Aging Brain 6 (2024) 100123

Contents lists available at ScienceDirect

Aging Brain

journal homepage: www.elsevier.com/locate/nbas

TMS-derived short afferent inhibition discriminates cognitive status in older adults without dementia

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ARTICLE INFO

Keywords:
Transcranial Magnetic Stimulation
Cognitive Aging
Dementia

ABSTRACT

Aging is a complex and diverse biological process characterized by progressive molecular, cellular, and tissue damage, resulting in a loss of physiological integrity and heightened vulnerability to pathology. This biological diversity corresponds with highly variable cognitive trajectories, which are further confounded by genetic and environmental factors that influence the resilience of the aging brain. Given this complexity, there is a need for neurophysiological indicators that not only discern physiologic and pathologic aging but also closely align with cognitive trajectories. Transcranial Magnetic Stimulation (TMS) may have utility in this regard as a non-invasive brain stimulation tool that can characterize features of cortical excitability. Particularly, as a proxy for central cholinergic function, short-afferent inhibition (SAI) dysfunction is robustly associated with cognitive deficits in the latter stages of Alzheimer's Disease and Related Dementia (ADRD). In this study, we evaluated SAI in healthy young adults and older adults who, though absent clinical diagnoses, were algorithmically classified as cognitively normal (CN) or cognitively impaired (CI) according to the Jak/Bondi actuarial criteria. We report that SAI is preserved in the Old-CN cohort relative to the young adults, and SAI is significantly diminished in the Old-CI cohort relative to both young and CN older adults. Additionally, diminished SAI was significantly associated with impaired sustained attention and working memory. As a proxy measure for central cholinergic deficits, we discuss the potential value of SAI for discerning physiological and pathological aging.

Introduction

As the population of Americans aged 65 and older is expected to double over the next forty years, it is paramount to refine our understanding of the neurocognitive and neurophysiological changes that accompany typical and pathologic aging [1]. Aging is a

Abbreviations: AD, Alzheimer's Disease; ADRD, Alzheimer's Disease and Related Dementia; BFCS, Basal Forebrain Cholinergic System; CANTAB, Cambridge Neuropsychological Test Automated Battery; CI, Cognitively ImpairedCN, Cognitively Normal; LAI, Long Afferent Inhibition; LBD, Lewy Body Dementia; M1, Primary Motor Cortex; MCI, Mild Cognitive Impairment; MEP, Motor Evoked Potential; MTT, Multitasking Task; PAL, Paired Associates Learning; ppTMS, Paired-Pulse Transcranial Magnetic Stimulation; RVP, Rapid Visual Processing; SAI, Short Afferent Inhibition; spTMS, Single-Pulse Transcranial Magnetic Stimulation; SWM, Spatial Working Memory; TMS, Transcranial Magnetic Stimulation.

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https://doi.org/10.1016/j.nbas.2024.100123
Received 11 November 2023; Received in revised form 29 June 2024; Accepted 14 July 2024

complex biological process characterized by the gradual accumulation of molecular, cellular, and tissue damage, leading to a progressive loss of physiological integrity, functional deficits, and increased vulnerability to pathology [2]. This biological entropy foments tremendous physiological and behavioral heterogeneity, further complicated by dynamic interactions with genetic and environmental factors that confer risk and resilience for the aging brain [3,4]. Collectively, this creates a challenging landscape for the study of cognitive aging [5]. While subtle cognitive deficits are commonly considered *benign* in typical aging, *malignant* behavioral deficits can accelerate alongside the pathophysiological cascade of neurodegenerative processes to elicit clinically evident impairment [6]. Dementia, the clinical endpoint of *malignant* cognitive aging, is characterized by severe and ongoing deterioration in cognitive abilities to an extent that impedes independent daily functioning [7]. With its rising prevalence, dementia is often cited as the leading health concern of older adults [8,9].

Dementia is a remarkably heterogeneous clinical syndrome with complex etiologies, mixed pathologies and variable trajectories [10]. Highlighting the pathological ambiguity that underlies dementia diagnoses, post-mortem examination of brain tissue from >1000 cognitively impaired individuals revealed 236 unique neuropathologic combinations, with 58 % of samples having 3+ neuropathologies [11]. Even when constrained to Alzheimer's Disease (AD), the most common form of dementia biologically defined by amyloid-beta (Aβ) plaques and neurofibrillary tau tangles, <9% of the 700 pathologically confirmed AD cases were absent of additional mixed pathologies [11]. The clinico-behavioral trajectories across the continuum of cognitive aging are equally diverse, as individuals with similar neuropathological loads can display dissimilar cognitive profiles and rates of decline [4,12]. Underscoring this point, a longitudinal investigation of the clinicopathologic coherence in AD, cerebrovascular disease, and Lewy-Body Dementia reported that the pathologic indices of these diseases only explained 41% of the variation in cognitive decline [13]. The instability of Mild Cognitive Impairment (MCI)—a non-specific syndromic construct defined as the transitional phase between typical aging and dementia—further underscores the inherent heterogeneity in cognitive aging, with potential outcomes ranging from reversion, stabilization, or progression of deficits to dementia [14]. This complexity is compounded by the increased recognition of a protracted, latent preclinical window of diseases like AD where individuals meeting the pathological criteria can remain asymptomatic for up to 20 years [15].

A wide range of factors influence an individual's course of cognitive aging, creating varying degrees of resilience to the detrimental effects of age-related pathologies in the brain [16]. Researchers have elucidated the phenomenon of resilience through the frameworks of *'brain reserve'* and *'cognitive reserve'*. Brain reserve, a passive construct attributed to stable factors like genetics and early life experiences, reflects the brain's capacity to tolerate neurological attrition before crossing a threshold of impairment [16,17]. As a relatively static physical trait, brain reserve can be conceptualized as an individual's baseline neuroanatomical capital and, thus, its capacity to withstand insults over time [17]. Alternatively, with brain reserve held constant, cognitive reserve constitutes the brain's functionality, plasticity, and adaptability [16]. This active model of resilience reflects the cognitive flexibility necessary to cope with and compensate for the functional and structural changes in the brain that accompany age and disease [17]. Cognitive reserve is thought to be influenced by a range of social and lifestyle factors, like premorbid IQ, educational history, occupational attainment, and social engagement [18].

