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Impairment of memory generalization in preclinical autosomal dominant Alzheimer's disease mutation carriers

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ABSTRACT

Fast, inexpensive, and noninvasive identification of Alzheimer's disease (AD) before clinical symptoms emerge would augment our ability to intervene early in the disease. Individuals with fully penetrant genetic mutations causing autosomal dominant Alzheimer's disease (ADAD) are essentially certain to develop the disease, providing a unique opportunity to examine biomarkers during the preclinical stage. Using a generalization task that has previously shown to be sensitive to medial temporal lobe pathology, we compared preclinical individuals carrying ADAD mutations to noncarrying kin to determine whether generalization (the ability to transfer previous learning to novel but familiar recombinations) is vulnerable early, before overt cognitive decline. As predicted, results revealed that preclinical ADAD mutation carriers made significantly more errors during generalization than noncarrying kin, despite no differences between groups during learning or retention. This impairment correlated with the left hippocampal volume, particularly in mutation carriers. Such identification of generalization deficits in early ADAD may provide an easily implementable and potentially linguistically and culturally neutral way to identify and track cognition in ADAD.

1. Impairment of memory generalization in preclinical autosomal dominant Alzheimer's disease mutation carriers

In the preclinical phase of Alzheimer's disease (AD), which can last years or decades, underlying pathology of the medial temporal lobe (MTL) region accumulates before reaching a "tipping point" where cognitive and clinical symptoms emerge and affect daily life (Sperling, 2011). In vivo markers of pathology are useful for early detection, allowing therapeutic intervention before cognitive symptoms emerge. Early identification of incipient symptoms is of particular interest in cases of late-onset AD (LOAD)—the most common form of the disease whose incidence increases after the age of 65 years to involve over 40% of persons aged 85 years and above (Evans et al., 1989). However, future development of overt dementia is often difficult to predict. The study of relatively young persons with autosomal dominant Alzheimer's disease (ADAD; typically with the age of onset between the 30s and 50s), in whom the future development of dementia can be predicted with essentially 100% certainty, can provide a model of the more common LOAD.

Several biomarkers show great promise for early identification of ADAD, including markers of beta-amyloid deposition, tau

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accumulation, changes in brain structure (e.g., hippocampal or MTL atrophy), and other biochemical changes (e.g., synaptic damage, oxidative stress; see Ringman et al., 2008). These measures provide the foundation for understanding the underlying neurobiological mechanisms of ADAD and can now be used as a validating standard for examinations that are more appropriate for the masses, that is, easy-to-administer, inexpensive, fast, and noninvasive cognitive screening tools. This article investigates 1 promising measure—the simple, computer-based acquired equivalence task.

In this task, individuals learn a series of antecedent-consequent pairs using feedback during an acquisition phase and then are challenged to transfer previous learning to new situations without feedback in a generalization phase, when familiar stimuli are presented in novel pairings. Early computational models predicted that dysfunction of MTL circuits would produce generalization failures when task demands change, despite intact learning of associations (Gluck and Myers, 1993). More recent patient work, including individuals with MTL damage such as post-traumatic stress disorder or hypoxia, has validated that generalization is a sensitive and selective behavioral marker of hippocampal dysfunction (Bodi et al., 2009; Levy-Gigi et al., 2012; Myers et al., 2008a). Recent work has also implicated generalization deficits in mild stages of AD (Bodi et al., 2009). Similar generalization tasks have shown poor generalization among nondemented elderly with hippocampal atrophy visible on structural imaging (Myers et al., 2002, 2003) and that generalization performance could predict cognitive outcome (normal, mild cognitive impairment [MCI], and probable AD) 2 years later among nondemented elders who showed no objective evidence of a disease state that could affect neural or cognitive function (Myers et al., 2008b).

The present study extends this approach to test generally healthy, preclinical, young adult carriers of fully penetrant autosomal dominant mutations in genes coding for presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), or amyloid precursor protein (*APP*) who will develop AD later in life (Kennedy et al., 1993; Sherrington et al., 1996). Although mutation carriers account for only a small percentage of AD cases, they provide a unique opportunity to sensitively and accurately evaluate the earliest cognitive manifestations of the disorder. Although minor qualitative and quantitative differences exist between ADAD and LOAD, overall the neuropathological changes, especially in the MTL, are similar (Ringman et al., 2016). For example, presymptomatic ADAD carriers showed increased hippocampus activity relative to noncarrier controls in a face-name associative encoding task that mirrored brain activity in AD patients (Quiroz et al., 2010). Similarly, relative to noncarrier kin, ADAD mutation carriers have reduced fractional anisotropy in the fornix, a major efferent of the hippocampus (Ringman et al., 2007), and show decreased MTL volumes as they approach the expected age of disease diagnosis (Lee et al., 2013). Such MTL atrophy in ADAD mutation carriers is consistent with early AD (Apostolova et al., 2011; Cash et al., 2013).

