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A novel method of evaluating semantic intrusion errors to distinguish between amyloid positive and negative groups on the Alzheimer's disease continuum

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ABSTRACT

Background: The development and validation of clinical outcome measures to detect early cognitive decline associated with Alzheimer's disease (AD) biomarkers is imperative. Semantic intrusions on the Loewenstein Acevedo Scales of Semantic Interference and Learning (LASSI-L) has outperformed widely used cognitive measures as an early correlate of elevated brain amyloid in prodromal AD and has distinguished those with amnestic mild cognitive impairment (aMCI) and high amyloid load from aMCI attributable to other non-AD conditions.

Methods: Since intrusion errors on memory tasks vary widely, we employed a novel method that accounts for the percentage of intrusion errors (PIE) in relation to total responses. Individuals with either high or low amyloid load across the spectrum of aMCI and dementia and amyloid negative cognitively normal older adults (CN) were studied.

Results: Mean PIE on indices sensitive to proactive semantic interference (PSI) and failure to recover from proactive semantic interference (frPSI) could distinguish amyloid positive from amyloid negative aMCI and dementia groups. Number of correct responses alone, while able to differentiate the different diagnostic groups, did not differentiate amyloid positive aMCI from their counterparts without amyloid pathology.

Conclusions: PIE, a novel and sensitive index of early memory dysfunction, demonstrated high levels of sensitivity and specificity in differentiating CN from amyloid positive persons with preclinical AD. Mean levels of PIE are higher for amyloid positive aMCI and dementia participants relative to their amyloid negative counterparts.

1. Introduction

Emerging treatments for Alzheimer's disease (AD) will likely be most effective in the earliest stages of illness, before significant multi-system neurodegeneration has occurred. It is therefore critical to the success of emerging AD clinical trials focusing on early disease states to target specific individuals that are at high risk for the disorder. The increased utility of AD biomarkers represents a major advancement in efforts to identify the first manifestations of underlying brain pathology. In particular, the validation of in-vivo amyloid β (Aβ) deposition in living individuals using positron emission tomography (PET) imaging (Landau et al., 2015) or in the cerebrospinal fluid (CSF) represents a significant achievement for early identification of individuals at high risk for developing clinical AD. In AD clinical trials, the use of biomarkers in the CSF and by PET brain imaging presents an advantage for selecting asymptomatic but at-risk participants based on the presence of underlying AD brain pathology; however, the reliance on AD biomarkers of amyloidosis or neurodegeneration to increase confidence

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in diagnostic determination remains challenging for several reasons. Beyond participants' reluctance to undergo a lumbar puncture, and PET imaging being highly cost prohibitive, brain Aβ has not yet proven to be an effective surrogate outcome measure. Further, brain Aβ burden has not been well correlated with cognition and/or clinically meaningful outcomes (Leung et al., 2012; Hedden et al., 2013; Posner et al., 2017), which are necessary for drug approval from the Food and Drug Administration (FDA).

Moreover, the relative insensitivity of clinical outcome measures to capture early cognitive changes in AD imposes critical challenges to AD clinical trials focusing on prevention. Thus, the field is recognizing the need to develop and validate clinical outcome measures that are able to detect early cognitive decline that is associated with underlying preclinical AD biomarkers such as amyloid, and markers of early neurodegeneration including tau deposition, and volumetric loss/cortical thinning in AD prone regions. One promising cognitive outcome measure, the Loewenstein Acevedo Scales of Semantic Interference and Learning (LASSI-L), has been shown to be significantly more sensitive to early cognitive impairment than traditional paradigms focused on impaired learning or increased rate of forgetting, which comprise the more traditional clinical paradigms used to assess memory deficits (Loewenstein et al., 2018; Matias-Guiu et al., 2017a). The LASSI-L has outperformed other widely used memory measures in detecting prodromal AD in both the United States and abroad (Matias-Guiu et al., 2017a; Rosselli et al., 2019; Sánchez et al., 2017), and has revealed early deficits that have been associated with prodromal and preclinical AD. These include proactive semantic interference (PSI), the failure to recover from the effects of proactive semantic interference (frPSI), and retroactive semantic interference (RSI) (Loewenstein et al., 2017). In addition to the number of correct targets recalled on trials susceptible to PSI, frPSI and RSI, there is emerging evidence that semantic intrusion errors may have specific utility in the assessment of prodromal AD. Loewenstein and colleagues (2018) found that semantic intrusion errors sensitive to PSI and frPSI on the LASSI-L could differentiate amyloid positive aMCI groups from amyloid negative aMCI groups with non-AD diagnoses. Moreover, these types of errors distinguished between individuals suspected to have prodromal Alzheimer's disease, even after statistically adjusting for dominant language (English versus Spanish), age, and total MMSE scores (Loewenstein et al., 2018). Torres and colleagues (2019), found that semantic intrusion errors could also distinguish between aMCI and cognitively normal controls.

