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Associations between Cortical Thickness and Metamemory in Alzheimer’s Disease

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Abstract

Metacognitive deficits affect Alzheimer’s disease (AD) patient safety and increase caregiver burden. The brain areas that support metacognition are not well understood. 112 participants from the Imaging and Genetic Biomarkers for AD (ImaGene) study underwent comprehensive cognitive testing and brain magnetic resonance imaging. A performance-prediction paradigm was used to evaluate metacognitive abilities for California Verbal Learning Test–II learning (CVLT-II 1–5) and delayed recall (CVLT-II DR); Visual Reproduction-I immediate recall (VR-I Copy) and

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Code availability No software was used for data collection. We used publicly available packages and functions described in methods for data analysis.

The UCLA Institutional Review Boards approved the study. All ImaGene participants or their legally authorized representatives provided informed consent for data collection and publication according to the Declaration of Helsinki, U.S. federal regulations, local state laws and regulations, and policies of the UCLA IRB.

Visual Reproduction-II delayed recall (VR-II DR); Rey-Osterrieth Complex Figure Copy (Rey-O Copy) and delayed recall (Rey-O DR). Vertex-wise multivariable regression of cortical thickness was performed using metacognitive scores as predictors while controlling for age, sex, education, and intracranial volume. Subjects who overestimated CVLT-II DR in prediction showed cortical atrophy, most pronounced in the bilateral temporal and left greater than right (L > R) frontal cortices. Overestimation of CVLT-II 1–5 prediction and DR performance in postdiction showed L > R associations with medial, inferior and lateral temporal and left posterior cingulate cortical atrophy. Overconfident prediction of VR-I Copy performance was associated with right greater than left medial, inferior and lateral temporal, lateral parietal, anterior and posterior cingulate and lateral frontal cortical atrophy. Underestimation of Rey-O Copy performance in prediction was associated with atrophy localizing to the temporal and cingulate areas, and in postdiction, with diffuse cortical atrophy. Impaired metacognition was associated to cortical atrophy. Our results indicate that poor insight into one's cognitive abilities is a pervasive neurodegenerative feature associated with AD across the cognitive spectrum.

Keywords

Biomarkers; MRI; Metacognition; Cortical atrophy; Awareness; Memory

Introduction

Anosognosia (unawareness of dysfunction) is a known hallmark of Alzheimer's disease (AD) (Ruijter et al., 2020). In general, metacognition, or one's insight into cognitive functioning, plays a key role in evaluating cognitive abilities (Hertzog & Hultsch, 2000; Craik & Salthouse, 2008; Fleming & Frith, 2014; Rothlind et al., 2017). The importance of metacognitive ability for cognitive health has been well established over the past decades (Cella et al., 2014; Hertzog & Hultsch, 2000; Flavell, 1979; Hart, 1965; Lai, 2011; Martinez, 2006; Shimamura, 2000). Self-awareness and self-monitoring (i.e., the ability to monitor one's own cognition to correct errors) are two parts of metacognition that can influence everyday living, and when deficient, have an impact on patient's safety resulting in the need for supervision (Rickenbach et al., 2015). Therefore, impairment of metacognition crucially impacts caregiver burden and poses day-to-day challenges for patients with neurological diseases such as Alzheimer's disease and related dementias (ADRD) (DeFeis et al., 2019; Sunderaraman & Cosentino, 2017).

Metacognitive abilities aid in the understanding of cognitive strengths and weaknesses in older adults who are susceptible to ADRD. The evaluation of these abilities can inform decisions regarding personal safety and independence in activities of daily living (ADLs). Previous studies revealed that aging may adversely affect one's metacognitive abilities (Chandler et al., 2016; Palmer et al., 2014; Sunderaraman & Cosentino, 2017; Woo et al., 2008). Deficits in metacognition and memory performance predictions (meta-memory) are commonly seen in dementias (Sunderaraman & Cosentino, 2017; Thomas et al., 2013). Hence, over 46 million people with cognitive impairment, or dementia, in the United States (Gibson & Richardson, 2016) are at greater risk for safety issues due to poor metacognition (Chandler et al., 2016; David et al., 2012).

