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The “Alzheimer's Type” Profile of Semantic Clustering in Amnestic Mild Cognitive Impairment

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Abstract

Impairments in learning and recall have been well established in amnestic mild cognitive impairment (aMCI). However, a relative dearth of studies has examined the profiles of memory strategy use in persons with aMCI relative to those with Alzheimer's disease (AD). Participants with aMCI, nonamnestic MCI, AD, and healthy older adults were administered the California Verbal Learning Test-II (CVLT-II). Measures of semantic clustering and recall were obtained across learning and delayed recall trials. In addition, we investigated whether deficits in semantic clustering were related to progression from healthy aging to aMCI and from aMCI to AD. The aMCI group displayed similar semantic clustering performance as the AD participants, whereas the AD group showed greater impairments on recall relative to the aMCI participants. Control participants who progressed to aMCI showed reduced semantic clustering at the short delay at baseline compared to individuals who remained diagnostically stable across follow-up visits. These findings show that the ability to engage in an effective memory strategy is compromised in aMCI, before AD has developed, suggesting that disruptions in semantic networks are an early marker of the disease.

Keywords

Memory disorders; Disease progression; Memory; Dementia; Verbal learning; Diagnosis

INTRODUCTION

Amnesic mild cognitive impairment (aMCI) is a risk state for Alzheimer's disease (AD) that is characterized by a deficit in memory with preserved daily functioning (Petersen, 2004). Over the years, several MCI subtypes have been identified that are thought to represent the prodromal stage of various dementias (e.g., nonamnesic MCI has been associated with frontotemporal dementia and dementia with Lewy bodies; Petersen, 2004). To date, aMCI has been the most commonly studied subtype, with the majority of research focusing on memory. Individuals with aMCI show poor retention or consolidation of information (e.g., Crowell, Luis, Vanderploeg, Schinka, & Mullan, 2002), as well as difficulties with acquisition and ineffective memory strategy use (e.g., Greenaway et al., 2006; Ribeiro, Guerreiro, & De Mendonça, 2007). The memory impairments are thought to be the result of early neuropathological changes seen in the hippocampus and related structures in individuals with aMCI (Apostolova et al., 2010; Jack et al., 1999), as well as AD-related changes in prefrontal regions (Braak & Braak, 1991; Perry & Hodges, 1999). To date, a few studies have shown reduced memory strategy use in aMCI relative to controls (Bröder, Herwig, Teipel, & Fast, 2008; Malek-Ahmadi, Raj, & Small, 2011; Price et al., 2010; Ribeiro et al., 2007); however, there is a dearth of research investigating whether individuals with aMCI display a similar pattern of deficiencies in strategy use as AD patients (see Perri et al., 2005, for a comparison between aMCI and AD strategy use).

Semantic clustering is an effective memory strategy that can be used to enhance recall. Here, participants actively reorganize items based on a shared semantic feature and then recall the words according to their superordinate category (e.g., recalling all “food” items followed by “jewelry” items; Delis, Kramer, Kaplan, & Ober, 2000). By “chunking” large amounts of information into smaller units, individuals can efficiently encode, store, and retrieve information more readily from memory (Baddeley, 2001). Several methods have been developed to measure clustering (Stricker, Brown, Wixted, Baldo, & Delis, 2002), including recall-based and list-based approaches. In recall-based methods, semantic clustering is calculated by using chance-expectancy scores based on the number of words recalled. Therefore, this method assumes that the organizational process occurs after the words are retrieved from memory, which may not accurately reflect this strategic process. Mori (1975) showed that when participants detected the semantic category of the list items at learning, memory and semantic clustering performance improved at recall. In contrast, providing undetected categories to participants at recall did not improve memory or semantic clustering performance. As such, Mori suggested that category clustering is not a product of retrieval but rather a product of the storage process (i.e., encoding and/or consolidation). In addition, Cinan (2003) found that semantic clustering of list items was disrupted by dual task performance at learning, but not by dual task performance at recall. Consistent with these data, Delis and colleagues (Delis et al., 2000; Stricker et al., 2002) developed a list-based method. In this approach, semantic clustering is calculated using the chance-

expectancy score derived from the number of words on the to-be-remembered list, thus avoiding the assumption that semantic clustering occurs after recall has already been performed.

In healthy controls, semantic clustering is subserved by the prefrontal and medial temporal regions (Becker & Lim, 2003; also see Alexander, Stuss, & Fansabedian, 2003, for intact clustering in patients with focal frontal lobe lesions) and is traditionally thought to be dependent, in part, on executive control. However, several studies have reported no significant relationship (Gaines, Shapiro, & Benedict, 2006) or only modest associations (Malek-Ahmadi et al., 2011; Tremont, Halpert, Javorsky, & Stern, 2000) between traditional measures of executive functioning (e.g., Trail Making Test – Part B) and semantic clustering.

Poor semantic clustering may be related more to a breakdown in semantic networks rather than executive dysfunction. The semantic network model proposes that one's general fund of knowledge is organized into complex associative networks in temporal and parietal cortices (Salmon, 2012) or more diffusely in the cortex (Fuster, 2003), with concepts that share many attributes being more strongly associated than those concepts that have fewer commonalities (Collins & Loftus, 1975; Fuster, 2003). For example, a *cow* and a *pig* would be more strongly associated within one semantic network than a *cow* and a *chair*, because these concepts share more salient attributes, such as being four-legged farm animals that are relatively similar in size. The theory of spreading-activation (Collins & Loftus, 1975) suggests that when a concept is processed, activation spreads throughout the semantic network along a decreasing gradient related to concept associations. That is, activation is inversely related to the strength of the associations between concepts within the network (e.g., the concept *cow* would be more likely to activate the concept *pig* than *chair*). Therefore, through spreading activation, memory performance is facilitated when words are more closely related. As neuropathological abnormalities in the temporal and parietal regions are evident early in the disease course, it is not surprising that AD patients show robust deficits in semantic processing relative to healthy controls (e.g., Huff, Corkin, & Growdon, 1986). In fact, a hallmark feature of AD is a breakdown in semantic networks (e.g., Chan, Salmon, & Butters, 1998).

