Associations between a neurophysiological marker of central cholinergic activity and cognitive functions in young and older adults

Marielle Young-Bernier1,2, Yael Kamil1, François Tremblay1,2,3 and Patrick S R Davidson1,2,4*

Abstract

Background: The deterioration of the central cholinergic system in aging is hypothesized to underlie declines in several cognitive domains, including memory and executive functions. However, there is surprisingly little direct evidence regarding acetylcholine’s specific role(s) in normal human cognitive aging.

Methods: We used short-latency afferent inhibition (SAI) with transcranial magnetic stimulation (TMS) as a putative marker of cholinergic activity in vivo in young (n = 24) and older adults (n = 31).

Results: We found a significant age difference in SAI, concordant with other evidence of cholinergic decline in normal aging. We also found clear age differences on several of the memory and one of the executive function measures. Individual differences in SAI levels predicted memory but not executive functions.

Conclusion: Individual differences in SAI levels were better predictors of memory than executive functions. We discuss cases in which the relations between SAI and cognition might be even stronger, and refer to other age-related biological changes that may interact with cholinergic activity in cognitive aging.

Keywords: Acetylcholine, Aging, Cortical inhibition, Executive function, Memory, Transcranial magnetic stimulation

* Correspondence: patrick.davidson@uottawa.ca
1 School of Psychology, University of Ottawa, 136 Jean Jacques Lussier Private, Ottawa, Ontario K1N 6N5, Canada
2 Élisabeth Bruyère Research Institute, University of Ottawa, Ottawa, Ontario, Canada
Full list of author information is available at the end of the article

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on the role of the cholinergic system in cognition. However, the extent to which age-related changes in cholinergic neuromodulation contribute to cognitive decline in normal human aging remains unclear. There are at least three reasons for this: First, making inferences from animal and computational models to humans has sometimes proven surprisingly difficult (e.g., [17,18]). Second, much of what we infer about the role of ACh in cognitive aging comes from studies in which Alzheimer’s patients are treated with cholinesterase inhibitors, including donepezil, galantamine, and rivastigmine (e.g., [19]). Unfortunately, these patients can be difficult to test and experience other confounding factors including significant structural and functional brain changes. Third, manipulation of ACh via agonist and antagonist drugs (e.g., scopolamine) has produced a vast amount of data, but strictly speaking this line of research tells us more about acute effects than it does about the long term decline in cholinergic activity seen in normal aging. There is thus a need to further examine the in vivo contribution of age-related alterations in central cholinergic function to declines in human cognition.

Recent advances in the field of non invasive brain stimulation have yielded new opportunities to examine the neurophysiological correlates of aging using markers of cortical excitability that can be linked with relative confidence to specific neurotransmitter systems [20]. One such marker involves pairing afferent nerve stimulation with transcranial magnetic stimulation (TMS) of the motor cortex to modulate motor responses evoked in contralateral hand muscles [21]. When applied at short intervals (e.g., 18–20 milliseconds [ms]) before TMS pulses, afferent nerve stimulation typically leads to a period of inhibition of the motor evoked potentials (MEPs). This short-interval afferent activation (SAI) is mediated at the cortical level through cholinergic-dependent GABA_A receptor activation [22]. The implication of cholinergic action in mediating SAI is supported by in vivo observations of its reduction or even abolition by administration of a selective muscarinic cholinergic receptor blocker (scopolamine) in healthy participants [23]. Further, SAI is lower than expected in Alzheimer’s patients but restored by cholinesterase inhibitors [22]. SAI is also reduced in other disorders characterized by cholinergic dysfunction, including Lewy body dementia [24], multiple sclerosis [25], and Wernicke–Korsakoff syndrome [26], but it is normal in frontotemporal dementia, a non-cholinergically mediated form of dementia [27]. Together, these observations provide strong evidence that SAI is a cholinergic-dependent marker of motor intra-cortical excitability.