Cognitive impairment can influence any neurological disease or age group (Rothlind et al., 2017). AD, the most common form of dementia, causes impaired awareness for disease-related cognitive impairment in older adults (Amanzio et al., 2011, 2013; McGlynn & Kaszniak, 1991; Sitek et al., 2011). In AD, loss of memory is a relatively early symptom, and metacognitive decline in memory-related performance can be quite pronounced even in the early disease stages.

According to the 2020 Alzheimer's Disease Facts and Figures report, an estimated 5.8 million Americans are currently living with a diagnosis of dementia (2020 Alzheimer's disease facts & figures, 2020). Research predicts that this number will escalate rapidly in coming years (2020 Alzheimer's disease facts & figures, 2020). It is crucial to monitor for changes in cognitive abilities that can impact ADL performance such as impaired metacognition from the earliest disease stages. Current diagnostic and disease monitoring practices overlook metacognitive skills. Furthermore, studies of the neural correlates of metacognitive functioning remain sparse in literature.

Metacognition is quantified by prediction (self-awareness) and postdiction (self-monitoring) of cognitive performance. The reports of age effects on metacognition are inconsistent in the literature (Devolder et al., 1990; Souchay et al., 2007; Trouillet et al., 2003; Woo et al., 2008). Woo et al. showed that cognitively healthy older and younger adults were similarly accurate in assessing their metamemorial abilities (Woo et al., 2008). Other studies indicated a lack of consistency between younger and older adults in predicting and postdicting performance on memory tasks. Devolder et al. suggested significant differences between prediction and postdiction accuracy at both age groups in which older adults outperformed younger adults in some tasks (Devolder et al., 1990). Souchay et al. showed age-related effects on reduced prediction/postdiction accuracy only in episodic memory-related tasks in older adults (Souchay et al., 2007). This suggests that age and disease status may independently affect metacognition in various tasks. In our study, we investigated metacognitive deficits in the cognitive spectrum from normal to dementia using assessment tools focused on metacognitive functioning similar to those that have been examined and evaluated in previous studies (Pannu & Kaszniak, 2005; Schmitter-Edgecombe & Woo, 2004; Woo et al., 2008).

Magnetic resonance imaging (MRI) allows researchers to evaluate the associations between neurodegenerative changes and cognitive function. To date, the examination of the neurodegenerative underpinnings of metacognition remains limited in literature (Ecklund-Johnson & Torres, 2005). Our study aims to fill this void by examining the relationship of brain atrophy with impaired metacognition. We used a cognitive paradigm for assessing metacognition (Devolder et al., 1990; Woo et al., 2008) and assessed its associations with cognitive and structural brain changes in the AD spectrum. Our analysis explored how prediction and postdiction of memory function relates to neurodegeneration measured by cortical thickness in the ImaGene study across the cognitive spectrum from cognitively normal to dementia and then separately within each diagnostic group. We hypothesized that impaired metacognition (loss of insight) would associate with cortical thickness loss in areas previously implicated in AD.

Methods

Participants

52 cognitively normal (CN) and 108 with mild cognitive impairment (MCI) men and women aged 50 and older were enrolled in the Imaging and Genetic Biomarkers for AD study (ImaGene) at the Mary S. Easton Center for Alzheimer's Disease Research at University of California, Los Angeles (UCLA). ImaGene is a five-year, longitudinal study that collected detailed clinical and cognitive measures, neuroimaging, and genetic (DNA, RNA) data. The inclusion/exclusion details for ImaGene were previously described (Clark et al., 2016; Ramirez et al., 2016; Wilhalme et al., 2017). All 160 participants underwent MRI and cognitive testing annually. Metacognitive testing was included in the ImaGene study later at the month 24–36 follow-up visits. By that time, 42 participants had dropped out. We considered the remaining 118 participants for our analyses. Of these, 5 participants were excluded due lack of MRI scan within 12 months of the metamemory assessment. The remaining 113 individuals all had clinical assessments, neuropsychological and metacognitive examinations, and corresponding MRI data. One participant with radiologic evidence of hydrocephalus was also excluded from the analysis. By month 24–36, 1 CN and 9 MCI participants progressed to dementia. Therefore, our final dataset included 45 CN, 57 MCI and 10 dementia (DEM) participants. Of all DEM participants, 7 had global clinical dementia rating (CDR) score of 0.5 and 3 had CDR of 1 (Morris, 1993); and 8 were sub-typed as probable AD and 2 dementia with Lewy Bodies at diagnostic consensus meetings.