The ability to use semantic clustering to improve memory performance is contingent upon the integrity of the associated semantic network. Price and colleagues (2010) explored the relative contribution of both executive and semantic processing to clustering on the Hopkins Verbal Learning Test (HVLT). They found that select measures of executive functioning did not predict clustering in participants with aMCI (also see Malek-Ahmadi et al., 2011 for similar results). In contrast, semantic processing (i.e., semantic fluency, the ability to rapidly generate a series of semantically related words) predicted clustering performance in individuals with aMCI. They suggested that poor clustering reflects a breakdown in semantic associations, which is consistent with evidence of semantic processing impairments in aMCI (e.g., Adlam, Bozeat, Arnold, Watson, & Hodges, 2006; Murphy, Rich, & Troyer, 2006).

Relative to healthy older adults, individuals with aMCI show impaired semantic clustering during learning and delayed recall. More specifically, Malek-Ahmadi and colleagues (2011) found reduced semantic clustering during learning and delayed recall trials on the HVLT using the recall-based method. Likewise, other researchers have shown aMCI-related reductions in semantic clustering across learning trials using the list-based approach on the HVLT (Price et al., 2010) and the recall-based approach on an experimentally developed word-list recall task (Perri et al., 2005). In the latter two studies, aMCI participants failed to show improvements in semantic clustering with repeated exposure to the list. Although Perri and colleagues (2005) included an AD group in their study, they did not investigate semantic clustering during delayed recall. Additionally, they used the recall-based approach when calculating semantic clustering scores. As such, it is unclear whether aMCI and AD participants display a similar pattern of semantic clustering deficits across learning and delayed recall trials using the list-based approach. Furthermore, to our knowledge, there have been no studies exploring semantic clustering in nonamnesic MCI. Considering that individuals with nonamnesic MCI can present with executive and semantic processing deficits (Petersen, 2004), these individuals may display a distinct pattern of semantic clustering from persons with aMCI. In the present study, we address these issues by examining semantic clustering in aMCI, nonamnesic MCI, and AD across learning and delayed recall trials on the California Verbal Learning Test-II (CVLT-II) using a list-based approach.

Changes in strategy use in aMCI may be due to the lack of spontaneous use of these compensatory methods. Ribeiro et al. (2007) found that relative to controls, aMCI participants showed reduced semantic clustering on total learning, short-delay, and long-delay recall trials. However, aMCI participants showed improved semantic clustering after they were given semantic cues. Ribeiro et al. (2007) proposed that this poor spontaneous use of semantic clustering in aMCI may reflect impaired executive functioning, difficulties detecting the semantic structure of the list, or some combination of the two.

Another important component of our study was the investigation of whether poor semantic clustering was associated with later development of aMCI in healthy controls and the progression to AD. There is evidence to suggest that poor recall performance and executive dysfunction are robust predictors of progression to AD in MCI participants (e.g., Albert, Moss, Tanzi, & Jones, 2001); however, despite the disrupted semantic networks in AD, few studies have explored whether changes in semantic clustering are also associated with the development of dementia. Furthermore, there is limited research exploring the cognitive factors that predict aMCI development beyond memory deficits. As such, we investigated whether clustering at baseline testing differed between converters (controls to aMCI and aMCI to AD) and non-converters.

In sum, the present study investigated semantic clustering during learning (first and fifth learning trials) and recall trials (short-delay and long-delay free recall trials) in aMCI, nonamnesic MCI, and AD groups. We hypothesized that individuals with aMCI would display an intermediate level of semantic clustering across trials relative to the control and AD groups. We also expected the nonamnesic MCI group to show more efficient semantic clustering relative to the aMCI and AD groups. Finally, we predicted that reduced semantic

clustering at baseline would be related to the development of aMCI in healthy controls, as well as to the progression to AD in aMCI participants at follow-up.

METHODS

Participants

All data were collected in compliance with UCLA Institutional Review Board guidelines. Fifty-three healthy older adults (OA), 82 individuals with aMCI, 30 persons with nonamnesic MCI (naMCI), and 30 individuals with AD participated in the study. All were participants in the University of California, Los Angeles (UCLA) Alzheimer's Disease Research Center longitudinal study. Exclusion criteria included non-degenerative and non-vascular causes of cognitive impairment, unstable medical conditions (e.g., active uncontrolled diabetes, organ failure, etc.), and major psychiatric disorder (e.g., recurrent depression, schizophrenia).