While it is recognized that intrusion errors represent early manifestations of neurodegenerative brain disease, a potential limitation of previous approaches is that the number of intrusion errors are often highly dependent on an individual's total responses on a particular trial. Thus, even a seemingly modest number of intrusion errors may actually represent an at-risk cognitive profile, depending on the total number of responses that are correct. For example, an individual may make a minimal number of intrusion errors on a given trial, which may appear to be clinically insignificant. However, if the number of total responses is low, even a modest number of intrusion errors may indicate impaired inhibitory processes and underlying brain pathology.

The purpose of the current study was to further evaluate the utility of semantic intrusion errors by expanding upon previous work. We include older adults with normal cognition compared to those who have aMCI and early dementia with high versus low amyloid load and employ a novel approach to evaluating intrusion errors as a function of total responses on trials.

To our knowledge, no previous investigations have explored the clinical utility of percentage of intrusion errors (PIE) in association to AD biomarkers. This approach recognizes the importance of intrusion errors, which Tropea and colleagues (2017) found to be predictive of cognitive decline over time while also examining intrusions in context of their relation to overall responses.

2. Methods and materials

2.1. Participants

We recruited 124 older adults (47% predominant Spanish speakers) from the 1Florida Alzheimer's Disease Research Center (ADRC) for this IRB-approved investigation. An experienced clinician administered a standard clinical assessment protocol, which included the Clinical Dementia Rating Scale (CDR), and the Mini-Mental State Examination (MMSE). Subsequently, a uniform neuropsychological battery comprising the tests described below was independently administered in either Spanish or English dependent on the participant's dominant and preferred language. Diagnostic groups were classified using the following criteria:

2.2. Amnestic MCI group (aMCI) (n = 72)

Participants met Petersen's criteria (2014) for MCI and evidenced all of the following: a) subjective cognitive complaints by the participant and/or collateral informant; b) evidence by clinical evaluation or history of memory or other cognitive decline; c) Global Clinical Dementia Rating scale of 0.5 (Morris, 1997); d) below expected performance on delayed recall of the HVLT-R (Brandt, 1991) or delayed paragraph recall from the National Alzheimer's Coordinating Center -Unified Data Set (NACC-UDS; Beekly et al., 2007) as measured by a score that is 1.5 SD or more below the mean using age, education, and language-related norms.

2.3. Dementia group (n = 31)

Participants were diagnosed with dementia using criteria a and b as described for the aMCI group and evidenced all of the following: a) Global CDR score of 1.0; b) below expected performance on the memory measures described above that scored 2.0 SD or more below the mean using age, education, and language-related norms.

2.4. Cognitively normal group (n = 21)

Participants were diagnosed as cognitively normal if all of the following criteria were met: a) no subjective cognitive complaints made by the participant and/or a collateral informant; b) no evidence by clinical evaluation or history of memory or other cognitive decline after an extensive interview with the participant and an informant; c) Global CDR score of 0; d) all memory and non-memory measures (e.g.: Category Fluency (Binetti et al., 1995), Trails A and B (Reitan, 1958)), WAIS-IV Block Design subtest (Wechsler, 2008) were no lower than 1.0 SD below normal limits for age, education, and language group.

