444)	-0.128 (0.343)
Concen	0.024 (0.885)	0.042 (0.795)	-0.251 (0.183)	0.145 (0.277)	-0.074 (0.582)	0.105 (0.435)	-0.077 (0.575)	0.267 (0.045)	0.149 (0.268)	0.216 (0.107)	-0.326 (0.013)*
Everyday	-0.076 (0.643)	0.267 (0.096)	-0.289 (0.070)	-0.119 (0.374)	-0.281 (0.032)	-0.226 (0.089)	-0.241 (0.076)	0.057 (0.674)	0.056 (0.679)	0.223 (0.096)	-0.192 (0.154)
Forgetful	-0.204 (0.207)	0.138 (0.394)	-0.473 (0.002)*	0.073 (0.588)	-0.007 (0.958)	-0.021 (0.874)	-0.150 (0.276)	0.265 (0.046)	0.176 (0.190)	0.159 (0.237)	-0.437 (0.001)*
Facial	0.127 (0.436)	-0.081 (0.621)	-0.099 (0.543)	-0.187 (0.159)	-0.232 (0.080)	0.125 (0.348)	-0.075 (0.584)	0.159 (0.239)	-0.138 (0.307)	0.270 (0.042)	-0.096 (0.478)
Total	-0.036 (0.824)	0.143 (0.377)	-0.279 (0.081)	-0.018 (0.894)	-0.220 (0.097)	-0.005 (0.970)	-0.174 (0.205)	0.231 (0.083)	0.100 (0.457)	0.233 (0.081)	-0.280 (0.035)

Abbreviations: MAC-S, Memory Assessment Clinics self-rating scale; MTL, medial temporal lobe; ICV, intracranial volume; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; HP, hippocampus; ILV, inferior lateral ventricle; AMY, amygdala; IMI, Immediate Memory Index; DMI, Delayed Memory Index; Concen, Concentration; Emory WCST, Emory version of the Wisconsin Card Sorting Test; #ID'd, number of sorting strategies initially identified; sorts, number of completed sorts; Persv, number of perseverative errors; Set Loss, number of set loss errors.

Bolded values = $P \leq .05$ (uncorrected).

*Correlations surviving the $P \leq .025$ false discovery rate correction threshold.

Table 4

Pearson correlations (*P*-value) between MAC-F scores, MTL volumes (in percent of total ICV), RBANS memory indices, and measures of executive functioning

MAC-S	Percent ICV (n = 34)			RBANS indices (n = 51)				Emory WCST (n = 50)			
	HP	ILV	AMY	IMI	DMI	Trails A	Trails B	# ID'd	Sorts	Persv	Set loss
Ability to remember scales											
Remote	0.278 (0.111)	-0.093 (0.602)	0.484 (0.004)*	0.060 (0.677)	0.241 (0.088)	-0.123 (0.390)	-0.236 (0.106)	-0.083 (0.566)	-0.053 (0.715)	0.021 (0.885)	-0.067 (0.644)
Numeric	0.439 (0.009)*	-0.294 (0.092)	0.532 (0.001)*	0.135 (0.345)	0.250 (0.077)	0.033 (0.816)	-0.044 (0.767)	-0.034 (0.815)	0.093 (0.519)	-0.016 (0.915)	-0.189 (0.190)
Everyday	0.293 (0.093)	-0.161 (0.362)	0.406 (0.017)*	-0.011 (0.938)	0.094 (0.513)	-0.030 (0.836)	0.004 (0.980)	0.117 (0.417)	0.061 (0.672)	0.012 (0.937)	-0.186 (0.197)
Semantic	0.376 (0.114)	-0.098 (0.583)	0.356 (0.039)	0.216 (0.127)	0.313 (0.025)	0.234 (0.099)	0.027 (0.855)	0.054 (0.710)	0.035 (0.810)	0.093 (0.519)	-0.196 (0.173)
Spatial	0.338 (0.051)	-0.178 (0.315)	0.386 (0.024)*	0.033 (0.817)	0.379 (0.006)*	0.121 (0.399)	0.087 (0.558)	-0.225 (0.117)	-0.191 (0.185)	0.150 (0.300)	-0.010 (0.947)
Total	0.377 (0.028)	-0.192 (0.276)	0.507 (0.002)*	0.100 (0.486)	0.327 (0.019)*	0.028 (0.846)	-0.051 (0.733)	-0.076 (0.601)	-0.039 (0.790)	0.081 (0.577)	-0.126 (0.382)
Frequency of occurrence scales											
Semantic	0.251 (0.153)	-0.161 (0.362)	0.388 (0.023)*	0.081 (0.571)	-0.071 (0.618)	-0.009 (0.950)	-0.018 (0.904)	0.020 (0.890)	0.060 (0.678)	-0.022 (0.877)	-0.081 (0.578)
Concentration	0.260 (0.137)	-0.167 (0.344)	0.223 (0.205)	0.105 (0.462)	0.133 (0.351)	0.188 (0.186)	0.138 (0.349)	0.007 (0.959)	-0.050 (0.731)	0.229 (0.110)	-0.138 (0.340)
Everyday	0.363 (0.035)	-0.238 (0.175)	0.323 (0.062)	-0.021 (0.885)	0.250 (0.077)	0.047 (0.742)	-0.069 (0.643)	-0.254 (0.075)	-0.125 (0.387)	0.186 (0.197)	0.031 (0.829)
Forgetful	-0.014 (0.937)	0.106 (0.550)	-0.116 (0.514)	-0.001 (0.993)	0.085 (0.553)	0.024 (0.868)	-0.156 (0.288)	0.089 (0.540)	-0.159 (0.269)	0.201 (0.162)	-0.075 (0.604)
Facial	0.380 (0.027)	-0.203 (0.249)	0.471 (0.005)*	-0.096 (0.503)	0.102 (0.478)	0.046 (0.748)	-0.040 (0.786)	-0.139 (0.337)	-0.217 (0.130)	0.182 (0.206)	0.079 (0.584)
Total	0.334 (0.053)	-0.196 (0.267)	0.336 (0.052)	0.032 (0.823)	0.119 (0.406)	0.087 (0.543)	-0.027 (0.856)	-0.066 (0.647)	-0.094 (0.518)	0.183 (0.203)	-0.059 (0.685)

