RESEARCH ARTICLE

Stronger implicit interference in cognitively healthy older participants with higher risk of Alzheimer's disease

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Abstract

Introduction: Abnormal cerebrospinal fluid amyloid beta $(A\beta)_{42}$ and tau levels have been revealed decades before symptoms onset in Alzheimer's disease (AD); however, the examination is usually invasive and inaccessible to most people. We thus aimed to develop a non-invasive behavioral test that targets early potential cognitive changes to gauge cognitive decline. Specifically, we hypothesized that older cognitive healthy participants would exhibit comparable performance when the task was explicit and relied on conscious cognition. However, when the task was implicit, the performance of participants at high and low risks for AD would bifurcate. That is, early changes in unconscious cognition could be linked to cognitive health.

Methods: We measured implicit interference elicited by an imperceptible distractor in cognitively healthy elderly participants with normal (low risk) and pathological (high risk) $A\beta_{42}$/total tau ratio. Participants were required to perform a Stroop task (word-naming or color-naming on an ink-semantics inconsistent word) with a visually masked distractor presented prior to the target task.

Results: We found that, under a high-effort task (i.e., color-naming in the Stroop task), high-risk participants suffered interference when the imperceptible distractor and the subsequent target were incongruent in the responses they triggered. Their reaction times were slowed down by approximately 4%. This implicit interference was not found in the low-risk participants.

Discussion: These findings indicate that weakened inhibition of distracting implicit information can be a potential behavioral biomarker of early identification of AD pathology. Our study thus offers a new experimental paradigm to reveal early pathological aging by assessing how individuals respond to subperceptual threshold visual stimuli.

KEYWORDS
aging, early identification, implicit processing, pre-symptomatic Alzheimer's disease

1 | INTRODUCTION

Alzheimer's disease (AD) has become a major mental and financial burden on our society as people have a longer life expectancy. Currently, nearly 6 million people in the United States aged 65 and above are diagnosed with AD. This number was projected to be doubled in 20 years.[1] Between 2000 and 2017, the number of deaths from AD increased 145%.[2] Importantly, this number could be severely underestimated as patients may die from complications indirectly caused by AD (e.g., respiratory system failure[3]). The hours of informal care provided in 2018 were estimated to be valued at nearly 234 billion USD. Patients on average remain alive and in need of extended care 4 to 8 years after the diagnosis of the disease,[4,5] causing a devastating psychological burden to the patient, the family, and the society.

Although currently there is no available treatment to cure or reverse the catastrophic cognitive decline of AD, early intervention has been shown to slow down disease progression.[2,6] The commonly used diagnostic biomarkers such as age-appropriate total tau level and cerebrospinal fluid (CSF) amyloid beta (Aβ)$_{42}$ indicate abnormality years before symptoms show up.[7] However, in this pre-symptomatic period, it is extremely difficult to identify high-risk populations without extensive and invasive examinations. That is, people in the pre-symptomatic period are cognitively healthy and exhibit no apparent signs of disease. Finding an effective behavioral assessment that reveals early cognitive decline can provide an opportunity for intervention and will benefit our aging society tremendously. The current study thus set out to differentiate high- and low-risk pre-symptomatic older participants with a non-invasive yet sensitive behavioral measurement.

Cognitive health is typically characterized by conscious and effortful thinking, focusing on memory, attention, and command-following (e.g., assessed by the Mini-Mental State Examination [MMSE][8]). Therefore, despite having different biochemical risk levels, older asymptomatic participants characterized as cognitively healthy in the neuropsychological assessment could exhibit a comparable level of behavioral performance in a cognitive task. Recent studies in perception sciences, however, have begun to show that high-level executive functions could play a role in regulating perception. For example, distributing attentional resources to a perceptual target improves performance, typically attributed to an enhanced gain of perceptual inputs.[9,10] These results have been expanded to subthreshold stimuli that observers are unable to perceive consciously.[11,12] Following this rationale, we aimed to examine if subtle changes in the high-level executive functions, which have not yet surfaced to conscious cognition to alter behavioral performance, could affect how observers respond to subthreshold, implicit perceptual information. That is, these early potential perceptual/cognitive changes are too subtle to be captured by standard neuropsychological testing but can be revealed by altered implicit responses to external imperceptible sensory stimuli.