As dementia is increasingly recognized as a medically refractory condition necessitating earlier intervention, the field is increasingly shifting its focus to earlier stages of the disease continuum, creating an imperative to better forecast the risk of cognitive deterioration in older adults [19–21]. Beyond the apparent real-world utility of enhanced prognoses, this capability is urgently needed to enrich clinical trials that are increasingly investigating disease-modifying therapies in the nascent stages of diseases like AD [22–25]. Given that the primary endpoints of these trials typically compare rates of decline, there is a critical assumption that participants assigned to the treatment and placebo groups should show similar rates of decline without intervention [25]. Thus, when the heterogeneity of progression is unaccounted for, potential treatment effects are exceptionally challenging to discern [23]. Beyond the conventional proxies of cognitive resilience introduced above, complementary measures of neurophysiological function may add depth and precision to characterizing an individual's trajectory along the disease continuum [20,26]. Indeed, as a prime example of neurophysiological resilience, there is a robust connection between cerebral glucose utilization and cognitive stability [27–30]. This well-described association highlights the prognostic value of neurophysiological measures, underscoring the need for ongoing research to identify and evaluate supplementary features capable of stratifying the risk of cognitive deterioration. Accordingly, this manuscript will focus on central cholinergic integrity, a neurophysiological feature with a well-founded theoretical basis for its potential impact on cognitive trajectories [31].

Through its widespread neuronal projections from the basal forebrain, the cholinergic system is integral to a broad set of cognitive processes. Reflected by the broad appeal "Cholinergic Hypothesis" of geriatric memory dysfunction, it has long been recognized that insults to the basal forebrain cholinergic system (BFCS) are fundamentally linked with physiologic and pathologic cognitive deficits associated with age [32]. While BFCS degradation in physiological and pathological aging is certainly still subject to a high degree of heterogeneity, several consistent findings spotlight cholinergic integrity as a compelling candidate for stratifying risk of cognitive deterioration. First, as elegantly reviewed elsewhere, in addition to supporting numerous high-order cognitive functions in healthy systems, an intact cholinergic neuromodulatory system may serve as a key physiological mechanism of cognitive resilience by facilitating the recruitment of alternative neural pathways to mitigate pathological deficits [31]. Empirical support linking BFCS integrity with cognitive reserve is provided by studies utilizing positron emission tomography (PET) to compare the functionality of the cholinergic system with conventional proxies of resilience [33]. Second, on the flipside of resilience, the BFCS demonstrates high selective vulnerability to insults associated with physiologic and pathologic aging [34]. As a derivative of this vulnerability, BFCS damage is a preliminary occurrence in the pathophysiological cascades of dementia-inducing diseases, supporting its relevance in the nascent stages of these conditions [35]. Lastly, findings consistently support the robust association between BFCS damage and cognitive deficits in cross-sectional investigations and its prognostic value for forecasting cognitive deterioration in longitudinal

studies [36–40].

To assess BFCS integrity *in vivo*, research to date has leveraged a multitude of technologies like Magnetic Resonance Imaging (MRI), Positron Emission Topography (PET), and Transcranial Magnetic Stimulation (TMS), each equipped with varying degrees of specificity and accessibility. This study will utilize TMS, a versatile, noninvasive brain stimulation tool with widespread adoption to examine the BFCS across the broad continuum of cognitive aging. Unrelated to the tool's vast therapeutic potential, single-pulse (spTMS) and paired-pulse (ppTMS) protocols do not produce persistent changes in neural activity but can instead be employed to generate evoked potentials that are measured either centrally with electroencephalography (EEG) or peripherally with electromyography (EMG). As initially demonstrated by Barker and colleagues in 1985, suprathreshold spTMS applied to the primary motor cortex (M1) elicits a focal muscle response that can be readily recorded with EMG as a motor-evoked potential (MEP) [41]. Compared to other noninvasive brain stimulation technologies, an essential characteristic of TMS's biophysical properties is that it activates cortical pyramidal cells *trans*-synaptically [42]. This critical feature makes TMS-evoked potentials sensitive to changes in cortical excitability, which can then be leveraged to examine neurophysiological features of the human brain *in vivo*. Decades of research integrating pharmaceutical agents with known mechanisms of action alongside M1-TMS protocols demonstrate that different outcome measures have distinct neurophysiological underpinnings with various degrees of specificity [43].

Of the diverse array M1-TMS measures, Short Afferent Inhibition (SAI) is considered a proxy for central cholinergic function [44]. SAI is derived from a broader inhibitory phenomenon whereby a preceding afferent sensory volley in a ppTMS protocol diminishes the subsequent TMS-evoked motor response. Experimenters probe this phenomenon by electrically stimulating a peripheral nerve prior to generating an MEP with M1-TMS. Thus, when both pulses are applied at a precise inter-stimulus interval (ISI), SAI represents the magnitude that a peripheral conditioning stimulus suppresses a TMS-evoked MEP. Supporting the cholinergic influence on this inhibitory intracortical circuit, studies in healthy young adults reveal that the magnitude of SAI is bidirectionally modulated by pro- (e.g., nicotine) and anti- (e.g., scopolamine) cholinergic compounds [45,46]. Further reinforcing the notion that SAI reflects central cholinergic activity, probing this M1-TMS metric during online memory retrieval in young adults revealed real time activation of cholinergic circuits [47]. This observation critically demonstrates SAI's capacity to reveal dynamic changes in cholinergic activity *in vivo*, offering insights into the functional implications of cholinergic modulation in cognitive processes. This point dovetails with converging evidence from cognitive aging research, indicating that the functional integrity of cholinergic circuits, as reflected by SAI, is diminished in pathological conditions that target the BFCS [40]. In addition to a reported association between basal forebrain volume and SAI [48], there are consistent reports that SAI corresponds with cognitive deficits in physiologic and pathologic aging [40,49]. In probable AD dementia, for example, investigations have observed that SAI is diminished in drug-naïve patients but can be restored with cholinergic therapy (acetylcholinesterase inhibitors; AChEIs), and the extent of SAI restoration significantly correlates with the therapeutic efficacy of the medication [50,51].