Participants underwent neurological and neuropsychological evaluations. See Table 1 for descriptive demographics and a summary of the neuropsychological test scores for each group. Diagnoses were determined during consensus conferences and were based on the National Institute of Neurologic and Communicative Disorders and Stroke and the AD and Related Disorders Association (NINCDS-ADRDA) criteria for AD (McKhann et al., 1984) and the Petersen (2004) criteria for MCI. A diagnosis of MCI was given to an individual who exhibited a cognitive impairment (i.e., at least 1.5 *SD* below the age- and/or education-adjusted norms) on at least one neuropsychological measure (Attention: WAIS-III Digit Span and Digit Symbol Coding, Wechsler, 1997a; Trail Making Test [TMT] – Part A, Tombaugh, 2004; Visuospatial: WAIS-III Block Design, Wechsler, 1997a; Rey-O copy, Meyers & Meyers, 1995; Language: Boston Naming Task, Kaplan, Goodglass, & Weintraub, 1983; Semantic Fluency [animals], Tombaugh, Kozak, & Rees, 1999; Memory: WMS-III Logical Memory II and Visual Reproduction II, Wechsler, 1997b; Rey-O 3-min delay, Meyers & Meyers, 1995; CVLT-II long delay free recall, Delis et al., 2000; Executive: TMT-Part B, Tombaugh, 2004; Phonemic Fluency [FAS], Tombaugh et al., 1999; Stroop – Interference; Demick & Harkins, 1997), in the context of generally intact activities of daily living. To avoid circularity, semantic clustering was never used as a criterion for the diagnoses of MCI and AD. All controls scored above -1.5 *SD* on their age and/or education-adjusted norms on the neuropsychological measures. The aMCI group consisted of 20 single domain and 62 multidomain participants; whereas the naMCI group consisted of 8 single domain and 22 multidomain participants.¹ The AD group included 23 participants with mild dementia (MMSE scores ≥ 21) and 7 participants with moderate dementia (MMSE scores = 10–20). As part of the longitudinal study, follow-up diagnostic information was available for a subset of control and MCI participants (number of follow-up visits ranged from 1 to 8 years).

¹For both aMCI and naMCI groups, there was no significant difference in semantic clustering scores between participants with single domain and multidomain MCI (all *p*-values $>.100$). Therefore, the aMCI and naMCI groups include both single and multidomain participants.

Measures

Chance-adjusted semantic clustering scores from the CVLT-II (Delis et al., 2000) were used to assess each participant's strategy use.² The CVLT-II is a standardized list-learning task, in which participants are presented with 16 words that can be grouped into four semantic categories: furniture, ways of travelling, vegetables, and animals. The list is presented orally across five learning trials, and recall performance is obtained after each trial. A second distractor list of words is then presented, followed by free recall for this list. Following the distractor trial, participants are administered short-delay free recall, short-delay cued recall (semantic categories are provided as a cue), long-delay (20-min) free recall, long-delay cued recall, and recognition trials for the first list.

Using the list-based approach (Stricker et al., 2002), we examined participants' raw chance-adjusted semantic clustering scores from learning trials 1 and 5, short-delay free recall, and long-delay free recall trials. A semantic cluster includes consecutive recall of a pair of categorically related words. To control for clustering that may occur by chance, the list-based clustering index (LBC) is calculated by subtracting the chance-expected clustering (EXP) score from the observed clustering score (OBS; total number of consecutive word pairs recalled) based on the number of words from the original list, as can be seen below:

$$LBC = OBS - EXP [(r - 1)(m - 1) / (N_L - 1)],$$

where r = the number of correct words recalled on that trial, m = the number of words in each semantic category, and N_L = the total number of words on the original list. The score ranges from -3 to 9 , with higher scores indicating more frequent use of semantic clustering. By calculating semantic clustering using the chance-expectancy score derived from the number of words on the to-be-remembered list (opposed to the number of words recalled), we avoid the assumption that semantic clustering occurs after recall has already been performed, an important distinction between the list-based and recall-based approaches to calculating semantic clustering.

RESULTS

Demographic data and mean neuropsychological test performances are presented in Table 1, and mean clustering performances are presented in Table 2. *Post hoc* comparisons were completed using a Dunnett's T3 procedure (equal variances not assumed). Groups had similar age [$F(3,191) = 1.62$; $p = .185$] and gender [$\chi^2(3, N = 195) = 2.45$; $p = .485$] distributions. There was a significant difference in education, $F(3,191) = 3.51$; $p = .016$, with controls ($M = 17.51$; $SD = 2.14$) attaining higher levels of education relative to the aMCI ($M = 16.34$; $SD = 2.89$) and AD ($M = 15.73$; $SD = 2.59$) groups. Therefore, education was a covariate in the univariate analyses. Age and education were modestly correlated with

²An index of serial clustering across learning trials is provided on the CVLT-II. Although we were primarily interested in semantic clustering, we also explored group differences in serial clustering. An ANCOVA (with age and education as covariates) assessing the impact of diagnosis (OA, naMCI, aMCI, AD) on serial clustering found a significant group difference, $F(3, 189) = 3.403$, $p = .019$, $\eta^2 = .051$; the OAs showed greater serial clustering relative to the aMCI group ($p = .017$, $d = 0.70$). No other between-group differences were observed (p -values ranged from .221 to 1.000).

semantic clustering (OA: age and Trial 1, $r = -.293$; $p = .033$, education and Trial 1, $r = -.288$; $p = .037$; naMCI: education and Trial 1, $r = -.387$; $p = .035$), and age was modestly related to recall performance (OA: age and Trial 1, $r = -.288$; $p = .037$, age and Trial 5, $r = -.336$; $p = .014$, age and Short Delay, $r = -.274$; $p = .047$; aMCI: age and Trial 1, $r = -.282$; $p = .010$, age and Trial 5, $r = -.494$; $p < .001$, age and Short Delay $r = -.402$; $p < .001$, age and Long Delay, $r = -.372$; $p = .001$; naMCI: age and Long Delay, $r = -.480$; $p = .007$; AD: age and Trial 1, $r = .440$; $p = .015$). Consequently, we included both age and education as covariates in our mixed-model analyses.