Given the clear decline in cholinergic modulation with age [28,29], one would predict that SAI would be altered in healthy older adults. Yet, very few studies have examined this issue. Oliviero et al. [30] compared SAI levels in healthy young and older adults and found no age differences. More recently, Degardin et al. [31] performed a similar study and reached a similar conclusion. However, as we and others [32] have argued previously, the use of varying test intensities to obtain a constant MEP size across participants might have contributed to masking any age effects in the two studies above. In line with this, we recently found a large and selective decrease in SAI in healthy seniors when we used a constant TMS test intensity approach [33]. Further, we found that age-related variations in SAI explained a substantial proportion of the variance in timed motor tasks assessing processing speed.

This study constitutes an extension of our previous findings; data were derived from the same sample of participants as already described [33]. In the present study, we examined possible relationships between SAI, as a putative marker of cholinergic-dependent cortical inhibition, and cognition in young and older healthy adults. Because mean differences between young and older adult groups are often small, especially relative to the extensive variability that can be seen among healthy older adults (e.g., some perform much more poorly than young people, whereas others are indistinguishable from the young [34]), we capitalized on the individual-differences approach used by Glisky and colleagues [35,36]. This approach allows the characterization of each participant’s long-term memory and executive functions using neuropsychological testing to construct aggregate scores reflecting performance across several tasks in each domain (for details, see Method). We hypothesized that age-related differences in SAI levels would be associated with age-related differences in memory and executive functions. For memory, several investigators have emphasized ACh’s putative role in binding information in memory [15], which we assessed using a canonical measure of paired associate learning (Verbal Paired Associates from the Wechsler Memory Scale-III; WMS-III [37]). We also examined face recognition from the WMS-III because recent studies have also described cholinergic modulation of face-memory-related activity in the fusiform gyrus [38]. Given the emphasis in the recent literature on the crucial role of ACh in modulating executive functions [19,39,40], we also expected correlations between SAI and our aggregate executive function measure.

**Method**

**Participants**

The present data were derived from the same group of participants previously described [33], with minor differences in the current sample (i.e. one young adult was excluded from the present study because of incomplete cognitive data). We analyzed data from 24 young adults (age range = 18 to 30 years; M = 22.67, SD = 3.49; 13 females) and 31 community-dwelling older adults (age range = 65 to 82 years; M = 70.29,
The two age groups were similar in education (young: $M = 16.08$ years, $SD = 1.89$; older adults: $M = 16.19$, $SD = 2.83$). All participants were fluent English and/or French speakers with normal or corrected-to-normal vision (one participant was blind in one eye, but had no difficulty with the visual tasks) and hearing, and were screened for depression (two participants were taking anti-depressants but their depression screening scores, TMS, and cognitive data were normal), dementia, psychiatric or neurological disorders, drug or alcohol abuse, and counter-indications to TMS. Participants’ medications were not altered for testing, with many older adults taking drugs related to vascular health (e.g., hypertension, statins cholesterol lowering drugs). None of the participants was taking neuroactive drugs such as neuroleptics, however one young adult and one older adult were taking antidepressants (as mentioned above, their TMS data were normal). Vascular risk factors were assessed for each participant and consisted of a cumulative score of 6 factors: body mass index with obesity defined as being greater than 30 kg/m$^2$, current smoking status, lack of physical activity, type-2 diabetes, history of hypertension, and history of cardiac symptoms [41,42]. Vascular risk factors for participants ranged from 0 to 3 ($M = 0.44$) with the maximum possible score being 6, suggesting generally good vascular health. All participants also completed the Montreal Cognitive Assessment (MoCA; [43]). Although some older adults (5/31) scored slightly below the recommended cutoff (i.e., >26), they were deemed eligible for the study based on the interview and their good performance on the other tasks, and on recent evidence that this cut-off may be too high [44]. The results of five additional participants were discarded because they did not meet inclusion criteria and thirteen more (including 6 older adults) because of incomplete testing (10 could not be reached for a second testing session resulting in missing TMS-SAI data and 3 decided to stop before completion). The Research Ethics Boards of the University of Ottawa and Bruyère Continuing Care approved the study procedure (two composite factors with two subfactors each). The second factor score, reflecting executive function, is made up of the number of categories achieved on the computerized Wisconsin Card Sorting Test [49], the total number of words produced to the cues $F$, $A$, and $S$ on a phonemic fluency test [50], and the Backward Digit Span and Mental Control measures from the WMS-III. In previous studies involving only older adults, the executive function factor had also included Mental Arithmetic from the Wechsler Adult Intelligence Scale—Revised (WAIS-R; [51]), but [35] reported that this measure did not load significantly on the executive function factor.