While SAI is consistently shown to be reduced in forms of dementia with primary cholinergic deficits such as AD and Lewy-Body Dementia, SAI findings are less consistent in others that do not primarily afflict the BCFS, like vascular dementia [52]. Additionally, diminished SAI has been linked to cognitive deficits in other clinical populations like Multiple Sclerosis and Obstructive Sleep Apnea [53,54] – two conditions that have been associated with BFCS damage [55–57]. It is also important to note that, while principally influenced by cholinergic circuits, SAI is also responsive to a broader set of pharmacological compounds that target distinct neurotransmitter systems [43]. For example, M1-TMS studies have reported that dopaminergic and GABAergic agents have restored SAI in patients on the Alzheimer's disease continuum [58–60]. This evidence suggests that SAI may not exclusively reflect cholinergic activity but rather an integrated circuit that is particularly sensitive to the pathologies of AD and related dementias [52].

Critically, however, despite the robust association between SAI and cognitive deficits associated with age-related disease, any emergent biomarker's clinical potential hinges on its established dynamics in healthy systems. It is essential to determine if SAI declines as a function of normative aging or if significant reductions more aptly reflect malignant cognitive deterioration. Marked by inconsistent findings to date, the influence of healthy aging on SAI remains unclear [61–66]. This ambiguity may be attributable to insufficient neuropsychological assessment of the supposed 'healthy' older adults enrolled in these prior investigations.

We sought to resolve this uncertainty by evaluating SAI across the broader spectrum of cognitive aging by enrolling healthy younger adults and community-dwelling older adults who underwent comprehensive neuropsychological screening. While no participants reported a clinical diagnosis of AD or MCI, this standardized screening facilitated the algorithmic classification of older adults as either cognitively normal (CN) or cognitively impaired (CI) according to previously published best practices [67]. The inclusion of healthy young adults provides a reference value of SAI, reflecting the standard activity of this cholinergically mediated intracortical circuit before the biological entropy of age. Further, by conducting comprehensive neuropsychological examinations in community-dwelling older adults, we can ascertain whether deviations from this reference value are associated with subclinical cognitive deficits. To our knowledge, this is the first study to comparatively assess SAI in normal and atypical cognitive aging. Additionally, as a secondary element of the study, we explored the behavioral correlates of SAI to assess if specific cognitive domains are associated with this TMS-derived proxy of central cholinergic integrity.

Materials and methods

Participants

Forty-five English speaking individuals participated in this study. All participants were recruited from the surrounding community using a mix of analog and digital advertisements. The participants were evenly distributed across three groups: a) young adults (age range: 18–33, mean age: 21.5 ± 4.1, 8F), b) cognitively normal (CN) older adults (age range: 50–80, mean age: 67.5 ± 9.2, 10F), and c)

cognitively impaired (CI) older adults (age range: 52–82, mean age: 69.9 ± 9.2, 8F) (Table 1). Inclusion criteria were as follows: (i) age between 18–35 (young) or 50–85 (old); (ii) absence of significant neurological condition (e.g., Alzheimer's, stroke, etc.); (iii) absence of medications or recreational drugs known to modulate cortical excitability (e.g., benzodiazepines); (iv) absence of contraindications to TMS (e.g., family history of seizures); (v) absence of self-reported sudden, steep decline in cognitive performance; (vi) ability to comprehend and willingness to sign informed consent form. While none of the older adults presented with a clinical diagnosis of MCI, participants were algorithmically classified as CI according to established neuropsychological actuarial criteria detailed further below [67] All experimental procedures were approved by the University of Arizona Institutional Review Board, and informed written consent was obtained in accordance with the Declaration of Helsinki (The Code of Ethics of the World Medical Association).

Neuropsychological evaluation

The cognitive evaluations included in this study comprise two distinct components. The first was a standardized neuropsychological battery used to algorithmically classify cognitive status as described below. Notably, this component was only completed by older adults and was conducted during an additional study visit. The second element was an abbreviated computerized cognitive evaluation conducted alongside TMS activities. Notably, this element was completed by all study participants, and it was used to explore the behavioral correlates of SAI. All cognitive evaluations were completed in a controlled environment under the supervision of trained research staff.

Cognitive screening & classification (Older Adults)

All older adults completed the National Alzheimer's Coordinating Center-Uniform Data Set 3.0 (NACC-UDS3) standardized neuropsychological battery to algorithmically classify cognitive status [68]. This is comprised of multiple cognitive tasks including the Montreal Cognitive Assessment (MoCA), Craft Story 21 Recall (immediate and delayed), Benson Complex Figure Copy (immediate and delayed), Number Span Test (forward and backward), Category Fluency, Trail Making Test, Multilingual Naming Test (MINT), the Verbal Fluency – Phonemic Test, Rey Auditory Learning Test (AVLT) (immediate and delayed), North American Adult Reading Test (NAART), and Stroop Task. Only the older participants underwent the NACC neuropsychological battery. Cognitive performance on each task was adjusted for age, sex, and education using the extensive normative data of the NACC [69].

Using these normalized scores across all components of this standardized neuropsychological battery, the older adults were algorithmically classified as CN or CI according to Bondi's 'comprehensive criteria'. Specifically, CI was operationally defined as a participant scoring over one standard deviation (SD) below the adjusted normative mean on either: a) two tasks within the same cognitive domain or b) three tasks across all domains [67]. Unlike abbreviated approaches confined to a single cognitive assessment score like the MoCA or MMSE, multiple empirical analyses support stratifying cognitive status according to this comprehensive criteria [70,71]. Despite the variable terminology affiliated with this approach, with descriptive labels including 'algorithmic,' 'empirical,' and 'actuarial,' its application is increasingly utilized in research contexts as studies continue to yield compelling evidence of its validity [72–77]. Nonetheless, it is important to note that the cognitive status determinations in this study were conducted strictly for research purposes and cannot be upheld as meeting a rigorous clinical diagnostic standard for MCI. Thus, to avoid misattribution of a clinical MCI diagnosis, the cohort of older adults identified as having cognitive deficits through this algorithmic/actuarial approach will be referred to as Old-CI.