Semantic Clustering Measures

A linear mixed-effects regression analysis (unstructured using correlations) was conducted to determine if the rate of change in semantic clustering across trials (trial 1, trial 5, short-delay, long-delay) differed based on diagnosis (naMCI, aMCI, AD) relative to controls (see Table 3). There was a significant effect of trial, $F(1,191) = 77.14$, $p < .001$, that was modified by a significant diagnosis $\times$ trial interaction, $F(3,390) = 16.05$, $p < .001$. As illustrated in Figure 1, the controls and the naMCI group showed a similar semantic clustering slope [$\beta = -.0211$; $\beta SE = 0.157$; $t(390) = -1.35$; $p = .178$], with steady increases in clustering over trials. In contrast, the aMCI [$\beta = -.0714$; $\beta SE = 0.1201$; $t(390) = -5.91$; $p < .001$] and AD [$\beta = -.0837$; $\beta SE = 0.157$; $t(390) = -5.35$; $p < .001$] groups displayed reduced semantic clustering slopes relative to the controls.

To determine whether the aMCI and AD groups differed in their strategy use across trials, a similar linear mixed-effects regression analysis was conducted for only these two groups. Again, an effect of trial was observed, $F(1,110) = 8.63$, $p < .004$, with a relatively modest increase in semantic clustering across trials for both groups. Of interest, there was no significant difference between the groups in the rate of change in clustering across trials [$\beta = -.0123$; $\beta SE = 0.0922$; $t(224) = -1.33$; $p = .184$].

To determine whether the groups differed in semantic clustering during individual trials, we conducted simple effects analyses with an ANCOVA, assessing the impact of diagnosis (OA, naMCI, aMCI, AD) on semantic clustering separately for each trial (see Table 2). Age and education were the covariates, and a Bonferroni correction was applied ($p = .017$). As shown in Figure 1, there was no significant difference between the groups in semantic clustering during trial 1, $F(3,190) = 0.29$, $p = .833$, $\eta^2 = .005$. In contrast, a group difference was observed on trial 5, $F(3,190) = 7.71$, $p < .001$, $\eta^2 = .108$, with the OAs showing greater semantic clustering relative to the aMCI ($p < .001$; $d = 0.78$) and AD ($p = .004$; $d = 0.72$) groups. A group difference was also observed for clustering during the short-delay trial, $F(3,190) = 20.48$, $p < .001$, $\eta^2 = .244$. Again, the OAs displayed greater semantic clustering relative to the aMCI ($p < .001$; $d = 1.28$) and AD ($p < .001$; $d = 1.29$) groups. Of interest, on the short-delay trial, the naMCI participants performed similarly to the OAs ($p = .087$; $d = 0.41$) and displayed greater semantic clustering relative to the aMCI ($p = .004$; $d = 0.91$) and AD ($p = .020$; $d = 1.17$) groups. Finally, on the long-delay free recall trial, a group difference was observed, $F(3,190) = 18.23$; $p < .001$, $\eta^2 = .224$. Again, the OAs displayed greater semantic clustering compared to the aMCI ($p < .001$; $d = 1.17$) and AD ($p < .001$; $d = 1.45$) groups. The naMCI group had similar semantic clustering scores as the controls (p

= .649; $d = 0.28$) and outperformed the aMCI ($p = .002$; $d = 0.89$) and AD ($p = .001$; $d = 1.38$) participants. Overall, the aMCI and AD groups displayed similar semantic clustering across all trials.

Recall Measures

Recall performance was not a primary outcome of this study. However, to generally contrast the clustering and recall profiles of the groups, a quadratic mixed-effects regression analysis was conducted to determine if the rate of change in recall performance across trials (trial 1, trial 5, short-delay, long-delay) differed based on diagnosis (naMCI, aMCI, AD) relative to controls. As can be seen in Figure 2, the analysis revealed a significant quadratic effect of trial, $F(1,386) = 226.17$, $p < .001$, that was modified by a significant diagnosis $\times$ trial (quadratic) interaction, $F(3,386) = 4.12$, $p = .007$. The aMCI [$\beta = 0.358$; $\beta SE = 0.177$; $t(386) = 2.02$; $p = .004$] and AD [$\beta = 0.702$; $\beta SE = 0.230$; $t(386) = 3.05$; $p = .002$] groups displayed a reduced recall slope across trials relative to the controls. The naMCI group displayed a similar recall profile as the controls [$\beta = -0.015$; $\beta SE = 0.230$; $t(386) = -0.07$; $p = .948$]. To determine whether the aMCI and AD groups differed in their performance across trials, a similar analysis was conducted with these two groups. A significant quadratic effect of trial was observed, $F(1,110) = 51.43$; $p < .001$, that was modified by a significant linear diagnosis $\times$ trial interaction, $F(1,222) = 5.26$; $p = .023$ [the quadratic interaction was non-significant, $F(1,222) = 2.64$; $p = .106$]. The AD group showed a reduced recall slope across trials relative to the aMCI group, $\beta = -2.481$, $\beta SE = 1.082$, $t(222) = -2.29$, $p = .023$. These findings indicate that the profiles of clustering and recall differ among the groups, and recall is not a direct function of clustering.

To determine whether the groups differed in recall during individual trials, we conducted simple effects analyses with an ANCOVA, assessing the impact of diagnosis (OA, naMCI, aMCI, AD) on recall separately for each trial. Age and education were the covariates, and a Bonferroni correction was again applied ($p = .017$). In contrast to the semantic clustering data, group differences were observed on each trial (see Figure 2). The aMCI participants recalled fewer words during each trial relative to the controls and naMCI groups, who performed similarly across trials (see Table 2). Finally, the AD participants recalled fewer words at each trial relative to the other groups.

Relationship between Semantic Clustering and Recall

The correlational analyses (with Bonferroni correction: $p = .0125$) between semantic clustering and recall performance are presented in Table 2. For the control group, increased semantic clustering was associated with increased recall across trials (all r s ranged from .415 to .718). In contrast, semantic clustering was not associated with learning trials 1 or 5 for the naMCI group, although it was associated with short- and long-delay recall. For the aMCI group, increased semantic clustering was related to recall performance on trial 5 and the short-delay and long-delay free-recall trials. Finally, semantic clustering was not associated with recall performance for the AD group on any trial, which may have been due to a floor effect for their recall scores.