Spanish language evaluations were completed with equivalent standardized neuropsychological tests and appropriate age, education, and cultural/language normative data (Arango-Lasprilla et al., 2015a, 2015b; Benson et al., 2014; Ostrosky-Solís et al., 2000; Pena-Casanova et al., 2009). Proficient bilingual (Spanish/English) psychometricians performed testing.

2.5. Loewenstein- Acevedo Scales for Semantic Interference and Learning (LASSI-L)

The LASSI-L was not used for diagnostic determination in this study. This cognitive stress test represents a novel paradigm that employs both controlled learning and cued recall to maximize storage of a list of to-be-remembered target words representing three semantic categories (Curiel et al., 2016). The LASSI-L subscales have shown adequate test-retest reliabilities, as well as, high discriminative and concurrent validity (Crocco et al., 2014; Curiel et al., 2013; Matias-Guiu et al., 2017a; Matías-Guiu et al., 2017b; Sánchez et al., 2017).

During the administration of the LASSI-L, the examinee is instructed

to remember a list of 15 common words representing 3 semantic categories (fruits, musical instruments, and articles of clothing) over two trials with category cues provided for recall (List A). The cued recall after the second presentation of List A is a measure of maximum storage capacity (Trial A2). Then, List B with 15 words representing the same semantic categories as List A is presented. Cued B Trial 1 recall is subject to proactive semantic interference (PSI) while the second cued recall trial of List B measures the failure to recover from PSI (frPSI). We have previously found that semantic intrusions on Cued List B1 and Cued List B2 represent deficits in source memory and response inhibition.

2.6. PIE ratio

The absolute number of semantic intrusions does not account for the number of total correct responses on a particular trial. For example, a modest number of intrusion errors on Cued B1 of the LASSI-L may be more relevant in light of a limited number of total responses and may be indicative of cognitive impairment and underlying brain pathology. As a result, we developed a new ratio that accounts for intrusion errors as a percentage of total responses on three LASSI-L subscales that have been highly sensitive to early cognitive impairment. Specifically, the ratio is denoted as follows: Total Intrusion Errors/(Total Intrusion Errors + Total Correct Responses). These ratios can be calculated individually for LASSI-L Cued B1 (a measure of susceptibility to proactive semantic interference) and LASSI-L Cued B2 recall (a measure of recovery from proactive semantic interference) and LASSI-L Cued A3 recall (a measure of susceptibility to retroactive semantic interference).

2.7. Amyloid PET imaging

PET Scan Imaging: A 3D Hoffmann brain phantom was used to establish a standardized acquisition and reconstruction method. Participants were infused with [18-F] florbetaben 300 MBQ over a 3-min period. Scanning commenced 70–90 min after the infusion for a duration of 20 min on a Siemens Biograph 16 PET/CT scanner operating in 3D mode (55 slices/frame, 3 mm slice thickness 128 X128 matrix). The PET data were reconstructed into a 128 × 128 × 63 (axial) matrix with voxel dimensions of 0.21 × 0.21 × 0.24 cm. A small number of participants had florbetapir as their amyloid tracer. Reconstruction was performed using manufacturer-supplied software and included corrections for attenuation, scatter, random coincidences, and dead time. Images for regional analyses were processed using Fourier analysis followed by direct Fourier reconstruction.