Aggregate data from the Dominantly Inherited Alzheimer Network confirm the development of cerebrospinal fluid changes, fibrillar amyloid deposition, regional hypometabolism, and measurable structural brain changes in ADAD carriers as long as 15–20 years before the anticipated time of overt clinical symptoms (Bateman et al., 2012). Similarly, using quantitative neuropsychological testing, cognitive deficits have been identified 5–12 years before functional decline and typically parallel to those seen early in LOAD, with deficits in memory and executive function often seen first (Aguirre-Acevedo et al., 2016; Almkvist et al., 2017; Ringman et al., 2005). However, conventional neuropsychological assessments typically involve paper-and-pencil tasks that are difficult to apply across diverse languages, cultures, and educational levels, and so tests with minimal language components have been proposed. For example, 1 computerized task involving short-term retention for the binding of features in a visual stimulus differentiated asymptomatic ADAD mutation carriers from healthy controls better than standard neuropsychological tests and did so in persons approximately 9 years before the onset of MCI (Parra et al., 2010). A flash-card version of this task has been developed, which might be of wider utility, for example, in primary care settings (Della Sala et al., 2016). Here, we evaluated whether our visual-matching acquired equivalence task, which has previously demonstrated sensitivity to MTL pathology and early cognitive decline in nondemented older adults, could differentiate performance among generally healthy, young, preclinical ADAD mutation carriers and their noncarrying kin before other overt cognitive decline. Arguably, this task is more useful for early detection than existent tasks because it takes approximately 15 minutes to complete, runs automatically on a standard laptop computer, is relatively engaging (similar to a short video game), and has been translated and successfully used in populations speaking Arabic, French, Chinese, Italian, Hungarian, and Hebrew.

Based on previous research showing that generalization in our acquired equivalence task depends on processing in the MTL (Herzallah et al., 2010; Myers et al., 2003, 2008a), we predicted that young ADAD mutation carriers would show significantly worse generalization than their noncarrying kin despite equivalent learning. Furthermore, we examined the neural correlates of this deficit. Specifically, prior studies have found hippocampal volume reduction in nondemented elderly correlates with poor generalization on this task (Myers et al., 2003) and similar tasks (Myers et al., 2002); accordingly, we predicted that worse generalization among mutation carriers in the present study would likewise be associated with smaller hippocampal volumes. We also examined a second MTL region, entorhinal cortex thickness, because it has been implicated in generalization in animal models of acquired equivalence (Coutureau et al., 2002), and because entorhinal atrophy accompanies (or even precedes) hippocampal atrophy in sporadic AD (Bobinski et al., 1999; de Toledo-Morrell et al., 2000). Finally, as a control region, we considered the frontal lobe; we predicted that generalization would not be associated with middle frontal gyrus thickness, based on results from a similar task showing that generalization does not involve the frontal cortex (Chase et al., 2008). Our expectation of a relationship between hippocampal volume and generalization would be consistent with the idea that MTL dysfunction appears early in the progression of preclinical ADAD and that generalization tests might have utility as behavioral markers of this dysfunction, before other cognitive and clinical symptoms emerge.

2. Methods

2.1. Participants

Subjects were a subset of participants in a study of ADAD being performed at UCLA. Participants were either native English- or Spanish-speaking. Participants older than 55 years were excluded to better age-match with noncarrying kin. All participants were nondemented and scored <1 on the Clinical Dementia Rating (CDR) scale, a structured interview of the subject and informant in which subjects are rated: 0 (asymptomatic), 0.5 (equivocal impairment), 1 (mild), 2 (moderate), or 3 (severe dementia) (Morris, 1997).

Participants included 34 nondemented carriers of ADAD mutations and 11 noncarrying kin; see Table 1, for demographic information. Participants came from 27 different families with pathogenic mutations in the *PSEN1*, *PSEN2*, or *APP* genes. Of the 45 participants, 13 were at risk for a common *APP* mutation (V717I) (Mullan et al., 1993) and 12 for a common *PSEN1* mutation (A431E) (Murrell et al., 2006). One subject was at risk for a *PSEN2* mutation (N141I),

Table 1
Demographics and neuropsychological performance

Demographics and neuropsychological performance	Mutation carriers (n = 34)	Noncarrying kin (n = 11)	t-value/χ^2 (n.s.)
Chronological age in years	35.6 (10.1)	32.4 (8.9)	−1.14
Female, n (%)	23 (68)	7 (64)	0.06
Years of education	11.65 (4.35)	13.45 (4.13)	1.21
Whose language of testing was Spanish, n (%)	14 (41)	2 (18)	1.92
Mutation in family (*PSEN, APP*)[a]	24/10	8/3	0.02
Positive for *APOE* ε4 allele, n (%)	4 (12)	4 (36)	3.44
Adjusted age (age relative to median age of dementia diagnosis in family)	−15.2 (8.5)[b]	−19.3 (9.5)	−1.45
MMSE score	27.8 (3.2)	28.2 (1.8)	0.47
CDR, global score	0.24 (0.25)	0.18 (0.25)	0.16
	(18 CDR = 0, 16 CDR = 0.5)	(7 CDR = 0, 4 CDR = 0.5)	0.39
Mean CASI score	92.81 (6.7)	92.86 (6.0)	0.02