The central question is, which aspect of high-level executive functions is the most plausible candidate for us to observe an interaction with implicit processing? A rich body of literature has explored how older participants react to cognitively challenging conditions, with a focus on inhibitory control.[13–17] Based on these previous findings,

we sought an experimental paradigm that challenged our participants cognitively with immense interference during their performance. For example, the Stroop task has been widely administered to assess cognitive control in which the participants are instructed to respond to colored words. When the task is color-naming, inconsistent semantics of the word (e.g., *green* colored in red) is retrieved effectively and interferes with performance (i.e., the Stroop effect). When the task is word-naming, the color inconsistency usually yields a weaker interference as color retrieval is less effective. In the younger and older participants, a similar Stroop effect size has been reported in several previous studies,[13,14] including an early meta-analysis study.[18] However, by manipulating the ratio of word-color congruent and incongruent trials, Mutter et al.[14] showed that older participants suffered from using this contextual information to suppress distracting information. Similar failure to suppress lexical information has been observed in other paradigms in the elderly. Using a word-fragment-completion task, Logan and Balota[19] found that older participants were more likely to use irrelevant information from a preceding distractor to perform the task, even when they were explicitly told not to do so. These studies have offered a solid foundation for the use of interference-based paradigms to pose a cognitive challenge and observe the harmful effects on task performance.

In the current study, we combined multiple layers of explicit and implicit interference in a task, including task-switching, Stroop interference, and subliminal distractor response incongruency. The first two factors were introduced to induce a cognitively challenging condition via the need to explicitly inhibit task-irrelevant stimulus features, potentially exhausting limited cognitive resources in the older participants. They were both based on the Stroop effect. As previously mentioned, color-naming requires stronger inhibition of the word meaning, and word-naming is relatively low effort because color retrieval is less automatic. Thus, a successful response in a Stroop task requires suppression of interfering information. Critically, we delivered a visually masked distractor prior to the target word. Although no task was given to the masked distractors, identical words to the target words were used and expected to trigger implicit responses.[20,21] Therefore, if the masked word and the subsequent target word triggered different responses, it was deemed incongruent and potentially caused a subliminal interference.

We recruited participants from a longitudinal study pool in which CSF amyloid/tau and neuropsychological assessments had been performed on each individual. Blind to both the experimenters and the participants, these participants had been identified as cognitively healthy with pathological Aβ42/total Tau protein ratio (CH-PATs) and cognitively healthy with Normal Aβ42/total Tau protein ratio (CH-NATs). This ratio was derived from their CSF A$\beta$$_{42}$ and total tau protein. It has been shown to have 85% sensitivity in discriminating AD among AD patients, mild cognitive impairment participants, and healthy controls in our prior study.[22] This biomarker has been applied in a series of previous studies to show accurate delineation between healthy controls and AD patients.[22–24] Preliminary data also suggest the predictive power of this biomarker: In an ongoing 4-year longitudinal study, 40% of the CH-PATs have declined cognitively

while all CH-NATs have remained healthy.[25] We thus defined the CH-PATs as at high risk and the CH-NATs as at low risk of AD in the current study. As both groups were cognitively healthy by the assessment of neuropsychological tests, we expected to see differentiation of performance only at the implicit/subliminal level. Specifically, we proposed two competing hypotheses with the assumption that high-risk participants have subtly declining attention capacity, compared to low-risk participants. First, stronger implicit interference signals weakened inhibitory control, which will predict worse performance in high-risk older participants due to stronger implicit interference. Second, stronger implicit interference entails available attentional resources. This hypothesis is motivated by our recent work on a young population showing the attentional requirement to process implicit distracting sensory information.[12] Conversely, this hypothesis will predict a stronger implicit interference in low-risk older participants.

2 | METHODS

2.1 | Experimental design and subject details

2.1.1 | General experimental apparatus

Participants performed the experiment in a quiet room. The visual stimuli were generated with E-prime (Psychology Software Tools, Inc.) on a Dell Precision T5610 with a 20″ screen. Participants were unconstrained and observed the visual stimuli from approximately 50 cm away.