2.8. Visual ratings of amyloid PET scans

All Aβ-PET scans were analyzed by an experienced rater (RD) who was blinded to the cognitive and clinical diagnosis, using a methodology similar to that described by Seibly and colleagues (2016). Tracer uptake was assessed in six cortical regions (orbitofrontal, frontal, parietal, lateral temporal, occipital and precuneus/posterior cingulate cortex, combining values from the left and right hemispheres) using the regional cortical tracer uptake (RCTU) system (Bullich et al., 2017). A final dichotomous (Amy + versus Amy-) diagnosis was rendered. Loewenstein and colleagues (2018) found extremely high agreement between our neurologist (RD) and an independent rater in interpreting these scans. Among a group of community dwelling elders, the concordance between RD and a neuroradiologist independently reviewing the scans was 93.2% for Amy + scans and 100% for Amy− scans. Visual ratings of amyloid load have been considered the “gold standard” in identifying amyloid plaques that are confirmed by histopathological data upon autopsy (Clark et al., 2012; Lizarraga et al., 2018; Salloway et al., 2017; Smith et al., 2004). For this study, amyloid positivity was determined by the visual rating.

2.9. Quantitative analyses of amyloid PET scans

The PET/CT scans, including the outline of the skull, were co-registered linearly (i.e., trilinear interpolation) with 12 degrees of freedom, onto the volumetric MRI scan using a T1-weighted (MP-RAGE) (Salloway et al., 2017; Smith et al., 2004). Region-of-interest (ROI) boundaries were defined manually using the structural MRI for anatomical reference, and criteria that have been proven to provide highly reproducible outcomes (Desikan et al., 2006). This registration process ensured that the florbetaben PET/CT image had the same accurate segmentation and parcellation as in the MRI scan. The average activity was calculated in the ROIs corresponding to cerebellar gray matter and cerebral cortical regions. A composite SUVR was calculated by the ratio of the mean volume-weighted SUVR of 5 cortical regions (frontal, temporal, parietal, anterior and posterior cingulate cortex regions, each region summed from left and right hemispheres) to whole brain cerebellum (Rowe et al., 2008).

Over 75% of our sample had Florbetaben as their PET tracer while the rest had Florbetapir. The Centiloid (CL) method has been widely used to create a common metric by which total amyloid uptake can be place on the same scale for different amyloid tracers (Jack et al., 2017; Rowe et al., 2017). Using normalization to the whole brain cerebellum, for Florbetaben, the Centiloid formula used was [(SUVR X 153.4) -(154.9)] and for Florbetapir the Centiloid formula used was [(SUVR X 183) −177]. This created a Centiloid score for each participant that could be used in subsequent analyses.

Because of two different amyloid tracers employed, we used the CL method to determine amyloid positivity. It has been found that a CL as low as 20 represents amyloid pathology (Rowe et al., 2018). In our laboratory, a negative visual reading with CL of < 15 denotes minimal amyloid deposition. To help ensure the optimal diagnostic integrity of our groups, participants who were deemed amyloid negative were required to have both a negative visual amyloid read and a CL value of less than 15. Conversely, those individuals with an amyloid positive visual reads were required to have a CL value of 20 or greater (Rowe et al., 2018).

2.10. Final diagnostic study groups

There were 36 aMCI individuals classified as amyloid positive (Amy +) and 36 aMCI individuals classified as amyloid negative (Amy-) by both visual reads and global CL scores as described above. Thirty-one participants diagnosed with dementia were classified as amyloid positive. Additionally, a group of 21 cognitively normal amyloid negative participants was included for specific comparisons.

2.11. Statistical analyses

For comparisons between diagnostic groups, a series of one-way analyses of variance were employed for interval level variables. Following a statistically significant result, post-hoc tests of means were examined using the Tukey Honestly Significant (HSD) test. Dichotomous variables were examined using Chi-square tests. The criteria for statistical significance was $p < .05$.

The relationships between CL values, total hippocampal volumes, and percentage of LASSI-L semantic intrusion errors as well as correct responses was examined using Pearson Product Moment Correlation Coefficients. In addition, the relation between CL values and LASSI-L scores were examined controlling for total hippocampal volume. Two-tailed tests of significance was set at $p \leq .05$.

3. Results

As depicted in Table 1, there was no statistically significant age, education, sex, or language of testing difference between any of the diagnostic groups. CN participants had the highest MMSE scores

Table 1
Demographic and LASSI-L Differences Between Amy + and Amy-aMCI and Dementia Participants.