Metamemory Assessment

The neuropsychological test battery used in this study has been previously described (Ramirez et al., 2016). At the time of the metamemory assessments, 13 participants were in their baseline visit and naïve to the battery. 99 participants were in their 2–4th annual visit and had previous exposure to the battery. Metacognitive abilities were assessed using a performance-prediction paradigm (Nelson et al., 2012; Woo et al., 2008) during the Visual Reproduction-I Immediate Recall (VR-I Copy) and -II 30-min Delayed Recall (VR-II DR) subtests of the Wechsler Memory Scale-III (WMS III), California Verbal Learning Test-II trials 1–5 learning (CVLT-II 1–5) and 30-min Delayed Recall (CVLT-II DR) and Rey-Osterrieth Complex Figure Copy (Rey-O Copy) and 3-min Delayed Recall (Rey-O DR) tasks (Ramirez et al., 2016). Before each cognitive task was administered, participants were introduced to the scenario of what the cognitive task consisted of: simple drawings, list of words or a complex figure. After a verbal description of each task, participants were asked to predict their future performance (prediction) by providing a rating of their scores on each test. After completion of each task, they were asked to rate their performance again (postdiction) (Devolder et al., 1990). For VR-I Copy and VR-II DR, the participant had to predict/postdict how many of 104 parts from five simple drawings they thought they would/did reproduce before and after task performance immediately (VR-I Copy), and from memory 30-min later (VR-II DR). For CVLT-II, participants were asked to predict how many of the 16 words they would be able to remember immediately during 5 trials of learning (CVLT-II 1–5) and from memory 30-min later (CVLT-II DR) before and after completing these tasks. Lastly, participants were presented with the Rey-O Figure, a

complex figure consisting of 36 parts, and were asked to predict/postdict how many of the 36 parts of the design they would be able to accurately copy immediately and draw from memory after delay.

For our analyses we derived prediction and postdiction performance scores by subtracting the percentage of correctly performed from the predicted and postdicted scores, respectively: % predicted – % performed and % postdicted – % performed. Positive scores indicate an overestimation and negative scores an underestimation of one's cognitive performance abilities.

MRI Data Acquisition

Participants were scanned at the Department of Radiology at UCLA, using a detailed protocol including coronal fast low angle shot three-dimensional (3D) 1.5 Tesla field strength, T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence with repetition time, 28 ms; echo time, 4.5 ms; field of view, 22 cm; matrix, 256 × 192; slice/gap, 1.5/0 mm (Ramirez et al., 2016). Participants with significant white matter hyperintensities (WMH) were excluded from ImaGene.

MRI Processing and Cortical Thickness Measurements

We downloaded preprocessed MRI data from LONI Image Data Archive (IDA) (<https://ida.loni.usc.edu>). Preprocessed scans were de-noised using an MRI Denoising package (Coupé et al., 2008; Gaser & Coupé, 2010) to improve image quality for quantitative imaging analysis. Within-subject registration was done using Statistical Parametric Mapping version 12 (SPM12:<https://www.fil.ion.ucl.ac.uk/spm/>). We utilized FreeSurfer version 6.0.0 (<https://surfer.nmr.mgh.harvard.edu>) with longitudinal stream (recon-all -long -all) (Fischl, 2012; Reuter et al., 2012) to generate cortical thickness measures from denoised, coregistered T1-weighted images. The images were registered to a FreeSurfer template (Fischl et al., 1999a). We generated average pial surfaces for all participants. The FreeSurfer cortical thickness pipeline and tools used in this study have been described previously (Dale et al., 1999; Fischl & Dale, 2000; Fischl et al., 1999a, 1999b; Han et al., 2006).