**Analysis of MEP data**

Mean individual values for conditioned and unconditioned MEP responses were measured off-line by averaging the amplitude (peak-to-peak) and latency of each trial. SAI level was determined in each participant in terms of percent of unconditioned MEP responses (i.e.%) $\frac{\text{MEP}_{\text{Conditioned}} - \text{MEP}_{\text{Unconditioned}}}{\text{MEP}_{\text{Unconditioned}}}$.

**Memory and executive functions**

Participants underwent neuropsychological testing in a quiet, well-lit room, in their language of choice. We created two composite $z$ scores for each individual, based on previous factor analyses [35,36]. The first factor score reflects long-term memory and is composed of five scores: the Logical Memory I, Faces recognition I, and Verbal Paired Associates I subscores of the WMS-III, Visual Paired Associates II from the Wechsler Memory Scale—Revised (WMS-R; [47]), and Long Delay Cued Recall from the California Verbal Learning Test—II (CVLT-II; [48]). The second factor score, reflecting executive function, is made up of the number of categories achieved on the computerized Wisconsin Card Sorting Test [49], the total number of words produced to the cues $F$, $A$, and $S$ on a phonemic fluency test [50], and the Backward Digit Span and Mental Control measures from the WMS-III. In previous studies involving only older adults, the executive function factor had also included Mental Arithmetic from the Wechsler Adult Intelligence Scale—Revised (WAIS-R; [51]), but [35] reported that this measure did not load significantly on the executive function factor.
executive function factor in their young adults. Therefore, we omitted this measure from the executive function z score in both groups to allow for direct age group comparisons.

Statistical methods
Independent t-tests, with adjusted p values for multiple comparisons (i.e. \( p = 0.0125 \)), were used to examine age group differences on baseline measures of excitability. Mixed analysis of variance (ANOVA) and independent t-tests were used to examine differences between age groups. We adjusted \( p \) values to correct for multiple comparisons in the between-group t-tests on the cognitive tasks (\( p = 0.05/8 \), that is, \( p = 0.00625 \)). We used Pearson’s correlations to examine associations among SAI levels and memory and executive function scores. All statistical tests were performed using the PASW software version 18.0 for Windows (GraphPad Software, San Diego California USA) or GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com).

Results
TMS and SAI
The TMS procedure was well tolerated and no participants experienced adverse effects. A thorough analysis of the physiological data has been reported previously [33] (see Table 1 for baseline TMS measurements). Briefly, young adults generally exhibited marked MEP suppression in response to afferent conditioning leading to high levels of SAI (18.13 ± 15.74). In contrast, seniors exhibited more variable afferent-induced inhibition with a substantial proportion of subjects (14/31) showing either low or absent inhibition (MEPcond ≥ 50% suppression). Accordingly, SAI levels estimated in seniors (51.36 ± 34.62) were significantly lower than in young adults (\( p < 0.001 \)).

Age differences in cognition
The young adults performed significantly better on several of the memory and executive function tasks than the older adults did (ANOVA: main effect of Age: \( F_{1,51} = 6.86, p = 0.01 \), significant Age X Task interaction: \( F_{7, 357} = 3.22, p = 0.003 \)). At the adjusted \( p \) value, post-hoc t tests showed that the young significantly outperformed the older adults on memory for Verbal Paired Associates I (\( t_{53} = 4.03, p = 0.0002 \)) and Faces I (\( t_{53} = 3.89, p = 0.0003 \)), and number of categories on the Wisconsin Card Sorting Test (\( t_{52} = 4.10, p = 0.0001 \)). Although the two age groups could not be compared on the Visual Paired Associates II measure using parametric methods because of ceiling effects in the young adults (that is, all the young adults scored 6 out of 6, whereas the older adults ranged from 4 to 6), a Chi-Squared analysis suggested a significant advantage for the young adults (\( \chi^2 = 9.82, p = 0.007 \)). The factor scores, by definition, reflected the individual test scores: The young had significantly higher scores than the older adults on the memory factor z score (\( t_{53} = 4.53, p < 0.0001 \)), but the groups were not significantly different from one another on the executive function factor z score (\( t_{53} = 1.65, p = 0.11 \)). The mean levels of performance on the individual cognitive tasks and the factor scores are shown in Table 2.