	Cognitively Normal Amy-(n = 21)	aMCI Amy-(n = 36)	aMCI Amy+(n = 36)	Mild Dementia Amy+(n = 31)	F-Value or Chi-Square	p-value
Age(52–98 Years)	69.90(SD = 6.5)	72.61(SD = 8.2)	74.80(SD = 7.3)	71.87(SD = 9.2)	1.41	.24
Education(5-22-Years)	16.05(SD = 3.0)	14.60(SD = 3.6)	14.67(SD = 3.5)	13.77(SD = 3.7)	2.29	.08
Sex % Female	57.1%	47.2%	50.0%	64.5%	2.36	.50
Tested in Spanish	47.6%	47.2%	40.0%	45.2%	.48	.92
MMSE (15–30)	29.14^{c}(SD = 1.0)	27.61^{ab}(SD = 2.6)	26.00^{b}(SD = 2.4)	21.74^{a}(SD = 3.6)	40.53	p < .001
Centiloid Value (−21.71 -216.71)	−2.17^{a}(SD = 7.4)	.01^{a}(SD = 8.8)	72.40^{b}(SD = 25.4)	87.08^{b}(SD = 36.6)	121.07	p < .001

followed by participants diagnosed with aMCI or dementia, who evidenced the lowest MMSE scores. There were no statistically significant MMSE differences between Amy+ and Amy-aMCI groups. As expected, the lowest CL scores were observed in the Amy- CN and Amy-aMCI groups while Amy + aMCI and Amy + dementia groups had the highest average (and equivalent) CL scores.

Diagnostic groups were then compared on the PIE indices and correct responses made on subscales susceptible to PSI, frPSI and RSI, by employing a series of one-way analyses of variance (ANOVA). Following a statistically significant result, post-hoc tests of means were examined by the Tukey HSD test. As depicted in Table 2, with regard to the mean PIE on the Cued B1 subscale, susceptible to PSI, aMCI Amy + participants evidenced a greater mean PIE (50.7%) compared to their Amy-aMCI counterparts (34.4%). Participants diagnosed with mild dementia who were amyloid positive had a greater mean PIE (61.2%) compared to the other diagnostic groups. Similar findings were observed with regards to performance on the Cued B2 subscale, susceptible to frPSI. Post hoc comparisons revealed that aMCI Amy + participants had a greater mean PIE (34.1%) than aMCI Amy-participants (19.2%). Participants diagnosed with mild dementia who were Amy + had a greater mean percentage of intrusion errors compared to the other diagnostic groups (48.6%). On a LASSI-L subscale that measures retroactive semantic interference (RSI), persons with aMCI who were Amy + also had a greater mean PIE (47.8%) versus aMCI Amy-groups (33.0%). On this subscale, participants diagnosed with mild dementia had a greater mean PIE compared to the other diagnostic groups (51.6%).

Interestingly, on measures of correct responses on LASSI-L measures susceptible to PSI, frPSI, and RSI, all groups were readily differentiated. However, unlike the PIE ratios described above, Amy + aMCI could not be differentiated from Amy-aMCI.

Table 3 depicts the relationship between global CL scores and total hippocampal volumes with different PIEs and correct response rates for all cognitively impaired participants. Even after adjusting for hippocampal volume, statistically significant correlations between PIE on indices sensitive to PSI, frPSI and RSI and global centiloid scores ranged from r = −.32 to r = −0.49. Only LASSI-L correct responses showed statistically significant relationships between frPSI and global centiloid scores.

4. Discussion

In this study, we showed that the percentage of intrusion errors (PIE) made on LASSI-L indices were particularly sensitive to early breakdowns in proactive semantic interference (PSI), failure to recover from proactive semantic interference (frPSI) and retroactive interference (RSI). These PIE deficits were more pronounced in amyloid positive versus amyloid negative aMCI. Virtually all intrusion errors were target words from List A (the first list), or a semantically associated word that was not a specific target on either of the two lists of the LASSI-L, consistent with what has been previously observed (Loewenstein et al., 2017; Torres et al., 2019). This highlights the importance of paradigms that include semantic cues at both encoding and retrieval.