All scores are given as mean (SD).
Key: APP, amyloid precursor protein; CDR, Clinical Dementia Rating; CASI, Cognitive Abilities Screening Instrument; MMSE, Mini–Mental State Examination; SD, standard deviation; PSEN, presenilin.
[a] Further breakdown by specific mutation is not shown to protect subject confidentiality.
[b] Data unavailable for 2 individuals. n.s. indicates that there were no significant group differences in demographics or neuropsychological performance (all p's > 0.08).

and the rest of the subjects were at risk for different *PSEN1* mutations (G206A [n = 5]; L235V [n = 4]; R269H [n = 3]; and A260V, E184D, E280A, H163R, S212Y, C410Y, and G378E [n = 1 each]).

The UCLA Institutional Review Board approved all experimental procedures, and research was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. The protocol included storing and sharing of data and biospecimens with collaborators and their use in future research studies. All participants provided written informed consent before initiation of any experimental procedures.

2.2. Clinical assessments

Subjects underwent clinical assessments in their preferred language. Assessment included the Mini–Mental Status Examination (Folstein et al., 1975) and the Cognitive Abilities Screening Instrument, which have both English and Spanish versions and have been used in cross-cultural studies of cognitive aging (Teng et al., 1994).

Each subject's age in relation to his or her estimated age of dementia onset was calculated. As the age of onset of symptoms is fairly consistent within a family and mutation but more variable between families, an "adjusted age" can be calculated that estimates how many years from disease manifestation a given subject is (Ryman et al., 2014). In our experience, the age of clinical diagnosis of dementia is a more reproducible measure; therefore, we calculated an adjusted age for each subject (regardless of mutation status) as his or her chronological age minus the median age of dementia diagnosis in his or her family. For example, someone who is 32 and comes from a family in which median age of dementia diagnosis is 40 years would have an adjusted age of "−8," indicating approximately 8 years until diagnosable dementia. Although noncarrying kin do not carry the mutation, we still calculated an adjusted age for each subject in the same way as mutation carriers for comparison purposes.

2.3. Genetic testing

Extraction of DNA and genotyping of apolipoprotein E were performed using standard techniques. Apolipoprotein (ApoE) single-nucleotide polymorphism (SNP) genotyping was carried out by real-time polymerase chain reaction (PCR) on an Applied Biosystems 7900HT Real Time PCR machine (Applied Biosystems, Foster City, CA, USA), using TaqMan SNP Genotyping Assays (#C___3084793_20 and C____904973_10 for rs429358 and rs7412, respectively). SDS, version 2.3, software was used to analyze the raw data and to call the genotype. The presence or absence of the specific mutation each subject was known to be at risk for was assessed using standard Sanger sequencing, according to published protocols and primers.

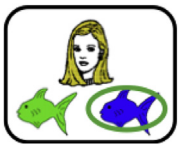
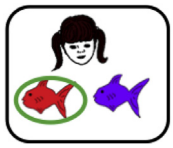
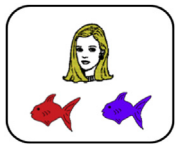
2.4. Acquired equivalence task

Participants were tested in a quiet room, using software programmed and presented using SuperCard (Allegiant Technologies, San Diego, CA, USA). Instructions were translated into Spanish for Spanish-speaking participants, but the task itself is otherwise essentially nonverbal. Methods follow those described previously (Myers et al., 2003). In brief, on each trial, the participant sees both a cartoon face (either a brown-haired man, a blonde-haired woman, a blonde-haired boy, or a brown-haired girl, labeled in Table 2 as A1, A2, B1, or B2) and a pair of colored fish (red, green, blue, or purple, labeled in Table 2 as X1, X2, Y1, or Y2). Assignment and mapping of faces and fish are randomized across subjects. Each face shares 1 binary-valued feature with another face: gender (male, female), age (child, adult), and hair color (blonde, brown). The participant is asked to indicate which fish belongs to each face. Correct responses (right vs. left) varied randomly. There is a 1-second pause between trials.

The task has 2 distinct phases: training and test. During training, participants receive feedback to guide learning (e.g., the selected fish is circled, and "Correct" or "Incorrect" is displayed for 1 second). Training has 3 stages, though the start of a new stage is not signaled. In the "shaping" stage, participants learn to pair 2 faces with specific colored fish (e.g., A1-X1, B1-Y1). This stage continues until the participant makes 4 consecutive correct responses or for a maximum of 20 trials. Next, in the "equivalence training" stage, participants learn to pair new faces with the same colored fish (e.g., A2-X1, B2-Y1). In the process, participants typically learn that some faces (e.g., A1, A2) are equivalent because they map onto the same consequent (e.g., X1). This stage terminates after 8 consecutive correct responses or a maximum of 32 trials. Finally, in a "new consequents" stage, participants learn to pair the original faces with a new colored fish (e.g., A1-X2); this stage terminates after 12 consecutive correct responses or a maximum of 60 trials. At each stage, maintenance trials with prior-trained pairs are interleaved with the new pairs.