2.1.2 | Participants

Forty-seven cognitively healthy elderly (age range 53–92) were recruited. These participants were pre-determined as CH-NATs and CH-PATs.[22] Please see the next section for more information. The status of each participant was not known to the participant and experimenter, making the study double-blinded. None of them reported vision difficulty during stimulus presentation. The institutional review boards (IRB) of the California Institute of Technology and the Huntington Medical Research Institutes (HMRI) approved this study (Quorum IRB, Seattle, Study #27197). All participants gave written consent prior to participation. Every participant completed a session lasting approximately 50 minutes. Three participants were excluded prior to analysis due to their inability to perform the task. Another three participants were excluded with accuracy three standard deviations lower than the group mean. One participant's status remained unknown and was not included. Forty participants thus entered the final analysis with 18 CH-NATs and 22 CH-PATs.

2.1.3 | Participant status classification

A complete description of classification, including a complete list of neuropsychological testing, magnetic resonance imaging diagnosis of

RESEARCH IN CONTEXT

1. **Systematic Review**: Early intervention for Alzheimer's disease (AD) requires early identification of the disease. Although significant advances have been made in localizing early biochemical markers of AD, non-invasive and more accessible behavioral markers remain unavailable. The results of the current study showed that while both high-risk and low-risk cognitively healthy older participants exhibited reaction time slowing due to explicit distracting information, only the high-risk individuals suffered from implicit distracting information.

2. **Interpretation**: These novel results revealed a new direction to understanding the implicit cognitive decline in pre-symptomatic AD. Specifically, how individuals implicitly inhibit irrelevant and detrimental information could be crucial to cognitive health.

3. **Future Directions**: Our findings suggest that information not accessible to our conscious cognition is processed differently in older cognitively healthy participants with different levels of risk of AD. More future studies are required to incorporate these findings and pinpoint a predictive behavioral and neural marker in AD.

small vessel disease, the biochemical analysis of lumbar CSF, was detailed in a previous study.[22] In summary, separate assessments performed prior to the experiment included a collection of demographic data, physical exam, blood work, disease severity and disability scales, and CSF amyloid/tau measurements. Participants with any cognitive impairment, that is, global Clinical Dementia Rating (CDR) scale scores > 0.0, were not recruited. Participants had a Uniform Data Set format examination with no classifiable psychiatric or neurological disorder and were all diagnosed as cognitively healthy. They enrolled in this study after a 5-hour comprehensive neuropsychological battery in which testing was performed independent/blind to the biochemical classification. Different cognitive domains including memory, executive function, language, attention, and visuospatial orientation were tested. All data were normalized to age, sex, and education normative tables. These formal neuropsychometric data were combined with CDR, Montreal Cognitive Assessment (MoCA), and MMSE, as described previously.[23] The CSF samples were run on both Innotest (Innogenetics, discontinued) and MSD platforms (K15121G, MSD) to determine total tau (cutoff value > 450 pg/mL) and $A\beta_{42}$.[26,27] Participants were then divided depending on individual CSF $A\beta$/total tau ratios compared to a cutoff value derived from a logistic regression model that correctly diagnosed > 85% of clinically probable AD participants.[22] Participants' demographics, including their age, sex, and education year, can be found in Table 1. There was no difference between the two groups.

TABLE 1 Demographics and post-study subjective effort exertion report of CH-NATs (low-risk) and CH-PATs (high-risk)

	CH-NATs (low risk)	CH-PATs (high risk)
Total number	18	22
Age	77.29 (8.01)	74.48 (8.85)
Sex	12 females 6 males	17 females 5 males
Education year	16.18 (2.10)	16.90 (2.45)
Post-study questionnaire	0: Not at all–3: Severe	
Did you have any physical troubles during the task?	0.11 (0.32)	0.36 (0.62)
Difficulty: Word responding to word responding	1.11 (0.70)	1.12 (0.76)
Difficulty: Color responding to color responding	1.03 (0.65)	1.24 (0.75)
Difficulty: Word responding to color responding	1.28 (0.77)	1.52 (0.66)
Difficulty: Color responding to word responding	1.31 (0.62)	1.60 (0.62)
How much effort did you use for the task?	1.89 (0.74)	2.02 (0.64)
Do you feel tired after the task?	0.72 (0.83)	0.74 (0.85)

Note: The two groups were comparable in each item with $P > .05$. The data are reported in mean (SD).
Abbreviations: Aß, amyloid beta; CH-NAT, cognitively healthy with normal Aß42/total tau protein ratio; CH-PAT, cognitively healthy with pathological Aß42/total tau protein ratio; SD, standard deviation.