It is noteworthy that PSI and frPSI deficits appear to be a defining feature of early aMCI, particularly those cases in which AD is considered an underlying etiological cause of cerebral dysfunction (Loewenstein et al., 2017). We have previously found that semantic intrusion errors related to proactive semantic interference may represent specific deficits in source memory and inhibitory processes (Loewenstein et al., 2018; Torres et al., 2019). In this investigation, using the PIE index, RSI also appeared to be related to amyloid pathology.

Merely accounting for the total number of intrusion errors, as done in previous studies, may represent a limitation because more responses are likely to yield a larger absolute number of intrusion errors. Further, even a few intrusions errors may be consequential in the presence of a modest number of correct responses. As such, we developed a novel ratio of intrusion errors to total responses [Intrusion errors/(Intrusion errors + correct responses)].

The current findings suggest correct responses on LASSI-L measures susceptible to PSI, frPSI and RSI could differentiate CN, aMCI and dementia groups. However, only PIE could differentiate Amy+ from Amy-groups. Indeed, the robust correlations seen in Table 3 indicate

Table 2
Performance of Different Diagnostic Groups on LASSI-L Measures.

LASSI-L Measure	CN	aMCI Amy-	aMCI Amy+	Dementia Amy+		
LASSI-L Cued B1 Percentage Intrusions (PSI) (0.0 %-100%)	18.37^{a} (SD = 16.3)	34.44^{b}(SD = 21.7)	50.72^{c} (SD = 20.1)	61.20^{c} (SD = 30.7)	17.33	p < .001
LASSI-L Cued B2 Percentage Intrusions (frPSI)(0.0 %-85.71%)	11.83^{a}(SD = 11.2)	19.54^{a}(SD = 15.3)	34.06^{b}(SD = 16.8)	48.61^{c}(SD = 22.2%)	25.11	p < .001
LASSI-L Short Delay Cued A Percentage Intrusions (RSI)(0.0%–100.0%)	21.21^{a}(SD = 18.8)	33.03^{a}(SD = 21.3)	47.75^{b}(SD = 18.6)	51.07^{b}(SD = 20.0)	12.63	p < .001
LASSI-L Cued B1 Correct Responses (PSI)(0–14)	9.00^{a}(SD = 2.2)	5.53^{b}(SD = 2.6)	5.69^{b}(SD = 2.1)	2.87^{c}(SD = 2.2)	29.55	p < .001
LASSI-L Cued B2 Correct Responses (frPSI)(1–15)	11.71^{a}(SD = 2.1)	8.86^{b}(SD = 3.0)	8.42^{b}(SD = 2.0)	4.29^{c}(SD = 2.7)	39.42	p < .001
LASSI-L Short Delay Cued A Correct Responses (RSI)(0–14)	8.76^{a}(SD = 3.1)	6.56^{b}(SD = 3.0)	6.06 ^{bc}(SD = 2.4)	4.55^{c}(SD = 2.3)	10.29	p < .001

Note: Means with different alphabetic superscripts are statistically significant by the Tukey's Honestly Significant Difference (HSD) Test.

Table 3
Association Between LASSI-L Percentage of Intrusion and Raw Scores and Centiloid Raw Scores Among Cognitively Impaired Participants.