Table 1
Participant Characteristics & TMS Parameters.

	Old-CI (n = 15)	Old-CN (n = 15)	Young (n = 15)
Demographics			
*Age** [a]	69.9 ± 9.2	67.5 ± 9.2	21.5 ± 4.1 [a]
Sex (F)	8	10	8
*Education** [a]	17.1 ± 2.5	16.5 ± 2.7	14.5 ± 1.9 [a]
MoCA	25.7 ± 3.2	27.4 ± 2.2	N/A
Self-Reported Comorbid Clinical Conditions			
Depression	4 *(27 %)*	2 *(13 %)*	0
Diabetes	1 *(7 %)*	0	0
Hypertension	5 *(33 %)*	4 *(27 %)*	0
Dyslipidemia	5 *(33 %)*	3 *(20 %)*	0
ppTMS Acquisition Parameters			
TMS Intensity (% MSO)	62.3 ± 8.2	62.9 ± 9.7	60.5 ± 9.5
Median Nerve Stimulation Intensity (mA)	6.3 ± 2.3	6.4 ± 2.9	4.5 ± 1.6
*SAI ISI (ms)** [b]	25 (n = 11) [b]	20 (n = 9)	20 (n = 13)

Numerical data is presented as mean ± standard deviation. Sex is defined as biological sex at birth.
*Significant group difference ($p < 0.05$). [a]Young group significantly different than both old groups. [b]Old-CI group significantly different than Old-CN and Young. No other significant group differences were observed. Abbreviations: CI: Cognitively Impaired; CN: Cognitively Normal; ISI: Interstimulus interval; LAI: Long Afferent Inhibition; mA: milli Amp; MoCA: Montreal Cognitive Assessment; ms: millisecond; MSO: Maximum Stimulator Output; Old-CI: Older adults with cognitive impairment; Old-CN: Older adults with normal cognition; ppTMS: Paired-pulse TMS; SAI: Short Afferent Inhibition

Computerized cognitive assessment (All)

A separate computerized neuropsychological assessment was conducted using the Cambridge Neuropsychological Test Automated Battery (CANTAB) to assess cognition across multiple cognitive domains (Table 2) [78]. More specifically, the CANTAB was comprised of 4 tasks that assessed different cognitive functions. These four tasks included: 1) Rapid Visual Processing (RVP) task to assess complex attention and working memory, 2) Spatial Working Memory (SWM) task to assess working memory and strategy, 3) Paired Associates Learning (PAL) task to assess episodic learning and memory, and 4) Multitasking Task (MTT) to assess attention and executive functioning. Unlike the NACC which was used to classify cognitive status of older adults, the CANTAB tasks were completed by all participants including those in the young adult group. With CANTAB data available for all groups, we were able to conduct exploratory analyses associating SAI with cognitive performance across the broader spectrum of cognitive aging.

TMS protocols

TMS was delivered with MagPro x100 equipment (MagVenture Ltd.). The stimulation parameters conformed to current International Federation of Clinical Neurophysiology guidelines, and the same practitioner performed all TMS procedures to avoid inter-investigator variability [79,80]. An infrared-based frameless stereoscopic system was used for 3D neuronavigation (Polaris System, Localite, *Version 3.0.41*) to enable precise and reliable placement of the TMS coil. Prior to obtaining outcome measures of interest, each participant's unique motor hotspot and resting motor threshold (rMT) were identified. The motor hotspot was defined as the optimal coil position for eliciting the most consistent and robust MEPs in either the abductor pollicis brevis (APB) or first dorsal interosseous (FDI). The rMT was then identified as the minimum TMS intensity delivered to the hotspot sufficient to evoke an MEP$>$50 μV in 5 out of 10 consecutive trials.

To measure MEPs, surface EMG electrodes (Trigno™ Wireless System; Avanti Sensors; Delsys, Natick, MA) were placed on the APB and FDI muscles. EMG signals were bandpass-filtered (20–450 Hz) and amplified (x1000) prior to analog-to-digital conversion (Micro 1401 MkII, Cambridge Electron Design, Cambridge, UK). All EMG data were sampled at 2 kHz with Signal software (Cambridge Electronic Design, Cambridge, UK).

Measures of afferent inhibition were obtained with a paired pulse TMS (ppTMS) protocol that incorporated a 200 μs monophasic pulse delivered by a constant-current stimulator (Grass S88 and optical isolation unit) to the median nerve proximal to the wrist using a bipolar surface electrode. The electrode was placed with the cathode proximal using a Velcro strap encircling the wrist. The peripheral 'conditioning stimulus' preceded the M1-TMS 'test pulse' to the cortical motor hotspot at a specific inter-stimulus interval (ISI). The TMS intensity was set to 120 % of the individual's rMT, and the strength of peripheral nerve stimulation corresponded with the intensity that produced a visible twitch in the thenar muscles. We acquired four blocks of 25 MEPs under discrete conditions in a randomized sequence: 1) SAI-20 (ISI=20 ms), 2) SAI-25 (ISI=25 ms), 3) LAI-200 (ISI=200 ms), and 4) SAI-baseline (no peripheral nerve stimulation). Within each block, the inter-trial interval was jittered. Based on values reported in the literature, we sampled SAI at two ISIs (20 ms and 25 ms) and of the two ISIs, the one producing the greatest inhibitory effect for each participant was selected to evaluate SAI [44,48].

In addition to SAI, we included a ppTMS block with a long-interval ISI (200 ms) termed long afferent inhibition (LAI). SAI and LAI are nearly identical ppTMS paradigms with only one distinguishing feature – the significantly longer ISI between the conditioning and test pulses in LAI. As their names suggest, SAI and LAI produce an inhibitory effect, but they have distinct neurophysiological underpinnings. While both appear to be modulated by GABAergic agents, SAI is the only one that is strongly influenced by central cholinergic tone [44,81]. Therefore, we included LAI as a control variable because it is not suspected to be associated with the

Table 2
CANTAB Tasks.