Abbreviations: MAC-F, Memory Assessment Clinics family-rating scale; HP, hippocampus; ILV, inferior lateral ventricle; AMY, amygdala; IMI, Immediate Memory Index; DMI, Delayed Memory Index; MTL, medial temporal lobe; ICV, intracranial volume; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; Concen, Concentration; Emory WCST, Emory version of the Wisconsin Card Sorting Test; #ID'd, number of sorting strategies initially identified; sorts, number of completed sorts; Persv, number of perseverative errors; Set Loss, number of set loss errors.

*Correlations surviving the $P \leq .025$ false discovery rate correction threshold.

declines as patients progress toward AD (or other forms of dementia) [also see 12].

Our data suggest that the previously noted limitations of self-report data can be overcome by using an informant. Specifically, we found that the Semantic, Spatial, and Total Ability scales of the MAC-F were related to patients' performance on the Delayed Memory Index of the RBANS. Informants also tended to rate everyday memory abilities as more impaired compared with patients. These findings add to recent reports that informant-based ratings are more closely related to objective memory test performance [10] and more sensitive to future decline [27] in those with MCI when compared with self-report. A unique aspect of our study was the inclusion of volumetric data, which revealed robust and positive relationships between multiple MAC-F scales and the volume of patients' amygdala and, to a lesser extent, hippocampus (see Tables 3 and 4). Thus, informant report appears to be sensitive to both patients' objective memory test performance and the integrity of MTL structures that are disproportionately affected in MCI and AD. It is interesting to note that these relationships were primarily limited to the Ability Scales and that they were completely unrelated to measures of executive functioning. Thus, informants may be more sensitive to actual memory abilities (i.e., the correct vs. incorrect recall of information) whereas patients focus on the frequency of memory lapses, which reflects executive dysfunction. This may be an important distinction that could explain some of the variability in the existing literature and also meaningfully shape future clinical and research efforts.

Overall, these results support current literature suggesting a shift in the utility of subjective measures as a function of disease severity. At an early stage, cognitively intact individuals who voice persistent concerns about memory (or cognitive) impairment may be at increased risk of subsequent decline [6,28]. The previous findings suggest that questions from the Semantic ability and several of the Frequency scales may be especially promising for early identification purposes but only as it relates to executive functioning. Once cognitively symptomatic, however, the evidence supports greater emphasis on informant-report because it is more predictive of objective performance [10] and subsequent conversion [6]. As alluded to previously, a major limitation in this line of research has been in the definition of, and measures used to assess, subjective complaints. Recent efforts from international work groups are helping to address these issues and hold promise for clarifying the role of such complaints in both research and clinical settings [29].

A considerable gap remains in the use of subjective complaints for treatment planning purposes. For example, patients who retain more insight are likely to be more amenable to cognitive rehabilitation (or other interventions) because they would recognize the need for assistance and be motivated to actively engage in treatment. This is consonant with our previous report that specific rehabilitative

approaches (e.g., mnemonic strategy training) are more appropriate for those with "early" MCI, whereas other approaches may be best for "late" MCI [30]. Likewise, informants who recognize memory changes may be more willing to facilitate or even engage in treatments, especially those with the promise of enhancing patient independence and reducing caregiver burden [31]. Such findings reiterate and extend our call for the consideration of disease severity in treatment planning [32].

Overall then, future diagnostic efforts should give informant-report of memory impairment greater weight than self-report when measuring memory abilities (i.e., the correct vs. incorrect recall of information) whereas focusing on the frequency of memory lapses may be a better reflection of executive deficits in patients themselves. However, additional work is needed to clarify the role that both types of information play in treatment planning.

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RESEARCH IN CONTEXT

1. Systematic review: We reviewed literature, identified via PubMed and ISI Web of Science, about the relationship between subjective memory complaints (self- and informant-based), objective memory test performance, and medial temporal lobe (MTL) volumes in patients with mild cognitive impairment (MCI).
2. Interpretation: Our results show that self-reported subjective memory impairment is generally unrelated to objective memory performance or MTL volumes; however, the frequency of memory lapses was related to measures of executive functioning. Conversely, informant-reported memory impairment is reflective of both objective memory performance and MTL volumes. Together, results suggest that informant-report is more useful for verifying memory deficits whereas self-report may reflect executive dysfunction.
3. Future directions: The point at which informant-reported memory complaints should take precedence over self-report needs to be identified. Furthermore, additional work is needed in examining the relationship between subjective memory complaints and the efficacy of cognitively focused interventions.

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