	Centiloid Score(n = 101)	Hippocampal Volume Score (n = 99)	Centiloid Score Corrected for Overall Hippocampal Volume (n = 91)
Cued B1 PIE (PSI)	**.29**(p = .003)**	**-.24**(p = .018)**	**.35***(p < .001)**
Cued B2 PIE (frPSI)	**.49 ***(p < .001)**	**-.20**(p = .043)**	**.49 ***(p < .001)**
Cued A3 PIE (RSI)	**.35***(p < .001)**	**-.26**(p = .012)**	**.32**(p = .002)**
Cued B1 Correct Responses	**-.19(p = .062)**	**.27**(p = .008)**	**-.17(p = .107)**
Cued B2 Correct Responses	**-.39***(p < .001)**	**.36***(p < .001)**	**-.31**(p = .002)**
Cued A3 Correct Responses	**-.23**(p = .024)**	**.14(p = .160)**	**-.20(p = .053)**

Note: **p < .05; ***p < .001.

that all PIE indices are associated with the severity of amyloid brain pathology. The implementation of the PIE measure may prove especially beneficial in clinical and research settings. For example, in clinical AD trials, PIE may enhance identification of at-risk individuals for enrollment, potentially reducing costs associated with screening for inclusion.

The focus on the percentage of intrusion errors in the current investigation differs in important ways from previous studies that have focused on diagnosing memory impairment or predicting progression by analyzing the total number of correct responses or focusing only on the raw number of intrusion error responses. The present study addressed the limitations imposed by these previous methods and analyzed the ratio of intrusion errors to the total number of responses provided. Thus, The PIE ratios derived from these analyses conveys comprehensive information about potential breakdowns in the cognitive system (Loewenstein et al., 2018; Tropea et al., 2017).

In our view, it is unlikely that the obtained findings reflect the direct effects of amyloid load. Rather, it is much more likely that downstream effects of amyloid load, such as synaptic disruption and the resulting loss of inter-connectivity between brain regions are responsible for the increase in intrusion errors that occurs well before actual neuronal loss resulting in structural brain atrophy. Indeed, Sánchez and colleagues (2017) demonstrated that among asymptomatic middle-aged offspring of late-onset AD patients, there were strong associations between intrusion errors on the LASSI-L and loss of functional connectivity on resting state fMRI. While these investigators did not examine the percentage of intrusion responses or amyloid load, their findings indicate that functional connectivity may play a role in the breakdown of important cognitive processes that may affect percentage of intrusion error responses. This is an area that deserves further research using functional neuroimaging modalities such as fMRI.

The strengths of this study include a robust number of carefully characterized participants, as well as visual and quantitative analyses of amyloid load, and a novel method of expressing different types of intrusion errors as a function of total number of responses on a given trial. Potential weaknesses include the lack of functional neuroimaging and quantification of tau pathology. It might be argued that centiloid values as low as 12 can be associated with very early amyloid deposition but it should be noted that our CL cut-off < 15 with the requirement of an amyloid negative visual read assured us that our Amy-participants had minimal amyloid load. While study groups contained equivalent numbers of Hispanic and Non-Hispanic participants, studies with larger numbers of diverse ethnic and cultural groups will be important to examine the generalizability of the reported findings. Nonetheless, the relationship between percentage of intrusion responses on tasks susceptible to PSI and frPSI and underlying dysfunction of brain circuitry is worthy of further research.

CRediT authorship contribution statement

Rosie E. Curiel Cid: Conceptualization, Methodology, Resources, Writing - original draft, Visualization, Project administration, Funding acquisition, Formal analysis, Investigation, Supervision. **Elizabeth A. Crocco:** Conceptualization, Methodology, Writing - original draft, Project administration, Formal analysis, Investigation. **Ranjan Duara:** Writing - original draft, Visualization. **Jessica M. Garcia:** Writing - review & editing, Visualization, Software, Data curation. **Monica Rosselli:** Writing - review & editing. **Steven T. DeKosky:** Writing - review & editing. **Glenn Smith:** Writing - review & editing. **Russell Bauer:** Writing - review & editing. **Cesar L. Chirinos:** Writing - review & editing. **Malek Adjouadi:** Writing - review & editing. **Warren Barker:** Writing - review & editing. **David A. Loewenstein:** Conceptualization, Methodology, Resources, Writing - original draft, Visualization, Project administration, Funding acquisition, Investigation, Software, Data curation, Formal analysis, Supervision.

Declaration of competing interest

The authors have no disclosures.

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