2.1.4 | Experimental design and procedure

An illustration of the task and stimuli is in Figure 1. Two words and two colors were selected to create word–color inconsistency in the stimuli: word GREEN/RED in color red/green. A fixation point remained on screen throughout the trial. Each trial consisted of two stimuli to induce task-switching (word-naming for the stimulus 1 and color-naming for the target, or vice versa) or non-task-switching trials (word-naming or color-naming for both stimuli). A gray distractor (GREEN/RED) was presented with a forward and a backward noise mask that consisted of random meaningless letters to disrupt its visibility. The (in)congruency between the distractor and the target was defined by the response induced by each stimulus.

Each trial began with a 500-ms blank stimulus-onset asynchrony (SOA). The first stimulus word in the trial was presented for 5000 ms or until response. Subsequently, a masked distractor (17 ms) was sandwiched between a forward and a backward mask (each 50 ms) and presented above or below the fixation dot. Each mask consisted of a 4 × 8 array of random letters and lasted 50 ms. Another blank period was inserted and lasted 500 ms. The target word appeared subsequently and lasted for 5000 ms or until response.

In each trial, participants responded to both colored words. Participants were instructed to name the color when the word was underlined (color-naming) and to name the word when the word was not underlined (word-naming) via button presses. No task was given to the masked word. It is important to point out that the second stimulus was the true target stimulus because both the task-switching and masked distractor effects could only be observed on this stimulus. Our analyses thus focused on the responses to the target word.

Every participant first underwent a short period of practice until they felt comfortable proceeding to the main experiment. Three blocks
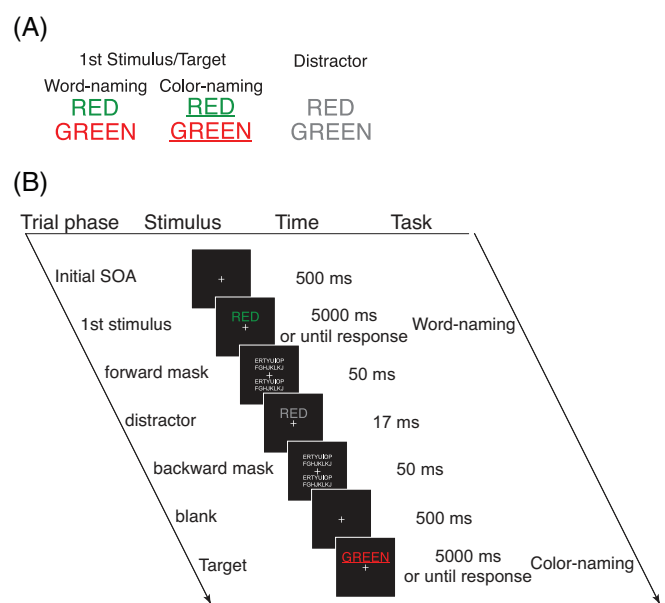

FIGURE 1 Stimuli, trial sequence, and task. A. Top. Stimuli. The stimulus words were RED/GREEN, colored in an inconsistent ink. When the word was not underlined, the task was word-naming. When the word was underlined, the task was color-naming. Distractors were the same words without colors. B. Bottom. Trial sequence and task. Shown here is a task-switching trial. Each trial began with a 500-ms fixation, after which the first word appeared for 5000 ms or until response. The masked word was presented for 17 ms in one of the two possible locations (above or below the fixation) and sandwiched by two 50-ms masks consisting of random letters. No task was given to the masked distractor. The target appeared after another 500-ms blank period and lasted for another 5000 ms or until response. Participants were instructed to respond as accurately as possible.

each containing 64 trials were completed in the main experiment. To assess the invisible nature of the masked distractor, a post-experiment surprise awareness test was performed. The temporal sequence of the masking paradigm was identical to that of the main experiment. Each trial began with a 500-ms blank SOA, followed by the masked word presentation. Participants were instructed to report the location (top/bottom) of the masked word as best as they could (i.e., two-alternative-forced-choice [2AFC]). Similarly, they had 5000 ms for a response.

All participants completed a post-study questionnaire (Table 1) to indicate their subjective physical and mental efforts exertion during the study. Seven questions were asked on a four-point scale (0: not severe at all—3: very severe). Participants were allowed to give subscale responses (e.g., 1.5).