A test phase follows in which participants no longer receive feedback. To measure retention, participants are tested on their recall of the trained fish-face associations in random order (12 trials per block). Intermixed within retention trials are 2 novel fish-face

Table 2
Acquired equivalence task and sample screen displays

Training phase (feedback) Stage 1: Shaping	Stage 2: Equivalence training	Stage 3: New consequents	Test phase (No feedback) Generalization and retention
			
A1→X1	A1→X1 **A2→X1**	A1→X1 A2→X1 **A1→X2**	A1→X1 A2→X1 A1→X2 **A2→X2**
B1→Y1	B1→Y1 B2→Y1	B1→Y1 B2→Y1 B1→Y2	B1→Y1 B2→Y1 B1→Y2 B2→Y2

During stage 1, participants learn the first 2 associations between difference faces (A1, B1) and fishes (X1, Y1). During stage 2, different faces (A2, B2) are associated with the same fishes (equivalence training), whereas during stage 3, new consequents (X2, Y2) are added. At each stage of the task, participants continued to receive maintenance trials with previously learned fish-face pairs. During the testing phase, participants are tested for retention of the associations learned in stages 1–3 and also on generalization to new pairings of faces and fishes (i.e., A2→X2, B2→Y2). Retention and generalization pairs are interleaved randomly during the test phase. Screen shots of the task (shown above) represent examples of the bolded items; however, note that assignment of specific faces and fishes to stimuli (A1, A2, X1, X2, etc.) is randomized across subjects.

pairings representing generalization (presented once each with the fish in either left-right order). Although these pairings were never explicitly trained, participants should show successful generalization, defined as predicting the same outcome (fish) for faces that were trained to be equivalent. For example, because A1 was trained to be functionally equivalent to A2 (in that both predict X1), and because A1 was also paired with X2, participants should generalize that A2 is also paired with X2. The test includes 3 blocks (36 retention and 12 generalization trials); trial order within a block is randomized across subjects.

2.5. Magnetic resonance imaging scanning and volumetric analyses

Subjects underwent structural magnetic resonance imaging (MRI) scanning using a 3D T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence using the following parameters: 192 slices at 1 mm slice thickness, voxel size = 1 × 1 × 1 mm^3, repetition time/echo time (TR/TE) = 1620/3 ms, inversion time (TI) = 950 ms, TE = 3 ms, and the scan time of 6 minutes. Volumetric segmentation of T1-weighted MPRAGE MRI volumes was completed automatically using FreeSurfer software, version 5.3.0 (surfer.nmr.mgh.harvard.edu). The automated cortical reconstruction procedure assigns a neuroanatomical label to each voxel in an MRI volume based on a combination of intensity mapping and probabilistic spatial atlases. FreeSurfer volumetric processing has been validated as an automated method to obtain subcortical volumes (Thompson et al., 1997; but see, Wenger et al., 2014). Full description of processing methods has been described previously (Fischl et al., 2002). Region of interest (ROI) volumes for cortical and subcortical structures are calculated during this process by multiplying the number of voxels in an ROI by the single voxel volume. To account for individual differences in total brain volume, a residual normalization approach was used to control for total intracranial volume. Therefore, the studentized residual for each region of interest was used in the partial correlation analyses with task performance.

Our brain regions of interest included the bilateral hippocampus, entorhinal cortex, and middle frontal gyrus. The hippocampus was selected based on (1) the memory construct measured by our task as predicted by Gluck and Myers (1993) computational model of corticohippocampal function in generalization and (2) findings relating poorer generalization to hippocampal atrophy, as measured by neuroimaging (Myers et al., 2002, 2003). The entorhinal cortex was selected based on animal models (Coutureau et al., 2002) and patients with broader MTL dysfunction [e.g., hypoxia (Myers et al., 2008a), post-traumatic stress disorder (Levy-Gigi et al., 2012), and AD (Bodi et al., 2009)]. We selected the middle frontal gyrus as a control region based on evidence that generalization deficits are unrelated to frontal functioning and volume (e.g., Chase et al., 2008; Farkas et al., 2008). No other brain areas were examined.