Rapid Visual Processing (RVP) *Complex Attention*	RVP is a complex sustained attention task. A white box appears in the center of the screen, and within it, a single digit rapidly flashes at a rate of 100 digits per minute. A target sequence of three digits (e.g., 5–2-7) is displayed next to the box, and participants must identify the target sequence as quickly as possible. The key outcome variables for the RVP include: 1) RVP Median Response Latency (i.e., the median response latency on trials in which the participant responded correctly, across all trials), and 2) RVP A' which is a signal detection measure of response sensitivity to the target stimulus (i.e., how well the participant can detect the target sequences).
Spatial Working Memory (SWM) *Working Memory & Strategy*	Participants must search through boxes on the screen to find hidden token(s). SWM requires the retention and manipulation of visuospatial information and is a self-ordered task that also assesses an individual's ability to formulate and implement a strategy. The key outcome variables for the SWM include: 1) SWM Between Errors (i.e., number of times a participant incorrectly visits a box across all the assessed trials), and 2) SWM Strategy (i.e., the number of unique starting points the participant began their search during the 6 and 8 box tasks); lower scores reflect better strategy.
Paired Associates Learning (PAL) *Episodic Learning & Memory*	PAL assesses the participants' ability to associatively learn objects and their respective locations. After an encoding phase, object patterns are revealed one at a time in the middle of the screen and the participant must correctly match the pattern to its original displayed location. The key outcomes variables for the PAL include: 1) PAL Total Errors Adjusted (i.e., the total number of errors adjusted for the stages not completed due to early discontinuation of the task), and 2) PAL First Attempt Memory Score (i.e., the number of times a participant chooses the correct box on their first attempt across each stage).
Multitasking Task (MTT) *Attention & Executive Functioning*	An arrow appears on the screen under two different conditions/rules: 1) indicate the direction the arrow is pointing in, and 2) indicate the location of the arrow (i.e., the side of the screen the arrow appeared). Some trial blocks consist of a single rule while the rule pseudo-randomly changes in other trial blocks. Performance is compared across conditions. The key outcome variables for the MTT include: 1) MTT Total Incorrect (across all trials), 2) MTT Median Reaction Latency (across all correct, assessed trials), 3) MTT Median Multitasking Cost (i.e., the difference between the median latency of response during assessed blocks in which both rules are used versus assessed blocks in which only a single rule is used).

cognitive deficits observed along the ADRD continuum.

Data analysis

EMG data were processed using a custom MATLAB script that: 1) measured the peak-to-peak amplitude of the MEP waveform for each trial, 2) discarded trials where background line noise exceeded 50 μV immediately preceding the TMS pulse, 3) controlled for outliers by assigning less weight to extreme values (i.e., Winsorization approach where extreme values were replaced by mean ± 2 SD), and 4) extracted mean MEP for each of the four trial blocks. The amplitude of conditioned MEPs was represented as a percentage relative to the mean amplitude of unconditioned MEPs. Smaller values reflect greater afferent inhibition from the peripheral conditioning stimuli.

Statistical methods

Broadly, the analyses below can be segregated into two distinct aims: 1) assess group differences for M1-TMS measures between the three distinct groups, and 2) examine behavioral correlates of SAI across the cognitive domains assessed with the CANTAB battery (Table 2). To assess behavioral correlates across multiple domains, all measures were re-scaled by generating Z-scores.

Supplemental Bayesian analyses were integrated alongside more traditional null hypothesis significant testing (NHST) to increase the reliability of the findings reported herein (Box 1). Notably, Bayesian analyses were conducted with noncommittal priors, which further hedges against spurious Type I errors slightly biasing results toward null models [82]. All data were inspected for normality and homogeneity of variance, and power root transforms were applied to obtain normal distribution where appropriate. Model diagnostics were visually and quantitively inspected for both Bayesian and NHST analyses. Where appropriate, we employed Fischer's Least Significance Difference (FLSD) in post-hoc analyses to identify significant differences across multiple comparisons. *All statistical analyses were performed in R, version 4.1.0 using the brms and bayestestR packages (R Core Tem, 2019).*

Results

Group differences

As shown in Fig. 1A, the SAI effect was significantly diminished in the group of non-demented older adults with cognitive impairment (Old-CI) compared to the more substantial inhibition observed in both cognitively intact older adults (Old-CN) and younger adults. A one-way ANOVA revealed significant group differences in the magnitude of SAI ($F(2,42) = 10.9, p < 0.001$). Post-hoc pairwise comparisons revealed significant group differences between Old-CI and Old-CN ($p_{adjust} < 0.01$) and Old-CI & Young ($p_{adjust} < 0.001$), but not between the Old-CN and Young groups (Fig. 1A). The companion Bayesian regression model further supported this main finding with no overlap in the 95% credibility intervals of the parameter estimates of SAI for the Old-CI group relative to the Young and Old-CN groups (Fig. 1B). Further, the Bayes Factor (BF=163) suggests the observed group difference in SAI is 163 times more likely than the null hypothesis. When binarizing SAI results to responder/non-responder with an arbitrary threshold of 10% inhibition, 8/15 are non-responders in the Old-CI group compared to just 1/30 in the two cognitively normal groups (see Fig. 1A).

Notably, no significant group differences were observed for LAI ($F(2,42) = 2.4, p > 0.05$) (Fig. 1C and D). A supplementary analysis of covariance (ANCOVA) was performed and revealed no significant effect of age as a covariate on SAI ($F(1,43) = 2.96, p = 0.09$) or LAI ($F(1,43) = 0.83, p = 0.37$). Lastly, upon inspection for potential methodological heterogeneity that may contribute to the group effects, there was no significant difference in the TMS or median nerve stimuli intensity across the three groups.

Behavioral correlates of M1-TMS measures of cortical excitability

Across all participants, we observed significant associations between SAI and some aspects of cognitive function (Table 3). The strongest associations observed were between SAI and performance on tasks of sustained attention ($rho = 0.47, p < 0.005$, BF=17.2)

Box 1
Bayesian Terminology.