Correlations between SAI and cognition
When we performed an analysis across all individuals [52,53]; but see [54,55], SAI significantly predicted the memory factor score (\( r = -0.31, p = 0.02 \)), whereas it did not predict the executive function z score (\( r = -0.09, p = 0.51 \); see Figure 1). The correlation between SAI and memory was modest in size (\( r^2 = 10\% \)), and when we performed an analysis across all individuals [52,53]; but see [54,55], SAI significantly predicted the memory factor score (\( r = -0.31, p = 0.02 \)), whereas it did not predict the executive function z score (\( r = -0.09, p = 0.51 \); see Figure 1). The correlation between SAI and memory was modest in size (\( r^2 = 10\% \)), and when

Table 1 Hand dominance and baseline measures of excitability in the two age groups (mean ± SD)

|                      | Young (n = 24) | Senior (n = 31) |
|----------------------|---------------|-----------------|
| Hand Dominance (L/R) | 2/22          | 1/30            |
| Resting MT (% output) | 66.00 ± 11.55 | 72.55 ± 12.71   |
| Test MT (% output)   | 79.17 ± 13.82 | 86.97 ± 15.15   |
| Resting MEP amplitude (μV) | 926.61 ± 774.34 | 427.22 ± 540.59* |
| Resting MEP latency (ms) | 22.27 ± 1.88  | 24.03 ± 1.87*   |
| Intensity MNS1       | 64.17 ± 1.80  | 72.87 ± 1.72    |

Key: MEP, motor evoked potential; MNS, median nerve stimulation; MT, motor threshold.
1 Conditioning intensity for median nerve stimulation (MNS).
*Significant difference at adjusted p-values (\( p = 0.0125 \)) for multiple comparisons (see [33] for a more elaborate analysis of these age differences).

Table 2 Cognitive performance in the two age groups (mean ± SD)

|                      | Young Adults (n = 24) | Older Adults (n = 31) |
|----------------------|----------------------|----------------------|
| Logical Memory I     | 30.46 ± 4.04         | 29.00 ± 6.77         |
| Visual Paired Associates II | 6.00 ± 0.00     | 5.50 ± 0.77 ***     |
| Verbal Paired Associates I | 26.63 ± 5.59      | 19.00 ± 7.84 ***    |
| Faces I              | 38.71 ± 4.31         | 34.67 ± 3.34 ***    |
| CVLT-II Long-Delay Cued Recall | 13.67 ± 1.81  | 12.39 ± 2.70        |
| Verbal Fluency (FAS) Test | 40.25 ± 9.81   | 41.00 ± 12.20       |
| Backward Digit Span  | 7.67 ± 2.67          | 7.42 ± 2.80          |
| Wisconsin Card Sorting Test | 4.25 ± 0.85   | 2.83 ± 1.51 ***     |
| Mental Control       | 27.13 ± 4.74         | 26.39 ± 4.10         |
| Memory factor (z score) | 0.39 ± 0.39      | -0.31 ± 0.68 ***    |
| Executive function factor (z score) | 0.16 ± 0.50   | -0.12 ± 0.71        |

1 California Verbal Learning Test-II.
Significant difference at adjusted p-values (\( p = 0.006 \)) for multiple comparisons *** \( p < 0.001 \).
examined the correlation separately within each age group it failed to obtain significance. Although in the young group alone a significant correlation between SAI levels and the executive function $z$ score emerged in our initial analysis ($r = -0.56$, $p = 0.004$), visual inspection suggested that this was driven by two data points; indeed, if we deleted these two cases the correlation was rendered non-significant.

Based on the hypotheses outlined at the end of the introduction, we also examined associations between SAI and specific individual subtest scores. First, we found a significant correlation between SAI and Verbal Paired Associates I ($r = -0.35$, $p = 0.008$), a canonical measure of memory binding, although this correlation became non-significant when we examined each age group on its own ($r \leq |0.21|$). Note that although Visual Paired Associates II is also a canonical measure of this ability, it was not explored further because of the ceiling-level scores in data, especially for the young adults. Second, we found a significant correlation between SAI and memory for faces (Faces I; $r = -0.31$, $p = 0.02$), although, again, it disappeared when analyses were performed separately within each age group ($r \leq |0.17|$).