Semantic Clustering and Progression to aMCI and AD

To determine whether poor memory strategy use at baseline was associated with progression to aMCI and AD on follow-up, we examined group differences in clustering in converters (i.e., controls who progressed to aMCI and aMCI participants who progressed to AD) relative to non-converters (i.e., stable controls and stable aMCI participants) using independent sample *t* tests. As part of the longitudinal study, follow-up diagnostic information was available for 44 controls and 56 aMCI participants (number of follow-up visits ranged from 1 to 8 years). Twenty-five control participants remained stable, 10 later met criteria for aMCI, and 9 were re-classified as naMCI at follow-up (mean number of follow-up visits = 2.55; *SD* = 1.80). Twenty-one aMCI participants remained stable, 9 aMCI participants were later classified as normal, 9 met criteria for naMCI at follow-up, 12 progressed to AD, and 5 were diagnosed with another type of cognitive disorder (e.g., dementia with Lewy bodies, vascular dementia, etc.; mean number of follow-up visits = 1.84; *SD* = 0.83). The subsequent analyses included control participants at baseline who met criteria for aMCI on any follow-up visit (control converters) or remained stable across visits (non-converters), and aMCI participants at baseline who progressed to AD (aMCI converters) or remained diagnostically stable across follow-up visits (non-converters).

Control converters—The independent *t* test analysis conducted on the baseline data revealed no group difference in age [$t(33) = -1.57$; $p = .127$] or education [$t(33) = 0.711$; $p = .482$] between the stable controls and control-converters. The control-converters displayed reduced semantic clustering during short-delay free recall relative to the stable controls [$t(33) = 2.12$; $p = .044$; $d = 0.66$]. Although the control-converters generally had reduced clustering across trials (see Table 4), there were no significant differences between groups on trial 1 [$t(33) = 0.98$; $p = .335$; $d = 0.37$], trial 5 [$t(33) = 1.23$; $p = .229$; $d = 0.46$], or long-delay free recall [$t(33) = 1.49$; $p = .148$; $d = 0.46$].

To explore whether deficiencies in semantic clustering were specific to the development of aMCI (and therefore more suggestive of underlying AD pathology), we also conducted similar analyses for stable controls and control participants who later met criteria for naMCI. There were no group differences in age [$t(32) = 0.077$; $p = .939$] or education [$t(32) = 0.165$; $p = .870$] between the stable controls and converters. Additionally, there were no differences in clustering between stable controls and participants who met criteria for naMCI on follow-up (*t*-values ranged from $-.093$ to $.207$, *p*-values ranged from $.837$ to $.926$).

aMCI converters—The independent *t* test analyses conducted on the baseline data revealed no group difference in age [$t(31) = -0.99$; $p = .332$] or education [$t(31) = -1.44$; $p = .159$] between stable aMCI and aMCI-converters. When semantic clustering was compared across trials, there were no significant differences between groups [trial 1: $t(31) = -0.12$; $p = .903$; trial 5: $t(31) = 0.98$; $p = .333$; short-delay free-recall: $t(31) = 0.50$; $p = .621$; long-delay free-recall: $t(31) = 1.93$; $p = .064$].

Relationship between Semantic Clustering and Neuropsychological Tests

To determine whether clustering was associated with semantic processing (i.e., Animal Fluency) and/or executive functioning (i.e., TMT-Part B and Stroop Interference),

correlation analyses were completed for each group (see Table 5). For the aMCI participants, semantic fluency was associated with clustering at short-delay free-recall, $r = .253$, $p = .022$, and long-delay free-recall, $r = .239$, $p = .031$. In addition, clustering at long-delay free recall was correlated with quicker response times on executive measures for the aMCI group [TMT-Part B: $r = -.309$, $p = .005$; Stroop Interference: $r = -.316$, $p = .005$]. Faster response times on the TMT-Part B were also associated with clustering at trial 5 for the aMCI group [$r = -.235$, $p = .034$] and at short-delay free recall for the naMCI group [$r = -.365$, $p = .047$]. In contrast, semantic clustering was not significantly associated with semantic processing or executive functioning across analyses for the control and AD groups (all r s ranged from $-.026$ to $.398$).

DISCUSSION

Previous research has demonstrated that aMCI is associated with poor memory consolidation and acquisition (e.g., Crowell et al., 2002; Greenaway et al., 2006; Ribeiro et al., 2007), as well as reduced semantic clustering (an efficient memory strategy; e.g., Malek-Ahmadi et al., 2011). These findings are consistent with the early AD-related neuro-pathological changes observed in the hippocampus and pre-frontal regions (Jack et al., 1999). Despite such reports, few studies have explored differences in semantic clustering between the subtypes of MCI or have investigated whether amnesic MCI participants show a similar pattern of deficiencies in clustering as individuals with AD. In the present study, we examined semantic clustering and recall patterns across learning and delayed recall trials in amnesic MCI, nonamnesic MCI, and AD. In addition, we explored whether reduced semantic clustering was related to the development of aMCI in healthy controls or the progression to AD in aMCI participants. Overall, we found that recall and clustering profiles did not mirror each other across groups. Semantic clustering and recall performance distinguished the amnesic MCI and AD groups from controls and persons with nonamnesic MCI group; the amnesic MCI and AD groups displayed similar semantic clustering but differed in recall performance. In addition, controls who progressed to amnesic MCI (and not nonamnesic MCI) showed reduced semantic clustering at the short-delay at baseline testing compared to stable controls. This suggests that poor clustering is more reflective of underlying AD pathology.