3 | RESULTS

The analyses below are reported in the format of mean (standard error of the mean [SEM]). To first establish that the masked distractor was indeed imperceptible, we examined the accuracy of the 2AFC location task in the post-experiment awareness test. The mean accuracy was 45.00% (2.07%) and slightly below chance (paired $t(33) = 2.42$, $P = 0.02$), indicating the implicit nature of the distractor. There was no difference between CH-NATs (low risk) and CH-PATs (high risk; two-sample t-test, $t[32] = 0.14$, $P = .89$). Six participants refused to complete this task, claiming that there was absolutely no word on the monitor. Their data were excluded only for the awareness test. Post-study questionnaire results indicated no differences between CH-PATs and CH-NATs in subjective effort exertion (Table 1). Particularly, although the experiment was designed to examine how the elderly responded to cognitively challenging conditions while using inhibitory control, participants reported low levels of difficulty.

The average accuracy rates (ACC) and reaction times (RT) on the target in each trial were first examined to gauge participants' performance. On average, the mean ACC was 92.75% (0.95%), and the mean RT was 1350 (21) ms. These data corroborated that our participants were cognitively healthy and performed the task well.

To further examine their performance with respect to our experimental design, two separate mixed-effect analyses of variance were performed on the ACC and RT with one between-subject factor (participant status: CH-NATs/CH-PATs) and three within-subject factors (switch/Stroop/distractor incongruency). The switch component denoted whether the current target was in a switch (e.g., color-naming for the first stimulus and word-naming for the second stimulus) or non-switch trial (e.g., color-naming for both stimuli). The Stroop component denoted whether the target stimulus (i.e., the second stimulus) was color-naming (i.e., the Stroop effect, high-effort) or word-naming (i.e., the reverse Stroop effect, low-effort). Finally, the distractor incongruency component was defined by the designated responses triggered by the distractor and the target. If they triggered the same button response, the distractor was deemed congruent, otherwise, it was deemed incongruent.

The analysis on the ACC yielded a main effect of switch, $F(1, 38) = 11.95$, $P = .001$, $\eta p2 = 0.24$, with no main effects of Stroop, $F(1, 38) = 0.56$, $P = .46$, $\eta p2 = 0.02$, distractor congruency, $F(1, 38) = 0.54$, $P = .47$, $\eta p2 = 0.01$, and participant status, $F(1, 38) = 0.14$, $P = 0.71$, $\eta p2 = 0.00$. This could be due to ceiling performance.

In contrast, the analysis on the RT yielded main effects of switch, $F(1, 38) = 103.63$, $P = .000$, $\eta p2 = 0.73$; Stroop, $F(1, 38) = 11.30$, $P = .002$, $\eta p2 = 0.23$; distractor congruency, $F(1, 38) = 3.58$, $P = .07$ (marginal), $\eta p2 = 0.09$, and no effect of participant status, $F(1, 38) = 0.14$, $P = .71$, $\eta p2 = 0.00$. Critically, a three-way interaction was observed across participant status, Stroop, and distractor incongruency, $F(1, 38) = 5.08$, $P = .03$, $\eta p2 = 0.73$. Based on our a priori hypothesis that distractor incongruency could slow down responses in participants with normal or pathological status, we treated the Stroop factor as an "effort" factor and examined the distractor incongruency effect in each group under the high-effort (color-naming) and low-effort (word-naming) conditions. This approach also limited the potential comparisons. A similar approach was taken in our recent study with a similar experimental design.[12] Two post hoc analyses were thus performed. The RT here were also normalized against the average RT of the comparing conditions so that the percentage increase or decrease could be cleanly assessed. In the high-effort color-naming trials, compared to CH-NATs, CH-PATs were interfered by an implicit response-incongruent distractor, indicated by RT slowing (CH-PATs: 4.3% vs. CH-NATs: –0.2%, $t[38] = 2.55$, $P = .015$, Cohen's $d = 0.83$, significant after Bonferroni correction, left panel, Figure 2). This effect was not found in the low-effort word-naming trials (CH-PATs: –1.3% vs. CH-NATs: 1.04%, $t[38] = -0.95$, $P = .35$, Cohen's $d = 0.31$, right panel, Figure 2). In short, during the more difficult color-naming condition, incongruent distractors slowed down RTs in CH-PATs but not CH-NATs.