We also performed all analyses while excluding the five older adults who had MoCA scores lower than the recommended cutoff. This did not yield any changes in the results.

**Discussion**

Deficits in central cholinergic activity are thought to underlie age-related cognitive decline, but evidence regarding the specific role(s) of ACh in human cognitive aging is still scarce. We investigated the relation of SAI, a putative neurophysiological marker of cholinergic activity, to memory and executive functions in aging.

**Age differences in SAI**

Consistent with reports of impaired cortical inhibition with age [56], as a group, our senior participants exhibited reduced intra-cortical inhibition, as reflected in the overall decrease in afferent-induced inhibition. The fact that SAI has been linked with cholinergic activity in the motor cortex in pharmacological and patient studies (e.g., [22,23,57]; but see below) provides further converging in vivo evidence of a decline in central cholinergic function in normal human aging (e.g., [58] for reviews, see [28,59]).

**Associations between SAI and cognition**

The young adults outperformed their older counterparts on several measures of memory, consistent with numerous previous reports [1-4]. Although memory was clearly impaired in the older adults, executive function was not. This finding is concordant with a similar study to ours [35], which noted that others too have found this pattern. For example, Lamar and Resnick [60] reported no age differences in verbal fluency, mental control, and digit span, which were included in the present executive function factor score.

SAI predicted individual performance in memory, although, contrary to expectations, it did not predict executive functioning. These results are consistent with some studies [61], but not with others [19,39,40] and may stem from the poor vascular health of the patients included in those studies. (This issue will be discussed further below.)

The association between SAI and memory is also consistent with Duzel et al. [52], who recently reported that a magnetic resonance imaging estimate of the structural integrity of the basal forebrain (the major source of cholinergic input into the cortex and hippocampus) predicted verbal memory in a mixed sample of young and older adults.

**Figure 1** Scatter plots showing the associations between SAI levels and composite $z$ scores of (A) memory and (B) executive functions. SAI levels correspond to the modulation of motor evoked potentials (MEP) induced by afferent conditioning at an inter-stimulus interval (ISI) of 20 ms (% Conditioned MEP/Unconditioned MEP).
In the present study, SAI levels explained approximately 10% of the variance in memory. Although this is comparable in size to the explanatory power of Duzel et al.’s [52] measure of basal forebrain integrity, we suspect that the relation between SAI and cognition might be even stronger under different circumstances. First, pharmacological studies indicate that ACh must decline past a certain threshold before changes in cognition are detectable [62-66]. Although we studied a representative group of older adults, only a small number of them exhibited relatively low SAI levels. Given that cholinergic function declines with age, one future possibility would be to recruit older seniors (i.e., over 80 years of age) with the expectation that stronger correlations with cognition would emerge. Also, one important putative cause of cholinergic decline in aging is microvascular damage to the ascending cholinergic pathways from the midbrain to the cortex [67,68]. Our older participants were in relatively good vascular health. Were we to focus on recruiting people in poorer vascular health, we might find stronger correlations between cholinergic function and cognition [39,40].

Second, it is possible that cholinergic modulation supports only relatively specific aspects of memory and executive functions and that these processes were not optimally assayed or taxed by the current neuropsychological battery. A general assertion is that for ACh to be significantly implicated in cognitive tasks, these tasks must be difficult and require effortful attention [11,59]. The tasks in the current study all fit this description. However, based on techniques that can target specifically the cholinergic system in animals (e.g., the immunotoxin 192 IgG-saporin), it has recently been argued that ACh is particularly important for certain memory functions, including encoding more so than retrieval, and remembering relational and contextual information in particular [15,69]. Consistent with the strong involvement of ACh in attention, studies have also suggested that the cholinergic system is more important for strategic and effortful processing of information to be remembered rather than when it is automatic [70]. Regarding executive functions, cholinergic activity may be especially important for task-switching, handling competition among possible responses, and suppressing unwanted responses [11]. Although we did measure several of these putative processes (e.g., memory binding with the visual and verbal paired associates subtests; switching and suppression with the Wisconsin Card Sorting Test), we are currently developing a new battery to probe some of these memory and executive sub-processes more specifically. Combined with our previous observation of an association between SAI and complex motor tasks (i.e. Grooved Pegboard Test, complex reaction times, go/no-go) but not with simple reaction times in aging [33], this study suggests that SAI may be a better predictor of memory than executive functions, but an even stronger indicator of motor performance and information processing speed.