Statistical Analyses

P-values from ANOVA and Pearson Chi-Square for demographic comparisons and cognitive measures were obtained in SPSS 24 (<https://www.ibm.com/analytics/spss-statistics-software>). Statistical models and mapping in imaging space were performed using SurfStat (<http://www.math.mcgill.ca/keith/surfstat/>), a statistical toolbox created for MATLAB (R2016a, The Mathworks, Natick, MA, www.mathworks.com), described in Worsley et al. (2009). We ran vertex-wise multivariate linear regression analyses, where cortical thickness was modelled as the outcome measure and metacognitive scores as the predictor variable while controlling for age, sex, education and intracranial volume (ICV). We applied random field theory (RFT) cluster-level-correction with a threshold of $p < 0.01$ (Hagler et al., 2006).

Additionally, we controlled for cognitive status and previous exposure time to cognitive testing and repeated the analyses within each diagnostic group (CN, MCI and DEM) to

further examine the distinct association between cortical thickness and metacognition by disease stage and in normal aging and previous experience to cognitive testing.

Results

Demographic and Clinical Characteristics

Descriptive demographic and cognitive characteristics of the groups are shown in Table 1. The CN, MCI and DEM groups did not significantly differ by age and gender. CNs had significantly more years of education than the MCI and DEM groups ($p = 0.013$). The table includes summary statistics for the raw cognitive performance scores. As expected, both MCI and DEM groups performed significantly worse than CNs, and DEM performed significantly worse than MCI on all cognitive tests ($p < 0.001$ for all).

SurfStat Results

The main analyses were performed in the pooled sample (combined groups). Figure 1 represents our significant results where the clusters in red indicate the highest T-values with $p < 0.05$. The significant clusters were RFT-corrected using a cluster-level threshold of $p < 0.01$. We observed negative associations between cortical thickness and all metacognitive measures, except for Rey-O Copy, which exhibited positive associations with cortical thickness. Negative associations represent those who overestimated their performance, yet had reduced cortical thickness. Positive associations in Rey-O Copy suggests that those who underestimated their performance had greater cortical atrophy. In addition to underestimation of this more complex visuospatial task performance and experience, overall impaired metacognition was associated with overestimation of task performance and experience related to verbal and visual memory.

The cortical associations showed an AD-like neurodegenerative pattern with wide-spread involvement of the medial, inferior and lateral temporal, and parietal lobes as well as the anterior and posterior cingulate cortices, and precuneus. As expected, we observed left-sided lateralization for the overestimations of verbal memory tasks (CVLT-II 1–5 postdiction and CVLT-II DR prediction and postdiction) and right-sided lateralization for the overestimations of visuospatial and visual memory tasks (VR-I Copy prediction and VR-II DR prediction). Interestingly, the underestimation of Rey-O Copy (visuospatial construction task) showed more diffuse spread with cortical atrophy, including the involvement of right posterior and left anterior cingulate, and bilateral inferior temporal cortices in prediction whereas bilateral involvement of paracentral lobule, superior and inferior parietal gyri in postdiction.

The strength of these cortical thickness associations differed between prediction (self-awareness) and postdiction (self-monitoring). For example, compared to CVLT-II 1–5 prediction, CVLT-II 1–5 postdiction showed robust associations in left medial and temporal regions. The opposite was true for delayed recall prediction (CVLT-II DR prediction) where impaired self-awareness followed much stronger associations with left medial, inferior and lateral temporal, and parietal regions than impaired self-monitoring (CVLT-II DR postdiction). VR-I Copy prediction also had more diverse and significant right-sided

associations than VR-II DR prediction. Similar patterns were seen for the underestimations of Rey-O Copy with stronger associations in postdiction rather than prediction.

Significant associations emerged mostly as clusters, not as peaks, suggesting that metacognition is affected by broad cortical regions and networks, rather than small isolated cortical regions. Impaired metacognition by overestimation of these cognitive tasks showed stronger cluster-level associations with cortical neurodegeneration in prediction of delayed verbal recall and immediate figure copy and postdiction of immediate verbal recall and complex figure copy (underestimated).