Although the participants in both groups were diagnosed as cognitively healthy, we further explored if their performance in the neuropsychological tests was correlated with the extent to which the incongruent, implicit distractor exerted an RT-slowing effect. Here we reported the MoCA and MMSE scores. Both scoring systems range from 0 to 30. Larger numbers indicate better cognitive ability. With all participants, there was a negative correlation between the distractor effect and MMSE: $r = –0.38$, $P = .02$ (Figure 3), but not between the distractor effect and MoCA: $r = –0.11$, $P = .52$. The group result indicated a link between worse cognition (i.e., lower scores in MMSE) and stronger subliminal distraction, which was consistent with our main finding. This negative correlation was not found within each group (CH-PATs: MoCA × distractor congruency: $r = –0.13$, $P = .46$; MMSE × distractor congruency: $r = –0.37$, $P = .09$; CH-NATs: MoCA × distractor congruency: $r = –0.32$, $P = .23$; MMSE × distractor congruency: $r = –0.43$, $P = .10$; note that there are two missing data points of the original MoCA and MMSE scores in CH-NATs, which are not included in this analysis). At least for the relationship between MMSE and distractor congruency, the lack of significance in each group was possibly due to smaller group sizes since both groups had the same trend.

Finally, we ran a logistic regression to directly estimate how predictive MMSE, MoCA, and the distractor congruency were to
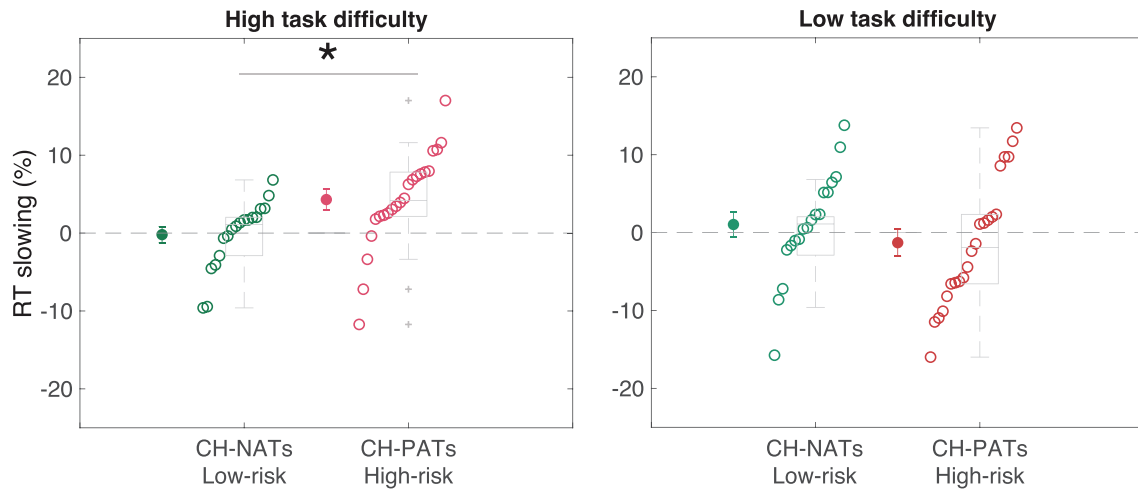
FIGURE 2 Implicit interference in CH-NATs (low risk) and CH-PATs (high risk). Percentage reaction time slowing was calculated by taking the RT difference between distractor incongruent and congruent trials, divided by the average of the two. Left, During color-naming, CH-PATs showed stronger RT slowing, compared to CH-NATs. Right, During word-naming, both groups were not interfered by incongruent distractors. CH-NATs are in green while CH-PATs are in red. Each circle represents an individual, while the solid disc indicates the mean. Error bars denote standard error of the mean. Individual data are ranked order by the effect. A box plot is embedded in the background to display data distribution. Following the convention, the line inside the box denotes median while the upper and lower limits denote 75th and 25th percentile. Whiskers extend to 1.5 interquartile range. Crosses represent data exceed this range. Asterisk denotes $P < .05$; CH-NAT, cognitively healthy with normal Aß42/total tau protein ratio; CH-PAT, cognitively healthy with pathological Aß42/total tau protein ratio; RT, reaction time
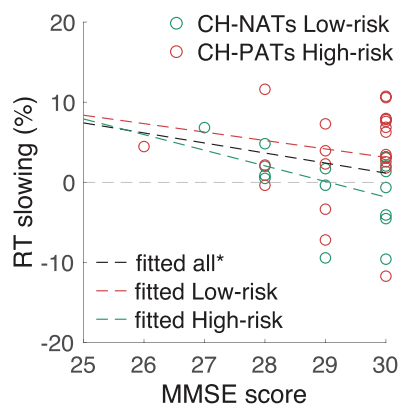