Semantic clustering and recall performance differed between subtypes of MCI. The nonamnesic MCI group performed similarly to controls across measures, whereas the amnesic MCI participants displayed attenuated semantic clustering that was similar in pattern and severity as the impairments exhibited by the AD group. Of importance, all four groups displayed similar semantic clustering at trial 1; however, the AD and aMCI groups failed to benefit from repeated exposure to the list (i.e., they showed a relatively flat semantic clustering curve). Additionally, the AD and amnesic MCI groups did not show a significant improvement in semantic clustering at long-delay recall trial, despite being provided with semantic cues at the short-delay. Although impairments in semantic clustering were similar in the aMCI and AD groups, the AD participants showed greater impairment on recall measures than the aMCI participants. These results suggest that deficits in semantic clustering associated with amnesic MCI are more pronounced than the deficits in acquisition and consolidation. As such, our findings indicate that semantic clustering

deficiencies occur early in the course of the disease process, before the diagnosis of dementia. These results have important practical implications for clinicians. That is, in addition to findings of poor recall in patients, poor semantic clustering provides greater evidence of AD-related pathology.

Poor semantic clustering in amnesic MCI and AD likely reflects a breakdown in associations within semantic networks. It has been argued that semantic knowledge is organized into complex associative networks in temporal and parietal regions (Salmon, 2012). Concepts that share many attributes are thought to be more strongly associated than concepts with fewer commonalities, and through the principle of spreading activation, memory performance is facilitated when information is more strongly related within the network (Collins & Loftus, 1975). The ability to use semantic clustering to improve memory performance is contingent upon the integrity of these semantic networks. As demonstrated previously, individuals with AD display semantic deficits relative to healthy controls on clinical neuropsychological evaluations (e.g., Huff et al., 1986; Rosser & Hodges, 1994) and under experimental conditions (e.g., Chertkow & Bub, 1990), both within and across modalities (e.g., Hodges, Salmon, & Butters, 1992). These deficits have been attributed to a loss of semantic knowledge (e.g., Hodges et al., 1992), as well as deterioration in accessing, retrieving, and manipulating semantic information (e.g., Bayles, Tomoeda, Kaszniak, & Trosset, 1991).

As semantic networks are disrupted early in AD, it is not surprising that individuals with aMCI also show deficiencies in semantic processing on standard neuropsychological measures (Adlam et al., 2006; Murphy et al., 2006) and experimental tasks (Hudon, Villeneuve, & Belleville, 2011; Joubert et al., 2010, 2008). Researchers have attributed poor semantic processing to a breakdown in semantic associations rather than degradation of exemplars (e.g., Murphy et al., 2006). Our findings that semantic clustering in aMCI and AD does not improve with repeated exposure to a list of semantically related words, or when provided with semantic cues, support the hypothesis that semantic processing is impaired in aMCI. Individuals with aMCI and AD are unable to spontaneously use the semantic structure of a list to enhance recall performance because of a disruption in semantic networks. Our correlation analyses further support this interpretation. That is, poor memory strategy use at short-delay and long-delay free-recall was associated with reduced semantic processing in the amnesic MCI group. However, it is noted that reduced executive processing also contributed to poor semantic clustering in amnesic MCI participants.

Clustering is considered an efficient memory strategy that helps individuals “chunk” large amounts of information into smaller units, which allows for more efficient encoding, storage, and retrieval of information (Baddeley, 2001; Delis et al., 2000). For the controls, semantic clustering was associated with recall performance across trials. This may reflect their intact ability to use learning strategies. In contrast, semantic clustering was only associated with short-delay and long-delay free recall for the nonamnesic MCI group, indicating that strategy use did not aid their initial acquisition. For the amnesic MCI participants, increased semantic clustering was related to better recall performance on trial 5 and the short-delay and long-delay trials. Finally, semantic clustering did not predict recall performance for the AD group, which likely reflects a floor effect in this group. It is unclear

why semantic clustering did not predict recall performance on select learning trials for the MCI groups, particularly the nonamnesic participants, given that their performance was similar to that of controls across measures. This unexpected finding may reflect the heterogeneous nature of nonamnesic MCI, in which participants can differ significantly in the underlying etiology (e.g., frontotemporal dementia and dementia with Lewy bodies).

Of importance, our study shows that semantic clustering in controls is related to later progression to amnesic MCI. Clustering was generally reduced in these converters relative to non-converters, indicating that subtle changes in strategy use are evident in the pre-symptomatic stages of MCI. Although our findings were only significant at short-delay free-recall, similar trends with medium effect sizes were noted across learning and recall trials, suggesting that these analyses may have been underpowered.

Our results inform our understanding of how memory strategy use is impacted in MCI and AD; however, there are several limitations to our study. First, our participants were highly educated (i.e., college graduates on average), with years of education related (albeit modestly) to semantic clustering for the healthy controls and nonamnesic MCI groups. Although we controlled for education across analyses, our results may not generalize to all individuals with aMCI, naMCI, and AD. Second, our sample sizes were significantly different across groups, which may have influenced our findings. Finally, our analyses regarding progression to aMCI and AD may have been underpowered, underestimating the role of clustering in conversion. Given these limitations, future research should explore semantic clustering in participants with a wider range of educational backgrounds, with equal sample sizes maintained across groups.

In conclusion, our research demonstrates that semantic clustering is attenuated in aMCI and AD, whereas individuals with nonamnesic MCI perform similarly to controls. In contrast, AD participants show greater impairment relative to aMCI participants on traditional learning and recall measures. Whereas recall declines across trials for all groups after initial learning, investigation of semantic clustering reveals an “AD-type” profile in amnesic MCI participants and may be a useful tool for determining the early changes in the disease course.