2.6. Statistical analysis

Mixed-design analysis of covariance (ANCOVA), using SPSS 20, compared mutation carriers and noncarrying kin on their cognitive performance during training (acquisition) and test (retention and generalization), followed by planned 1-way analysis of variance (ANOVAs) and Fisher's least significant difference post hoc tests. Partial correlations examined relationships between generalization performance and our 3 brain regions of interest (hippocampal volume, entorhinal cortex thickness, and middle frontal gyrus thickness), separately for the left and right regions. Analyses were performed for all subjects and, where appropriate, separately for all mutation carriers and noncarriers, and for carriers of *APP* and *PSEN* mutations. We controlled for chronological age and education in all analyses. These covariates were selected because separate analyses using chronological age and education as independent variables revealed significant differences in task performance (p's < 0.05). The level of significance was set at $\alpha = 0.05$.

3. Results

3.1. Subjects

All demographic and neuropsychological results are presented in Table 1. Genetic testing confirmed which participants were carriers or noncarrier kin. Participants were all younger or middle-aged adults (mutation carriers: mean [M] = 35.6 years, standard deviation [SD] = 10.1, range: 19–48 years; noncarrying kin: M = 32.4 years, SD = 8.9, range: 19–53 years) and were, on average, 16 years from expected age of dementia onset (mutation carriers: $M = -15.0$ years, $SD = 8.3$, range: −35 to −4 years; noncarrying kin: $M = -19.1$ years, SD = 9.4, range: −34 to −1 year). As shown in Table 1, groups did not differ significantly in chronological age, gender, education, language of testing, mutation in family,

prevalence of the ε4 allele of *APOE*, adjusted age to typical familial dementia onset, or neuropsychological performance (all p's > 0.08).

3.2. Training phase

All participants reached criterion, by completing each training stage in fewer than the maximum allowed trials. On average, mutation carriers required 54 ± 30 trials to reach criterion across training, whereas noncarriers required 53 ± 24 trials.

A Group (mutation carriers, noncarrying kin) × Training Stage (1–3) mixed-design ANCOVA on mean number of total errors, with chronological age and education as covariates, revealed no significant main effects of Group [F (1, 41) = 0.27, p = 0.61, η^2= 0.02] or Training Stage [F (2, 82) = 1.04, p = 0.36, η^2= 0.03], as well as no interaction [F (2, 82) = 0.12, p = 0.89, η^2= 0.01 (see Fig. 1)].

3.3. Testing phase

A mixed ANCOVA on mean proportion of errors, with Group and Trial Type (Generalization, Retention) as independent variables and chronological age, education, and learning performance (i.e., number of total training trials) as covariates (see Fig. 2). We controlled for learning here because generalization (at least partially) depends on representational changes that occur over the course of training (Shohamy et al., 2008), and indeed, learning performance did correlate with generalization [r (43) = 0.58, $p <$ 0.001]. A main effect of Group [F (1, 40) = 6.91, p = 0.012, η^2 = 0.15] revealed that noncarrying kin made fewer errors overall than mutation carriers. There was no main effect of Trial Type [F (1, 40) = 1.68, p = 0.20, η^2 = 0.04], indicating that errors were approximately equal across groups for retention and generalization. However, the critical interaction was significant [F (1, 40) = 5.29, p = 0.027, η^2 = 0.12]. Follow-up tests revealed no group differences on retention (p = 0.25); however, as predicted, mutation carriers showed worse generalization (M = 33.8% errors) than noncarrying kin (M = 12.6% errors) (p = 0.02).

Because we were interested in cognitive changes during preclinical stages of AD, we reran all analyses excluding individuals who had a total Mini–Mental Status Examination score less than 25 (n = 4, all mutation carriers). Patterns of significance were unchanged with these individuals removed. Similarly, because a CDR score of 0.5 may be considered already in a symptomatic/clinical stage, we added CDR scores as an independent variable. This produced no significant main effects or interactions; all patterns of significance remained otherwise unchanged, indicating no differences in task performance between the subgroups with CDR = 0 and CDR = 0.5.

Finally, to examine the utility of our behavioral task across cultures and ethnic groups, we examined whether language of testing (English, Spanish) had any influence on generalization. Results showed no significant main effect of language [F (1, 41) = 1.63, $p >$ 0.05].

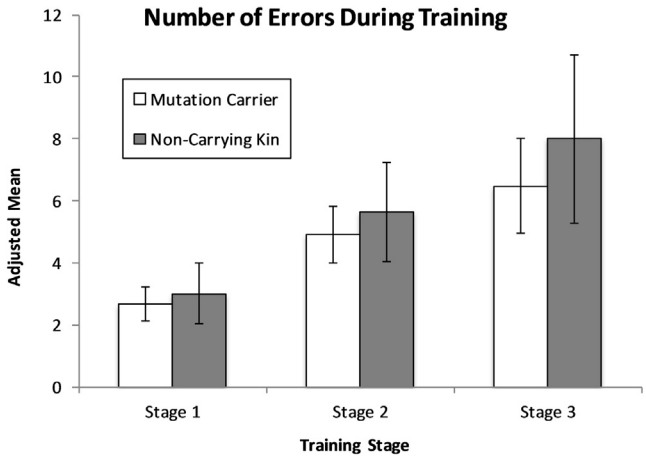


Fig. 1. Performance on the training phase of the acquired equivalence task. Adjusted mean error scores for the training phase. Covariates include chronological age and education. Error bars represent the standard error of the mean.