Correcting for cognitive status resulted in weaker associations between the metacognitive measures and cortical thickness, except for Rey-O Copy (Supplementary Figure S1). Within each group analyses showed that the associations are driven mainly by the cognitively impaired subjects and analysis controlling for cognitive status (Supplementary Figures S2–S4). Overall, the strongest effect on almost all measures was seen in the DEM group with the exception of Rey-O Copy which was the strongest in the MCI group. For CVLT, however, no diagnostic category claims the overall main effect as seen in the pooled sample (except maybe CN in CVLT-II DR prediction), thus we would conclude that metamemory for CVLT is not as driven by cognitive stage but it is rather distributed across the cognitive continuum. These results should be however interpreted with caution due to the small sample sizes by diagnosis.

Supplementary Figure S5 represents the results of analysis excluding participants who were naïve to the test battery (i.e., metacognitive assessment during the baseline visit). Overall, the patterns and associations with cortical thickness remained similar to the main results. The majority of the maps became weaker (except for VR-1 Copy prediction) which could be due to exclusion of the test naïve subjects yet one must consider that the sample size became smaller.

Discussion

Previous studies on metacognition focused mainly on self-awareness processes in healthy CN older adults without looking at neurobiological mechanisms (Thomas et al., 2013). Other studies suggested that AD or other neurological disorders cause impairment in metacognition (Devolder et al., 1990; Rosen et al., 2014; Souchay, 2007). In this study, we assessed the association of metacognition and cortical thickness among a group of CN, MCI and DEM older adults. To our knowledge, ours is the first comprehensive report on the effect of metacognition on MRI-based phenotypes (gray matter thickness).

Previous research suggests that impaired metacognition (e.g., overestimation of cognitive abilities) is an early indicator of cognitive decline (Perrotin et al., 2007). An imaging study, after introducing a metamemory training paradigm to cognitively normal elderly, observed associations with the precuneus, cuneus and posterior cingulate cortical thickness (Park et al., 2018). Our results show that impaired metacognition is associated with loss of cortical thickness in AD-signature brain areas and indicate that poor insight into one's cognitive abilities is a pervasive neurodegenerative feature of AD. In our study participants who

overestimated their cognitive abilities and thus lack insight into their cognitive deficits, showed an AD-like neurodegenerative pattern with wide-spread involvement of temporal, parietal and cingulate cortices. The cortical regions that were associated with poor CVLT-II 1–5 postdiction, CVLT-II DR prediction and postdiction, poor VR-I Copy and VR-II DR prediction and to lesser extent Rey-O copy postdiction were similar to those reported by Park et al. (Park et al., 2018). This implicates these regions in one's ability to learn from task experience and correct cognitive errors.

A recent systematic review examined the associations of anosognosia with brain perfusion, metabolism, activation and connectivity in MCI (Mondragón et al., 2019). This review article reported that anosognosia is associated with 1) hypoperfusion in the bilateral lateral and medial frontal lobes, the bilateral anterior cingulate cortex and middle cingulate gyri, and the left inferior parietal region, 2) hypo-metabolism of the posterior cingulate cortex, precuneus, right hippocampus, bilateral temporal cortex, left inferior parietal lobule, the left angular gyrus, and the left superior temporal gyrus, 3) lower activation in the bilateral medial prefrontal and posterior cingulate cortices, and 4) reduced functional within-network connectivity between the precuneus and bilateral inferior parietal lobes, left posterior cingulate cortex, left orbitofrontal cortex and reduced functional connectivity between the right hippocampus and left medial temporal cortex and right fusiform gyrus (Mondragón et al., 2019). The overall agreement between the regions reported in this meta-analysis and our findings is striking. Together, the data indicate that the medial and lateral frontal lobes, cingulate gyrus, temporal and parietal cortices play a crucial role in metacognition and self-awareness.