FIGURE 3 Negative correlation between MMSE scores and the implicit interference in the high difficulty task in all participants. CH-NATs are in green while CH-PATs are in red. Each circle represents an individual. Three dotted lines were linearly fitted to the correlation in all participants (black), CH-NATs (green), and CH-PATs (red). Asterisk denotes $P < .05$; CH-NAT, cognitively healthy with normal Aß42/total tau protein ratio; CH-PAT, cognitively healthy with pathological Aß42/total tau protein ratio; MMSE, Mini-Mental State Examination

TABLE 2 A logistic regression model using MMSE, MoCA, and RT interference (RT slowing by an implicit distractor) to estimate their predictive power to Alzheimer's disease risk level

Term	Coefficient estimate	95% confidence interval		SE	P
Intercept	−6.6802	−25.2020	11.8415	9.4499	.48
MMSE	−0.0979	−0.7430	0.5473	0.3292	.77
MoCA	0.3491	−0.0615	0.7597	0.2095	.10
RT interference	16.0548	1.7245	30.3851	7.3114	.03*

Note: RT interference is the only factor that significantly concurs with the risk level. Coefficient estimate denotes probability of being CH-PATs compared to CH-NATs in each term. Positive values denote higher probability while negative ones denote lower probability. That is, a unit increase in RT interference increases the log odd of being CH-PATs approximately 16 times. SE denotes standard errors of coefficient estimates. Asterisk denotes $P < .05$.
Abbreviations: MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; RT, reaction time.

4 | GENERAL DISCUSSION

participants' biochemical status/risk level. Our results showed that distractor congruency was the only factor that significantly concurred with participants' status (Table 2). That is, higher interference significantly predicted high-risk level. These results suggest better agreement between the risk level and implicit perception than the risk level and explicit cognitive function.

Our study served as one of the first attempts to directly examine how the elderly at high and low risk of AD suffered from distracting, implicit interference. Multiple layers of response interference were introduced to examine the capability of inhibition control, including task-switching, Stroop interference, as well as subliminal distractor incongruency. We found that when the interference was explicit and consumed conscious effort, both the low-risk (CH-NATs) and high-risk

(CH-PATs) participants slowed down during task-switching and color-naming (i.e., the classical Stroop effect). The performance between the two groups was comparable. However, when the interference was implicit and subliminal, the two groups' performance bifurcated: Under high task difficulty (i.e., color-naming), high-risk participants suffered more interference from imperceptible and response-incongruent distractors, compared to low-risk participants. When the task difficulty was lower (i.e., word-naming), both groups were not interfered by the distractor. These results revealed early changes in inhibitory control over latent and implicit visual information, while participants remained cognitively healthy and exhibited similar level of interference from conscious, explicit visual information. Our findings thus indicated the importance of investigating subliminal perception in providing a potential pre-clinical behavioral marker to differentiate older participants into high- or low-risk status in AD.

Our main finding indicates that inhibitory control in suppressing implicit distracting information can be key to differentiate high- and low-risk pre-symptomatic AD. Low-risk participants appeared to have an intact ability to suppress unwanted information and hence were protected from implicit interference. Intriguingly, high task difficulty was another key factor in revealing the differences between low-risk and high-risk participants. One potential explanation is that the attentional resources required to suppress explicit and implicit distracting information were shared, which is illustrated in our recent study in the young healthy adults.[12] In the easier task (i.e., word naming), both groups were able to use these limited attentional resources to suppress the distraction from the implicit stimulus (i.e., the incongruent distractor). On the other hand, when the task at hand was difficult (i.e., color naming), the attentional resources of high-risk, but not low-risk participants, were exhausted by the explicit distracting information. Therefore, the inability to suppress implicit interference, which led to reaction time slowing, was only observed in high-risk participants and only when the task was challenging. These results suggest that the subtle deficits in suppressing implicit information could be a more sensitive indicator for early cognitive decline, compared to conscious and effortful inhibition over explicit information.