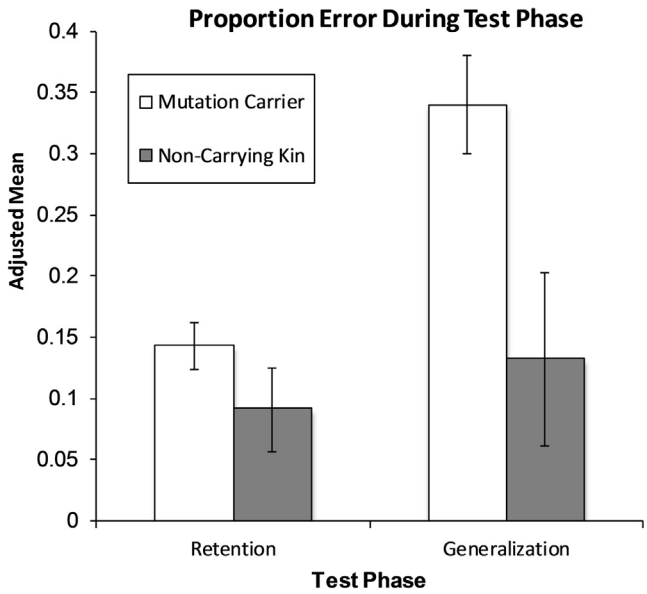


Fig. 2. Performance on the test phase of the acquired equivalence task. Adjusted proportion error scores for the test phase: Retention (old pairs) and generalization (new pairs). Covariates include chronological age, education, and learning performance (i.e., number of total training trials). Error bars represent the standard error of the mean.

3.4. MRI volumetric analyses

Only 41 participants had available T1 MRI data (30 mutation carriers and 11 noncarrying kin); 4 scans were either not obtained due to claustrophobia in the scanner or not available for analysis. In this subset, we observed no group differences in the left or right hippocampal volume (p's > 0.49), entorhinal cortex thickness (p's $>$ 0.43), or middle frontal gyrus cortical thickness (p's > 0.24).

Partial correlations, controlling for chronological age and education, examined the relationship between mean proportion of generalization errors and our brain regions of interest, separately for the left and right regions. In the left hippocampus, a negative correlation across all participants [r (37) = −0.34, p = 0.034] showed that those with more generalization errors had smaller left hippocampal volumes. In a subgroup analysis stratified by mutation status, the association between generalization and hippocampal volumes persisted in the gene mutation carriers only [r (30) = −0.43, p = 0.014 (see Fig. 3A)] and not in noncarrying kin [r (7) = −0.01, p = 0.98]. This association was present both for carriers of *APP* mutations [r (5) = −0.89, p = 0.008] and *PSEN* mutations [r (19) = −0.47, p = 0.031], despite the smaller numbers in both of these groups. No significant associations were found with the right hippocampus and generalization (see Fig. 3B, all p's > 0.21).

To test the specificity of this relationship between hippocampal volume and generalization, we used partial correlations to demonstrate that bilateral hippocampal volume did not generally correlate with task performance (i.e., acquisition and/or retention).

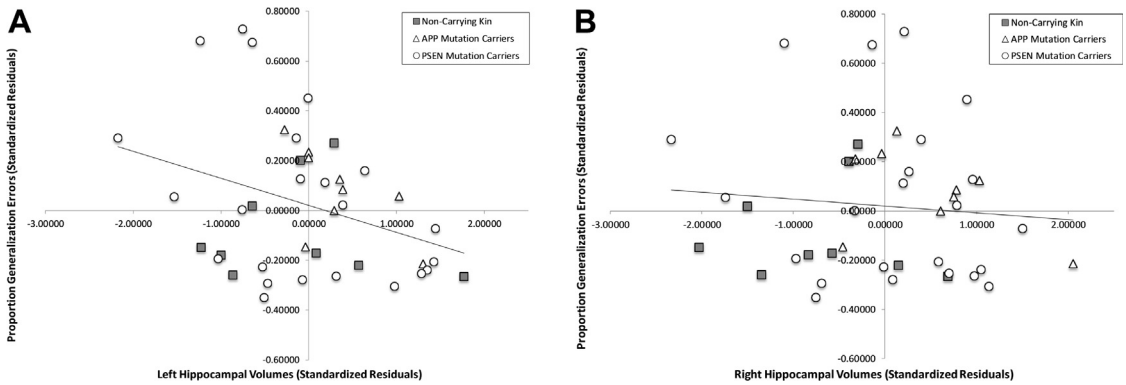


Fig. 3. Partial correlation for generalization (proportion error) and left (A) and right (B) hippocampal volumes. Standardized residuals are reported, using chronological age and education as covariates. Abbreviations: APP, amyloid precursor protein; PSEN, presenilin.