Interestingly, we found that reduced cortical thickness was associated with overestimation of one's future or past performance for some cognitive measures and underestimation for others. We found negative associations between cortical thickness and metacognition in verbal and visual memory, yet a positive relationship between reduced cortical thickness and metacognition for visuospatial function as measured by complex figure copy. The latter reveals perhaps greater insecurity in one's performance among cognitively impaired individuals when confronted by an overwhelmingly complex visuospatial task.

Overall, we found an association between reduced cortical thickness and worse metacognitive abilities indicating poor awareness of cognitive deficits among those with cortical atrophy. Poor insight readily affects patient's safety. Individuals with impaired metamemory posit a higher risk when performing everyday tasks (e.g., cooking, driving, financial decisions, judgement, etc.). Consequently, caregiver burden increases as metacognitive impairment increases (Seltzer et al., 1997). Poor awareness can also lead to delay in clinical evaluation and diagnosis and resistance to care.

Several strengths and limitations of our work are worth noting. The major strength of our study is our pooled sample approach. Metacognitive dysfunction is not a disease-specific process. Pooling the diagnostic groups together allowed us to more accurately model the metacognitive associations with cortical thickness as they exist in real life. Severity of cognitive impairment plays a crucial role in metacognition. Previous research shows that impaired metacognition is observed in various neurological and psychiatric disorders

(David et al., 2012; Koren et al., 2006; Schmitter-Edgecombe & Woo, 2004; Wilson et al., 2016). However, findings on the correlations between severity of cognitive impairment and metacognitive deficits are not consistent (Mazzoni et al., 1998; Muñoz-Neira et al., 2019; Seltzer et al., 1997; Sevush, 1999). We hypothesized that impaired metacognition may predict cortical neurodegeneration and would associate with cortical thickness loss in regions previously implicated in early stages of AD dementia, across the cognitive spectrum. However, we also examined the effects of cognitive status as a supplementary in our study.

Using the ImaGene dataset is another strength as this five-year study protocol included a rigorous clinical, neuroimaging, and genetic biomarker characterizations for all enrolled subjects at a single site. An inherent limitation of such an approach is that all observations made here need to be further replicated in the general population. Another limitation to our analysis is that it is cross-sectional. From our data alone it is unlikely to reliably draw conclusions about changes in metacognition and cortical thickness over time. Longitudinal studies investigating and monitoring changes in metacognition in a wider spectrum of aging and disease states are warranted.

Conclusions

In conclusion, we find an association of poor metacognition with AD-relevant brain atrophy in older adults with and without cognitive impairment. Our work advances our understanding of the link between metacognition and cortical integrity in an AD-like pattern. Future studies should focus on monitoring metacognition longitudinally across the cognitive continuum (Jack & Jr., 2013) and along the ATN framework (Jack et al., 2016, 2018), and on investigating the demographic, genetic and environmental contributions to metacognitive impairment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest

Tugce Duran, MS, Ellen Woo, PhD, Diana Otero, PhD, Shannon L. Risacher, PhD, Eddie Stage, PhD, Apoorva B. Sanjay, BS, Kwangsik Nho, PhD, John D. West, MS, Meredith L. Phillips, MS, Naira Goukasian, BS, and Kristy S. Hwang, MD have no relevant conflicts of interest to report. Liana G. Apostolova, MD, MS has served on Advisory Boards for Eli Lilly, Biogen and Two Labs, and has received research support from GE Healthcare, AVID Radiopharmaceuticals Inc., Life Molecular Imaging and Roche Diagnostics. Dr. Apostolova serves on a DSMB for IQVIA.

Data availability

MRI data is available through LONI Image Data Archive (IDA) (<https://ida.loni.usc.edu>).