Tackling how older adults suppress implicit/subliminal information in the current study provides a novel direction for future research to assess cognitive health. Past studies have repeatedly shown that suppressing explicit/supraliminal task-irrelevant information is key to cognitive health. Using the Stroop paradigm, Davidson et al.[13] showed that older adults (mean age = 73–74 years old) consistently exhibited larger word interference to color naming, compared to younger adults (mean age = 20 years old). Similar results were found comparing AD patients to control participants: larger Stroop interference in AD.[28] A 2010 longitudinal study tracked 47 healthy individuals (tested in 1992–1994) until 12 of them subsequently developed AD.[29] The results showed that the error rate in incongruent Stroop trials was the strongest predictor of developing AD. All these studies suggest that a behavioral cognitive task (e.g., the Stroop task) can pose a significant challenge to the inhibitory control system and further help identify individuals with distinct capabilities to suppress distracting information. Consistent with these findings, our study further established that

older adults' ability to inhibit implicit distracting information concurs with their risk of developing AD, assessed by the CSF Aß42/ total tau protein ratio. This approach can be particularly powerful when the targeted older adults are cognitively healthy and pre-symptomatic despite having different levels of risk.

Our findings provide evidence in support for non-invasive psychophysical tasks in categorizing pre-symptomatic older participants into high- and low-risk groups. Early identification of the risk of developing AD has been a central topic in aging research. Several genes have been associated with changes in Aβ, including *PSEN1*, *PSEN2*, and *APP*. In a seminal study comparing carriers of *PSEN1* mutation to non-carriers, Bateman et al.[30] have shown early anomaly in behavioral, physiological, and neuropsychological measurements before symptom onset. For example, an increased tau level was detected 15 years prior to symptom onset, a decline in the concentration of CSF Aβ42 appeared 25 years prior to symptom onset. Cognitive impairment came a lot later and could be detected 5 years prior to onset. This direction of research has revealed multiple potential causes of AD, including age, genetics, and the environment. Our study further offers a novel behavioral, pre-symptomatic marker before any cognitive impairment has emerged with a minimally invasive procedure.

Once an early identification is in place during the long latent period in which no explicit cognitive decline is surfaced, early intervention could tremendously slow down disease progression. A 2-year multidomain intervention in high-risk older participants, including diet, exercise, cognitive training, and vascular risk monitoring, has shown benefits in cognition, measured by neuropsychological tests.[31] More importantly, these benefits were gained regardless of participants' baseline characteristics,[6] including their age, sex, education, socioeconomic status, and so on. Early identification of AD is essential to harnessing early intervention. An early decline in a specific domain of cognition is not only a target of identification but also a target of intervention.

Although at the group level we showed a significant difference between the low-risk and high-risk participants, it remains challenging to perform classification at the individual level (Figure 2, left). We believe that more predictive power can be harnessed when different aspects of cognitive functions are taken into consideration, and more data in the longitudinal trajectory within the same person are collected. Both approaches will shed light on the heterogeneity of human cognition and perception. Recent studies have implemented a within-person approach to allow accurate prediction of an individual's future performance. For instance, Stawski et al.[32] have shown that response speed predicted working memory better than attention switching did between individuals, while attention switching predicted working memory better than response speed did within individuals. Although this study had been completed within a short time window, it nevertheless indicated the importance of task selection in within-person, longitudinal tracking of cognitive performance. Our recent studies also indicated that combining other physiological data such as those from electroencephalogram and heart rate variability increased the performance when classifying older participants into higher and lower risk groups.[27,33] The ultimate goal of the current research

direction is to find sensitive cognitive domains that either provide individual classification with a psychophysical test or can be combined with other critical physiological measures to form an informative index, both with the goal to inform the risk to develop AD.

As our population moves into an aging society (1 in 6 people will be > age 65 by 2050[34]), cognitive aging has become an important topic for scientists, medical practitioners, and policy makers to consider. Unfortunately, an early decline in cognition is very often implicit and silent. We thus have to fight such a collapse while cognitive flexibility is still abundant, especially before it leads to an irreversible disease such as AD. Our study here provides a new perspective on using multiple levels of interference in a behavioral task and shows that higher susceptibility to implicit interference may be a key feature in high-risk older participants.

CONFLICTS OF INTEREST

The authors declare no competing interests. Author disclosures are available in the supporting information.

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