95 % Credibility Interval (CI): given the observed data, there is a 95 % probability that the true (unknown) parameter estimate lies within this interval. One can probabilistically infer 1) robust group differences when 95 % CIs do not overlap, 2) robust effect when the interval does not contain 0.

Bayes factors (BFs): a continuous measure of evidence supporting either the null or alternative hypothesis. BF=1 implies no evidence in either direction; BFs < 1 favor the null; and BFs > 1 favor a true effect. BFs exist on an infinite continuum, with no sharp thresholds or fixed 'significance' levels. That said, a BF>3 is thought to reflect mild evidence in favor of a true effect that is commensurate with $p < 0.05$, and the inverse BF of 1/3 would reflect equal evidence in favor of the null.

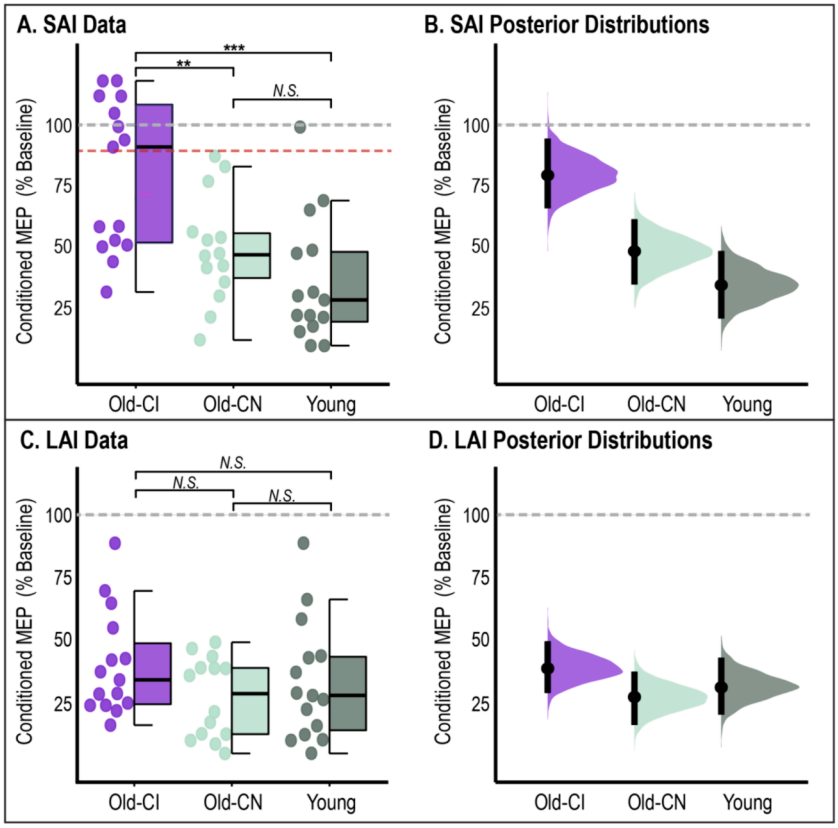

Fig. 1. Significant Group Differences are Exclusive to SAI: The dots represent each participant's mean conditioned MEP amplitude plotted as a percentage of the mean unconditioned MEP amplitude. Box plot elements: the black horizontal line represents the median, the colored box expands the inter-quartile range (IQR: 25 %-75 %), and the boxplot whiskers extend to capture up to 1.5x IQR. Data points above the dotted red line were considered non-responders, as they had less than 10 % inhibition relative to their unconditioned MEP amplitude. A) Short Afferent Inhibition (SAI): The one-way ANOVA revealed a significant group effect for SAI magnitude ($p < 0.001$). Post-Hoc comparisons revealed that the Old-CI group had significantly diminished SAI effect relative to both the Old-CN group ($p_{adjusted} < 0.01$**) and the Young Group ($p_{adjusted} < 0.005$***). **B)** Posterior distributions of conditioned MEP amplitude for SAI. The black circle represents the median parameter estimate, and the black bar indicates the 95 % credibility interval. When 95 % credibility intervals do not overlap, there is strong evidence of a credible group difference as is the case for the Old-CI group compared to the other two groups. **C)** Long afferent inhibition (LAI) for each group. The one-way ANOVA revealed no significant group-effect for magnitude of LAI. **D)** Posterior distributions of conditioned MEP amplitude for LAI. The 95 % credibility intervals estimated from LAI overlap across the three groups. CI: Cognitive Impairment, CN: Cognitively Normal, N.S.: No significant difference. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and the spatial working memory (*rho* = 0.39, $p < 0.05$, BF=5.2), indicating that participants who exhibited stronger SAI showed improved sustained attention and working memory. Diminished SAI was also statistically associated with poorer episodic memory on the PAL task, but the complementary Bayesian analysis suggests that this is not a robust finding (*rho* = 0.35, $p < 0.05$, BF=1.8). LAI was not correlated with any CANTAB measures, with some BFs providing support in favor of this null finding (Table 3).

Discussion

This study examined SAI, a putative marker of cholinergic integrity (Fig. 1), across the broader spectrum of cognitive aging by including healthy young adults, cognitively intact older adults, and older adults with evident cognitive impairment. As a congruent extension of what is routinely reported in later stages of Alzheimer's Disease and Related Dementias (ADRDs) [40], we report: 1) SAI is significantly diminished in the Old-CI group, 2) SAI is relatively preserved in the Old-CN group, and 3) SAI is significantly correlated with cognitive performance on tasks that hold relevance for the nascent stages of ADRDs. These findings enhance our understanding of SAI (dys)function as a nuanced neurophysiological indicator that may be sensitive to neurodegenerative processes in the brain associated with *malignant* age-related cognitive decline.

In the context of pathological aging, substantial evidence demonstrates a strong association between SAI (dys)function and ADRDs. Our recent *meta*-analysis, examining TMS-derived measures of cortical excitability in clinical populations with probable AD, identified SAI as the most reliable discriminator between affected individuals and healthy controls, with a sizeable pooled effect size of 1.89 (Cohen's D) across nineteen studies [40]. Further extending these findings, additional research reveals that SAI (dys)function

Table 3
Behavioral Correlates of SAI and LAI.