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Fig. 1.
Group mean semantic clustering scores ($\pm$ SEM) as a function of trial.

Fig. 2.
Group mean recall scores ($\pm$ SEM) as a function of trial.

Table 1

Demographic variables and neuropsychological test scores for each group

Variable	OA			aMCI			naMCI			AD			ANOVA	
	M	SD		M	SD		M	SD		M	SD		F	p
Age (years)	69.04	9.23		69.88	8.73		71.0	11.29		73.77	12.11		1.62	.187
Age range		51–88			53–92			51–93			46–91			
Sex (F:M)		24:29			47:35			14:16			14:16			
Ethnicity (% Caucasian)		92.5%			82.9%			76.7%			73.3%			
Education (years) ^{a,b}	17.51	2.14		16.34	2.89		16.53	2.64		15.73	2.59		3.51	.016
GDS ^{a,c}	4.00	3.88		7.09	4.95		7.42	5.12		5.41	4.29		5.48	.001
MMSE ^{a,b,d,e}	28.60	1.60		26.84	2.47		28.00	2.32		21.93	4.54		42.66	<.001
WAIS-III Block Design ^{a,b,c,d,e}	13.37	2.96		9.59	3.07		10.43	2.81		6.75	3.46		31.37	<.001
Rey-O Copy ^{a,b,c,d,e}	32.68	2.59		28.92	5.47		28.57	4.55		21.60	10.38		22.80	<.001
WAIS-III Digit Symbol Coding ^{a,b,c,d,e}	63.28	12.54		50.26	14.67		52.62	12.48		31.21	14.48		33.36	<.001
WAIS-III DS Forward ^{b,d,e}	6.73	1.24		6.40	1.22		6.54	1.07		5.50	1.28		6.80	<.001
WAIS-III DS Backward ^{a,b,d,e}	5.37	1.32		4.42	1.21		5.00	1.39		3.23	1.36		18.35	<.001
WMS-III LM-I ^{a,b,c,d,e,f}	41.76	8.98		25.21	11.30		35.38	8.31		13.50	9.27		57.81	<.001
WMS-III LM-II ^{a,b,d,e,f}	26.10	6.76		12.26	8.67		21.96	6.93		3.50	4.89		70.75	<.001
WMS-III VR-I ^{a,b,c,d,e,f}	80.92	13.34		60.28	19.50		70.97	14.63		29.7	15.65		63.01	<.001
WMS-III VR-II ^{a,b,c,d,e,f}	56.94	21.54		22.81	18.96		42.63	19.67		1.83	4.96		68.89	<.001
Rey-O – Recall ^{a,b,c,d,e,f}	17.53	5.43		8.13	5.40		12.93	4.39		2.66	3.94		65.23	<.001
TMT-Part A (in sec) ^{a,b,c,d,e}	27.34	10.09		40.12	18.96		33.90	10.03		71.07	45.88		24.73	<.001
TMT-Part B (in sec) ^{a,b,c,d,e}	71.08	34.35		136.35	74.01		106.37	43.57		227.28	87.58		36.37	<.001
Boston Naming Test ^{a,b}	57.71	1.79		50.97	8.96		53.20	8.42		47.20	9.25		13.38	<.001
FAS Fluency ^{a,b,d,e}	43.53	10.52		34.98	12.93		40.63	16.19		26.93	11.41		12.52	<.001
Animal Fluency ^{a,b,c,d,e}	21.89	4.56		17.71	5.14		18.53	5.64		11.73	6.01		24.46	<.001

Variable	OA		aMCI		naMCI		AD		ANOVA	
	M	SD	M	SD	M	SD	M	SD	F	p
Stroop Color (in sec) ^{a,b,d,e}	65.42	12.42	78.86	26.88	69.10	16.14	100.83	30.03	16.35	<.001
Stroop Word (in sec) ^{b,d,e}	49.87	10.37	55.71	15.49	51.00	10.37	67.46	18.25	10.60	<.001
Stroop Interference (in sec) ^{a,b,d,e}	125.62	31.47	162.04	57.63	141.73	45.17	217.95	54.25	19.05	<.001

Note. GDS = Geriatric Depression Scale (raw score out of 30; $N = 178$; Brink et al., 1982); MMSE = Mini-Mental State Examination (raw score out of 30; $N = 195$; Folstein, Folstein, & McHugh, 1975); WAIS-III = Wechsler Adult Intelligence Scale – 3rd Edition; Block Design (age-corrected scaled scores; $N = 190$; Wechsler, 1997a); Rey-O (raw score out of 36; $N = 194$; Meyers & Meyers, 1995); Digit Symbol Coding ($N = 181$; Wechsler, 1997b); DS = Digit Span (longest digit length; $N = 181$; Wechsler, 1997b); WMS-III = Wechsler Memory Scale – 3rd Edition; LM = Logical Memory (raw score out of 75 and 50 for LM-I and LM-II, respectively; $N = 182$; Wechsler, 1997b); VR = Visual Reproduction (raw score out of 104; $N = 195$; Wechsler, 1997b); TMT = Trail Making Test ($N = 194$ for part A and $N = 190$ for part B; Strauss et al., 2006); Boston Naming Test ($N = 180$); FAS and Animal Fluency ($N = 195$); Stroop ($N = 189$ for color and word trials, and $N = 152$ for interference). Non-Caucasian participants included African-American ($n = 17$), Hispanic ($n = 11$), and Asian ($n = 5$) individuals. Multiple one-way ANOVAs were completed on the demographic and neuropsychological data, with post hoc comparisons completed using a Dunnett's T3 procedure (equal variances not assumed).