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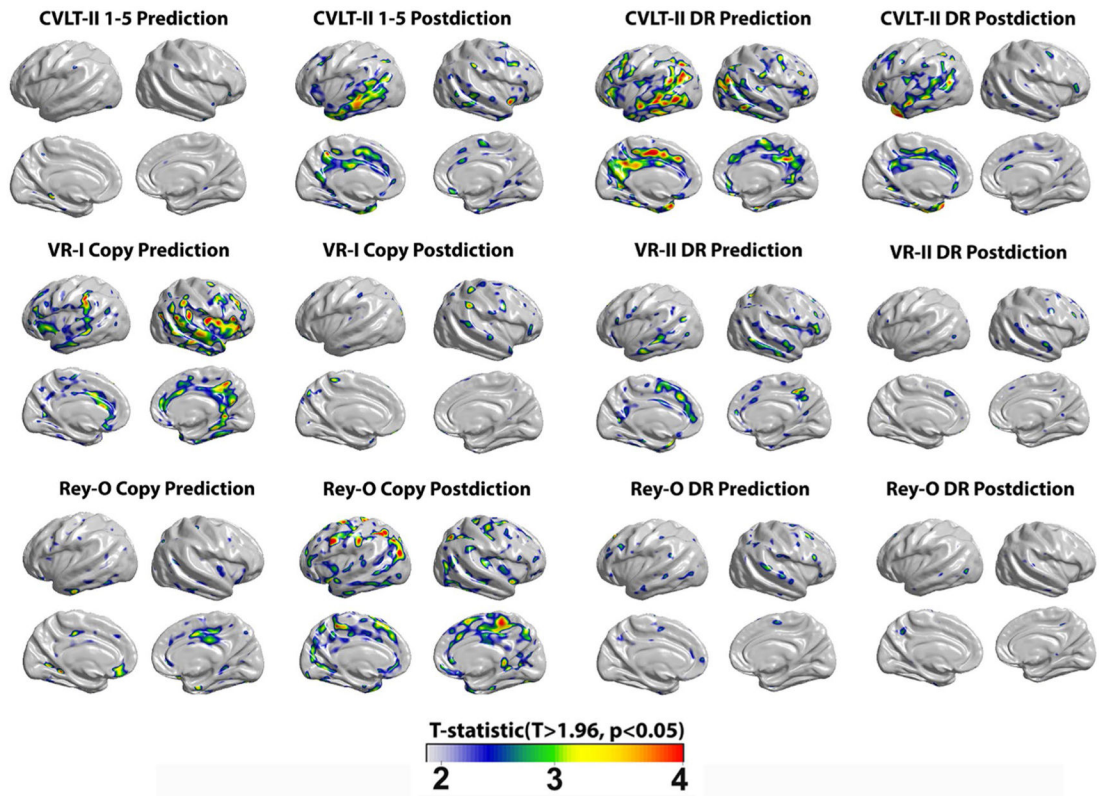
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All significant areas showed negative associations with the exception of Rey-O Copy

Fig. 1.
Significant clusters are shown as statistical t-maps at a cluster threshold of $p\text{-cluster} < 0.01$

Table 1

Participant demographic characteristics and cognitive measures by group status

	CN (N = 45)	MCI (N = 57)	DEM (N = 10)	<i>p</i> -value
Age, mean years (SD)	71.0 (9.0)	69.1 (8.4)	74.2 (6.5)	0.17
Sex, N female (%)	21 (46.7)	33 (57.9)	6 (60.0)	0.49
Education, mean years (SD)	17.0 (2.3)	15.6 (2.4)	15.5 (3.0)	0.013
MMSE, mean (SD)	28.2 (2.1)	27.1 (2.1)	22 (4.2)	< 0.001
CVLT-II 1–5, mean (SD)	50.3 (11.3)	39.7 (12.0)	26.1 (5.5)	< 0.001
CVLT-II DR, mean (SD)	11.2 (3.6)	6.9 (4.7)	1.8 (2.7)	< 0.001
VR-I IR, mean (SD)	84.7 (11.4)	67.8 (16.7)	42.6 (17.0)	< 0.001
VR-II DR, mean (SD)	66.4 (21.2)	38.5 (26.6)	10.8 (24.3)	< 0.001
Rey-O Copy, mean (SD)	32.0 (2.6)	27.8 (6.0)	24.9 (7.0)	< 0.001
Rey-O DR, mean (SD)	20.2 (6.8)	11.2 (7.0)	3.8 (5.3)	< 0.001

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