TMS	CANTAB	NHST Rho	p-value	BF	BF Interpretation
SAI	**RVP Latency**	**0.47**	**0.0028****	**17.9****	***Strong evidence: diminished SAI is associated with impaired sustained attention (longer response time)***
	RVP A'	−0.21	NS	0.74	NS
	SWM Strategy	**0.39**	**0.015***	**4.8***	***Moderate evidence: diminished SAI is associated with reduced strategy/planning***
	SWM Errors	−0.31	0.051	1.9	Unclear relationship between SAI and spatial working memory
	PAL Errors	0.35	0.025*	1.9	*Marginal evidence: diminished SAI is associated with worse performance on episodic memory task (increased error rate)*
	MTT Cost	0.1	NS	0.42	NS
LAI	RVP Latency	0.01	NS	0.35	NS, weak evidence supporting null
	RVP A'	0.06	NS	0.38	NS, weak evidence supporting null
	SWM Strategy	0.07	NS	0.39	NS, weak evidence supporting null
	SWM Errors	0.04	NS	0.37	NS, weak evidence supporting null
	PAL Errors	0.05	NS	0.42	NS
	MTT Cost	0.09	NS	0.41	NS

BFs = 1 equate a toss-up with no evidence in either direction. BFs < 1 favor the null hypothesis (no association between the two variables), while BFs > 1 favor the alternative hypothesis (i.e., credible association between the two variables).
A': Signal Detection Accuracy; LAI: Long afferent inhibition; MTT: Multi-Tasking Task; NS: No significant association; PAL: Paired Associates Learning; RVP: Rapid Visual Processing; SAI: Short Afferent Inhibition; SWM: Spatial Working Memory.

correlates with levels of Aβ and phosphorylated tau in the cerebrospinal fluid of patients newly diagnosed with AD [83]. Conversely, previous investigations of SAI (dys)function in physiological aging have yielded inconsistent results. Some studies suggest that SAI remains unaffected with age [61–63], while others report a significant age-dependent decline in SAI function in healthy populations [64–66]. This discrepancy may be a derivative of how this previous research has screened and accounted for cognitive status in otherwise asymptomatic older adults. For example, one study reporting significant SAI dysfunction in healthy older adults did not account for cognitive status in their analyses despite reporting that roughly one-third of the enrolled older individuals screened with MoCA scores $\leq$ 25 [64]. Thus, it has remained unclear whether SAI declines as a function of normative aging or if this neurophysiological indicator is sensitive to discerning pathological processes associated with ADRDs. By comprehensively screening and stratifying older adults by cognitive status, our study provides clarity by demonstrating that SAI is relatively preserved in cognitively intact older adults but significantly diminished in older adults with objective cognitive impairment.

Further, accepting SAI as a putative marker for cholinergic integrity, our findings are congruent with the well-established "cholinergic hypothesis" of cognitive dysfunction in aged populations. When first formalized by Bartus in the 1980s, he emphasized that the hypothesis "states nothing about etiological factors" but rather that it generally describes the impact of cholinergic dysfunction on cognitive impairment [36,84]. After receding in prominence over recent decades, other authors have recently noted a distinct 'comeback' of cholinergic hypotheses of cognitive dysfunction [85]. Facilitated by technological advancements that better characterize this neuromodulatory system in physiological and pathological aging, this resurgence has reaffirmed Bartus's original assertion that cholinergic dysfunction is etiologically agnostic [85]. Although the focus was historically concentrated on AD, growing evidence increasingly highlights the pivotal role of cholinergic deficits in non-AD dementias, reinforcing its broad appeal as a neurophysiological indicator of cognitive deterioration [86].

The AD-specific literature vividly illustrates the pivotal role of BFCS integrity in distinguishing physiological and pathological brain aging. These findings highlight that: 1) the BCFS is implicated early in the pathogenesis of AD [35,87–89], 2) BFCS deficits are present and correlate with the pathological burden in asymptomatic, preclinical stages of AD [35,87,90–92], 3) cholinergic deficits correspond with cognitive deterioration across the disease continuum [37,93–100], and 4) the integrity of the BFCS serves as a valuable prognostic indicator, predicting cognitive trajectories over time [89,93,101–106]. Beyond AD, multiple cross-sectional and longitudinal investigations have reported that degeneration of the BFCS precedes and predicts subsequent development of Lewy Body Dementia (LBD) [107–112]. One significant study of *de novo* PD patients reported that individuals with significant BFCS atrophy had a 3.5-fold greater risk of cognitive deterioration over a five-year period [109]. Other findings comparing patients with AD and various non-AD dementias reveal that while BFCS deficits are a prevalent feature of dementias, cognitive deficits manifest in a disease-specific manner [113–116].

This broad research base underscores the value of characterizing cholinergic function to distinguish between physiological and pathological brain aging, particularly in the nascent stages of the disease continuum. The longitudinal investigations referenced above include reports that BFCS atrophy in asymptomatic older adults can predict the onset of dementia years before the manifestation of clinically evident cognitive decline [104]. Critically, this reinforces that clinically meaningful cholinergic deficits are detectable in subclinical populations. While this is reflected by our findings, future longitudinal investigations are required to determine the prognostic potential of SAI to stratify risk for clinically evident cognitive deterioration. Additionally, while subtle insults to the cholinergic system can be expected as a natural consequence of physiological aging, these deficits are exacerbated in pathological conditions to produce behavioral deficits [94,97,117]. Though it should be interpreted with caution in the absence of biomarkers, this is also congruent with our findings as we report a non-significant trend for diminished SAI as a function of age, but a statistically

significant disruption is only observed when older adults are stratified by cognitive status.