That is, neither the right nor left hippocampus correlated with acquisition (p's > 0.14) or retention (p's > 0.22). Furthermore, in contrast to the results linking the hippocampus with generalization, partial correlations revealed that generalization was not associated with entorhinal cortex thickness [right: $r\,(37) = 0.05$, $p = 0.731$ and left: $r\,(37) = 0.004$, $p = 0.983$]. Similarly, partial correlations revealed no significant associations between generalization and frontal middle gyrus [left: $r\,(37) = -0.10$, $p = 0.53$ and right: $r\,(37) = 0.10$, $p = 0.55$].

4. Discussion

This study examined whether young, preclinical individuals carrying ADAD mutations show deficits in generalization, before other overt cognitive decline. Otherwise healthy ADAD mutation carriers, who were on average 16 years younger than the expected age of AD diagnosis, exhibited poor generalization relative to their noncarrying kin. This deficit is consistent with MTL dysfunction and emerged despite intact learning and retention of stimulus pairs. Our pattern of results supports previous observations in a group of nondemented, healthy older adults with hippocampal atrophy (consistent with preclinical sporadic AD) who also showed spared learning and retention but impaired generalization compared to non–atrophied controls (Myers et al., 2008b). Furthermore, in the present study, we observed worse generalization among those mutation carriers with smaller left hippocampal volumes. The specificity of the relationship between hippocampal volume and generalization was underscored by findings that hippocampus volume did not relate to learning or retention, and that generalization was not associated with middle frontal gyrus or entorhinal cortex thickness. Taken together, our findings suggest that computer-based generalization tests may be a sensitive measure of the preclinical effects of ADAD.

While the noncarrying kin sample was small relative to the carriers, their low error rate on generalization ($M = 13\%$) matched what has been previously reported among healthy adult controls (typically between 10% to 15%) in studies that used this task (Herzallah et al., 2010; Levy-Gigi et al., 2012; Mattyassy et al., 2012). More importantly, the larger generalization error rate for young, preclinical mutation carriers (mean = 34%) is similar to what has been reported in sporadic AD patients (~50%; Bodi et al., 2009), individuals with impaired hippocampal function due to alcohol dependence (~25%; Mattyassy et al., 2012), older adults with confirmed hippocampal atrophy (~40%; Myers et al., 2003), and amnesic patients with bilateral hippocampal damage (~45%; Myers et al., 2008a). Thus, by demonstrating poor generalization among younger adult ADAD mutation carriers, we reveal cognitive deficits that likely reflect functional changes in the MTL that accompany preclinical AD. The observed relationship of more pronounced generalization deficits in ADAD patients who had smaller left hippocampal volumes confirms this idea. While our task may have utility as a screening tool to detect risk for developing ADAD or in tracking response to therapeutic interventions in early preclinical disease, substantial variability in generalization performance among mutation carriers (despite the fact that these individuals will develop ADAD with near certainty) suggests that more work is needed to examine the factors that lead to impaired generalization in ADAD.

The present study overcomes some limits of previous work in interpreting generalization deficits as an indicator of later AD diagnosis. For example, reports using our same task found at-chance generalization in both nondemented individuals who had documented hippocampal atrophy consistent with early AD (Myers et al., 2003) and in older adults greater than 75 years of age (Simon and Gluck, 2013) when hippocampal declines may accelerate (Zhang et al., 2010); however, hippocampal atrophy and advanced age are imperfect predictors of future development of AD. Similarly, a different task showed that generalization at baseline, together with delayed paragraph recall, could predict 2-year outcome for which nondemented elderly adults would be diagnosed with MCI (Myers et al., 2008b). Yet, in some cases, individuals who had been diagnosed with MCI were reclassified as cognitively normal 2 years later, demonstrating the difficulty in assessing later development of AD from a single evaluation in preclinical populations (see Bruscoli and Lovestone, 2004). Our findings, in contrast, examine individuals within whom rates of progression to AD are not as variable; ADAD mutation carriers will develop AD with essentially 100% certainty.

The selective generalization impairment among ADAD mutation carriers does not reflect impaired learning; mutation carriers and noncarrying kin produced similar error responses during learning and required the same number of trials to reach criterion. In fact, generalization was impaired among mutation carriers even when controlling for learning performance. This is consistent with literature showing that learning, but not generalization, is intact among AD patients (Kennedy et al., 1993; Sherrington et al., 1996), whereas the reverse is true in patients with disruption to the striatal system only (Bodi et al., 2009). Poor generalization is also not due to forgetting of the trained pairs that support flexible transfer because mutation carriers and noncarrying kin had nearly equivalent error rates at retention. It is also unlikely that generalization deficits

reflect prefrontal dysfunction that may accompany AD (Klunk et al., 2007; Ringman et al., 2011), as we observed no relationships between generalization and the middle frontal gyrus in our groups. This finding is consistent with previous work; generalization abilities do not correlate with tests of frontal lobe functioning, such as Wisconsin Card Sorting, *n*-back working memory, Trail Making, and Controlled Oral Word Associations (Chase et al., 2008; Head et al., 2005), and generalization deficits were not reported in patients with frontal damage (Farkas et al., 2008).