- ^a Significant difference between OA and aMCI groups ($p < .05$).
- ^b Significant difference between OA and AD groups ($p < .05$).
- ^c Significant difference between OA and naMCI groups ($p < .05$).
- ^d Significant difference between aMCI and AD groups ($p < .05$).
- ^e Significant difference between naMCI and AD groups ($p < .05$).
- ^f Significant difference between naMCI and aMCI groups ($p < .05$).

Table 2

Clustering and recall performance across trials on the CVLT-II, and corresponding Pearson correlation coefficients

	<u>Clustering</u>		<u>Recall</u>		<u>Correlation Analyses</u>	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>r</i>	<i>p</i>
Controls						
Trial 1	0.023	0.833	5.51	1.51	.415 *	.002
Trial 5	1.717	3.050	11.94	2.76	.565 *	<.001
Short-delay	2.355	2.470	9.70	3.24	.718 *	<.001
Long-delay	2.845	2.767	10.36	3.48	.697 *	<.001
naMCI						
Trial 1	−0.087	0.751	4.93	1.72	.299	.108
Trial 5	0.993	2.221	11.37	2.37	−.159	.400
Short-delay	1.427	1.826	9.03	3.01	.592 *	.001
Long-delay	2.100	2.578	9.63	2.62	.569 *	.001
aMCI						
Trial 1	−0.049	0.626	3.99	1.69	.039	.727
Trial 5	0.088	1.454	7.65	2.57	.363 *	.001
Short-delay	0.213	1.156	4.65	3.54	.357 *	.001
Long-delay	0.566	1.409	3.96	3.66	.663 *	<.001
AD						
Trial 1	−0.060	0.526	2.80	1.77	−.125	.512
Trial 5	0.080	0.853	5.10	2.29	.331	.074
Short-delay	0.160	0.334	1.20	1.75	.002	.990
Long-delay	0.160	0.225	0.53	1.01	−.298	.110

Note. CVLT-II = California Verbal Learning Test-II (raw chance-adjusted semantic clustering scores: −3 to 9, raw recall scores: 0 to 16; Delis et al., 2000)

* Significant correlation between clustering and recall measures ($p < .0125$).

Table 3

Results from the mixed-effects regression analyses for the clustering (linear) and recall (quadratic) data

	Clustering				Recall			
	<i>b</i>	<i>SE</i>	<i>t</i>	<i>p</i>	<i>b</i>	<i>SE</i>	<i>t</i>	<i>p</i>
Age	−0.002	0.008	−0.27	.789	−0.051	0.0140	−3.63	.001
Education	−0.022	0.029	−0.78	.435	0.015	0.0528	0.28	.780
Trial	0.911	0.094	9.68	<.001	8.447	0.7068	11.95	<.001
Trial × Trial	—	—	—	—	−1.443	0.1382	−10.45	<.001
Group								
AD	0.412	0.320	1.28	.200	2.557	1.2887	1.98	.048
aMCI	0.229	0.244	0.94	.349	1.378	0.9917	1.39	.166
naMCI	−0.116	0.315	−0.37	.712	−0.462	1.2843	−0.36	.719
OA	—	—	—	—	—	—	—	—
Trial × Group								
AD	−0.837	0.157	−5.35	<.001	0.702	0.2298	3.05	.002
aMCI	−0.714	0.121	−5.91	<.001	0.358	0.1773	2.02	.044
naMCI	−0.211	0.157	−1.35	.178	−0.015	0.2298	−0.07	.948
OA	—	—	—	—	—	—	—	—

Note. SE = standard error; AD = Alzheimer's disease; aMCI = amnesic mild cognitive impairment; naMCI = nonamnesic mild cognitive impairment.

Table 4

Semantic clustering and recall performance at baseline for stable controls, aMCI-converters, stable aMCI, and AD-converters

Trial	<u>Stable Controls</u>		<u>Control-converters</u>		<u>Stable aMCI</u>		<u>aMCI-converters</u>	
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>
Semantic Clustering								
Trial 1	0.120	1.013	-0.220	0.649	-0.057	0.563	-0.033	0.481
Trial 5	2.168	3.348	0.740	2.385	0.048	1.161	-0.317	0.711
Short-delay	2.800	2.520	1.300*	1.578	0.133	1.078	-0.033	0.531
Long-delay	3.192	3.085	1.940	1.814	0.352	0.790	-0.017	0.289

Note.

* Group difference between stable controls and control-converters ($p < .05$).

Table 5

Correlations between semantic clustering on CVLT-II and neuropsychological test performance

	Trial 1	Trial 5	Short-delay	Long-delay
Controls				
Animal Fluency	-.046	.246	.131	.059
TMT-Part B	-.156	-.027	-.116	-.108
Stroop Interference	.146	-.188	-.151	-.115
naMCI				
Animal Fluency	.184	-.258	.253	.171
TMT-Part B	-.104	-.043	-.365**	-.271
Stroop Interference	-.059	.297	-.112	-.158
aMCI				
Animal Fluency	.051	.161	.253*	.239*
TMT-Part B	-.101	-.235*	-.174	-.309**
Stroop Interference	-.034	-.170	-.188	-.316**
AD				
Animal Fluency	-.099	.230	-.057	.114
TMT-Part B	-.158	-.274	-.110	-.084
Stroop Interference	-.026	-.405	.398	.065

Note. CVLT-II = California Verbal Learning Test-II (raw chance-adjusted semantic clustering scores: -3 to 9; raw recall scores: 0 to 16; Delis et al., 2000); naMCI = nonamnesic mild cognitive impairment; aMCI = amnesic mild cognitive impairment; AD = Alzheimer's disease; TMT = Trail Making Test.

* small effect size.

** medium effect size.