Beyond group-level differences in SAI, we examined the CANTAB data for behavioral correlates of SAI and LAI. This exploratory analysis revealed that SAI was significantly correlated with cognitive performance (Table 3). The behavioral measure exhibiting the strongest relationship with SAI was response latency on the rapid visual processing task, a complex attentional task that also taxes aspects of working memory. Separate pharmacological work in young, healthy adults indicates that performance on this particular cognitive task is highly sensitive to pharmacological manipulation of the central cholinergic system [118]. This novel finding also converges with parallel lines of research in ADRD patient populations, as attentional deficits have been identified as cognitive correlates of central cholinergic dysfunction [37,38,96,119]. Relatedly, congruent with this finding, pharmacological studies of patients with central cholinergic deficits indicate that acetylcholinesterase inhibitors are more effective for preserving attentional ability than memory [120].

While our study provides valuable insights into SAI in the context of cognitive aging, it is important to discuss potential limitations, which offer refinements for future research methodology and prompt caution in interpreting results. First and foremost, this preliminary study lacked the resources necessary to integrate plasma biomarkers, making it impossible to directly link SAI findings with disease-specific pathology. Relatedly, we did not employ standard clinical measures and procedures to diagnose participants' cognitive status. Rather, this study employed the Jak/Bondi actuarial neuropsychological classification method that is well-validated in MCI research [72–77]. While this method has been demonstrated to outperform traditional clinical criteria for identifying MCI [72], it does not involve a clinical neurological diagnosis. Consequently, to avoid potential misattribution to a clinical diagnosis of MCI, we have used the term 'Old-CI' throughout our manuscript. Nonetheless, while the cognitive classifications in this study cannot be upheld as meeting a rigorous clinical evaluation standard, we believe that the findings hold merit and relevance for cognitive aging research. Future research in this area would benefit from incorporating clinical evaluations and plasma biomarkers, thereby refining the understanding of this neurophysiological marker in the context of age-related cognitive impairment.

Relatedly, the absence of detailed clinical evaluations may have resulted in the inclusion of participants with subclinical disorders whose conditions have not yet manifested clinically. This inclusion could potentially affect the interpretability of our findings, as the neurophysiological measures assessed might reflect undiagnosed conditions that were not identified with a clinical evaluation. Additionally, as is common in this field of research, we also acknowledge the potential for group biases [121]. While volunteer-based recruitment can yield valuable insights into cognitive impairments in a community-based setting, we acknowledge it limits the generalizability of our findings, particularly in terms of their applicability to clinical populations seen in memory clinics. Another common bias of volunteer groups is that they often over-index for backgrounds with higher educational attainment and socioeconomic status [121], which is reflected in our sample. Future studies would benefit from incorporating a more diverse array of recruitment methods, including outreach to clinical settings, to ensure a broader representation and enhance the external validity of the research findings. This dovetails with the need for increased racial and ethnic diversity in study enrollment, which was lacking in the current dataset.

Additionally, while we include discussions about the potential prognostic utility of SAI, we acknowledge that this interpretation of our findings is limited due to the cross-sectional design of this preliminary study. In order to characterize the prognostic value of M1-TMS measures for stratifying the risk of cognitive deterioration, future studies will require longitudinal follow-up. The variance in the SAI effect within our Old-CI group further underscores this point, as there are two discrete clusters of the SAI effect in this population (Fig. 1A). Could SAI responder/non-responder status be a leading indicator of subsequent cognitive decline? Despite this limitation, the current cross-sectional findings did provide data from healthy young adults, which enabled the observation that SAI is relatively preserved in cognitively intact older adults. We also acknowledge that our small sample size is a limiting factor for this preliminary study. This limitation, however, is mitigated by an *a priori* power analysis indicating that this study is sufficiently powered to detect group differences in SAI. Lastly, future studies could incorporate EEG-based measures that inform the latency of evoked potentials from median nerve stimulation to more precisely time the ISI for SAI acquisitions to each participant's unique latency [44]. As a potential limitation, we did not acquire this EEG-based measure and instead sampled SAI at two time points (20 ms and 25 ms) within the range of ISIs shown to reliably produce SAI effects in aggregate [122].

Beyond these addressable limitations, some innate constraints on M1-TMS data should be acknowledged. The SAI measure described above does not directly assess central cholinergic integrity in the brain, and it should be viewed as an indirect proxy measure developed and elucidated through multimodal research in preceding decades. Nevertheless, M1-TMS measures can provide important insight into neurophysiological features of cognitive aging, and they do so non-invasively and at low-cost [40].

Conclusion

With increasing recognition that dementias are preceded by a prolonged preclinical phase of pathological brain aging, marked by considerable heterogeneity in clinical progression, there is an imperative to characterize neurophysiological indicators that can effectively stratify the risk of cognitive deterioration. The BCFS, due to its selective vulnerability to early pathological alterations and well-established clinicopathological coherence, emerges as a promising target for such investigations. Compared to other methodologies, M1-TMS provides an affordable, cost-effective, and widely accessible tool to characterize the functional integrity of this pivotal neuromodulatory system through SAI. In this study, we evaluated SAI in healthy young adults and older adults who, though absent clinical diagnoses, were algorithmically classified as cognitively normal or cognitively impaired according to the Jak/Bondi actuarial criteria. With this approach, we report that significant deviations in SAI are only observed in the cohort of cognitively impaired older adults. Further, central to the functionality of the cholinergic system, our exploratory analysis revealed that attentional deficits were the strongest behavioral correlate of SAI dysfunction. These preliminary findings highlight the potential of SAI as a

neurophysiological indicator capable of detecting early pathological brain aging, underscoring the need for further investigation.

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Consent Statement

Informed written consent was obtained from all participants prior to research activities.

Funding

This work was supported by the Department of Defense NDSEG Fellowship (M.S), and the National Institutes of Health R01 [grant number AG062543] (PI: Y.-H. C.) and R21 [grant number AG077153] (PI: Y.-H. C.).

CRediT authorship contribution statement

Mark H. Sundman: Writing – review & editing, Writing – original draft, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Jacob M. Green:** Writing – review & editing, Writing – original draft, Data curation. **Andrew J. Fuglevand:** Writing – review & editing, Writing – original draft, Resources, Conceptualization. **Ying-hui Chou:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank Dr. Koeun Lim for her efforts in the equipment upgrades that enabled this project, as well as Jonny Baham, Tessa Spangler, and Bernie De Vault for their assistance with participant recruitment and data collection.

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