It is not clear why only the left hippocampus would show a significant relationship with generalization errors in ADAD. To our knowledge, there is no clear evidence for hemispheric lateralization in hippocampal atrophy as conveyed by genetic carriage. Previous studies have suggested that hippocampal volume loss occurs more with some ADAD mutations (e.g., those in *APP*) than others (e.g., in *PSEN1*) (Scahill et al., 2013). However, despite our small sample size, we found similar correlations between generalization performance and left hippocampal volume among carriers of *APP* and *PSEN* mutations, providing further evidence that the left hippocampus underlies this ability and our findings do not reflect an idiosyncrasy of a specific mutation type. Given that the task could be viewed as a visual matching task, one might have predicted that the right hippocampus would be more involved in generalization (Smith and Milner, 1981). However, our task uses visual stimuli that can be verbalized (i.e., the participant can describe each of the stimuli in a verbal way, such as "blonde woman"), which may recruit left hemisphere processes (Brown et al., 2007; Heilbronner, 1992). That said, our findings align with 2 recent meta-analyses: 1 revealed that atrophy of the left MTL is, on average, slightly more severe, which may make it more sensitive to early AD pathology (Shi et al., 2009), and another found that reduced left hippocampal volume is the most consistent neurostructural biomarker in predicting development of AD in MCI patients (Ferreira et al., 2011). Similarly, our results complement data from different associative learning tasks that required participants to generalize previously acquired information. For example, 1 study found that activity in the left posterior hippocampal region alone correlated with the ability to transfer knowledge to novel settings (Kumaran et al., 2009). Moreover, the left hippocampus has been implicated in context-dependent episodic memory (Burgess et al., 2002). Nonetheless, future studies need to elucidate laterality issues of the hippocampus in supporting generalization in ADAD given that the precise division of labor between the right and left hippocampi is not yet clear.

Moreover, future work will need to disentangle the specificity of generalization deficits to the left hippocampus as compared to the MTL more broadly. We did not necessarily expect an absence of association between entorhinal cortex and generalization, especially given evidence that entorhinal atrophy and hippocampal atrophy are often correlated in sporadic AD (Bobinski et al., 1999; de Toledo-Morrell et al., 2000) and that the entorhinal cortex has been implicated in generalization in animal models of acquired equivalence (Coutureau et al., 2002). Our results could reflect a true lack of involvement of the entorhinal cortex in generalization. Alternatively, the association may be difficult to detect due to decreased precision in measuring entorhinal cortex thickness or that this structure may change less predictably with neuronal loss in ADAD than sporadic AD (Ringman et al., 2014). Furthermore, the small size of the entorhinal cortex may hinder the ability to detect volumetric changes even if functional changes are occurring, or our small sample may limit our power to detect significant brain-behavior correlations in this region. Additional studies, especially involving those involving cases of sporadic AD, may clarify whether hippocampal volume measurements are simply a better marker of general MTL atrophy in ADAD or whether the hippocampus is more functionally involved in generalization than other MTL structures.

The present study is limited by a relatively small sample size, the heterogeneity of the different mutations included, and uncertainty regarding the degree to which results with ADAD mutation carriers can be applied to sporadic LOAD. Furthermore, some previous work suggests the automated segmentation algorithm used by FreeSurfer may overestimate hippocampal volumes when compared to manual tracings (Morey et al., 2009; Wenger et al., 2014). That said, our participants were relatively young and therefore had fewer comorbid illnesses (e.g., hypertension) that might contribute to preclinical cognitive decline. In addition, our kin control group limits some environmental or biological factors that might otherwise confound the results.

Our study included both native English and Spanish speakers, suggesting our task has utility as a "linguistically neutral" assessment tool to assess cognitive impairment in early AD. Similar to the study by Parra et al. (2010), this linguistic neutrality likely reflects that our task uses primarily visual versus verbal stimuli, in contrast to other commonly used tests of hippocampal-dependent memory, such as explicit verbal recall. Thus, our quick, easily implementable, inexpensive task may provide a culturally neutral way to identify and track cognition in AD in a way that complements standard neuropsychological tests. Such early prediction of AD is critical, given that existing pharmacological interventions for AD are typically aimed to slow advancement of the disease, rather than reverse or stop its progress.

Disclosure statement

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Authors' contributions: JMR, CEM, and MAG developed the study concept and study design. CEM provided experimental software. Testing and data collection were performed by authors DMW, LDM, and MC under the supervision of JMR. JRP performed the behavioral data analysis and interpretation under the supervision of JMR, CEM, and MAG. JP and ZH provided the neuroimaging analysis. JRP drafted the manuscript, and JMR, CEM, and MAG provided critical revisions. All authors approved the final version of the manuscript for submission.

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