Third, recent microdialysis studies have described phasic cholinergic release during attention-related tasks in rats [71,72]. These studies suggest that indices of relatively tonic ACh levels (including SAI, positron emission tomography, and magnetic resonance spectroscopy) in the brain will need to be supplemented with methods that have higher temporal resolution when they become available in humans. Finally, like most studies, this one was cross-sectional. Complementary longitudinal studies of within-subject changes must be completed to yield a more complete understanding of the relationship between the onset and course of cholinergic dysfunction and cognitive decline in normal and pathological aging (e.g., [73] cf. [74,75]).

Strong evidence that SAI is a reliable marker of cholinergic function comes from pharmacological and patient studies [22,23,57], but gamma-aminobutyric acid (GABA), dopamine, and serotonin may also contribute to the signal (e.g., [76,77]). For example, as we have noted previously [33], our older adults showed greater inter-individual variability in SAI than did our young adults, with approximately half the seniors exhibiting either poor or absent intra-cortical inhibition. These older adults were indistinguishable from the other seniors in terms of age and vascular health, and there was no evidence that these individuals were in a preclinical stage of dementia. One possibility, however, is that these individual differences in intra-cortical inhibition are related to variability in changes in motor cortex GABA\textsubscript{A} receptors in aging [78,79]. Future pharmacological and neuroimaging work must verify that SAI is strongly, although perhaps not exclusively, reflective of activity in the cholinergic system.

**Conclusion**

We found that individual differences in episodic memory could be explained in part by SAI, a putative marker of central cholinergic functioning. However, cholinergic decline is only one of many brain changes that occur in aging [80-82]. The goal of future research on the biological bases of cognitive aging should be to combine multiple methods to increase explanatory power, for example by combining multiple neuroimaging methods (e.g., [83,84]) with genetic information (e.g., [52,85]). The short afferent inhibition marker of cholinergic integrity reported in this study is a minimally-invasive, relatively inexpensive, significant predictor of cognition. Combining it with neuroimaging, genetic, and other cognitive neuroscience methods should prove useful in future studies.
Endnote

*Three older adults each did not complete one cognitive measure (Faces I, Wisconsin Card Sorting Test and Visual Paired Associates II); their factor z scores were calculated by computing the mean of the remaining tests.

Abbreviations

AcCh: Acetylcholine; GABA: Gamma-aminobutyric acid; CBT-II: California Verbal Learning Test - II; ISI: Inter-stimulus interval; MEP: Motor evoked potentials; MoCA: Montreal Cognitive Assessment; RMT: Resting motor threshold; SAI: Short-latency afferent inhibition; TMS: Transcranial magnetic stimulation; WAIS-R: Wechsler Adult Intelligence Scale – Revised; WMS-III: Wechsler Memory Scale – III; WMS-R: Wechsler Memory Scale – Revised.

Competing interests
We declare no actual or potential conflicts of interest.

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Author details

1School of Psychology, University of Ottawa, 136 Jean Jacques Lussier Private, Ottawa, Ontario K1N 6N5, Canada. 2Élisabeth Bruyère Research Institute, University of Ottawa, Ottawa, Ontario, Canada. 3School of Rehabilitation Sciences, University of Ottawa, Ottawa, Ontario, Canada. 4Heart and Stroke Foundation Centre for Stroke Recovery, University of Ottawa, Ottawa, Ontario, Canada.

Authors’ contributions
MYB participated in the design of the study, carried out the cognitive and behavioural testing, performed the statistical analyses, and drafted the manuscript. YK participated in the cognitive testing. FT conceived of the study, participated in its design, and helped with the behavioural testing. PD conceived of the study, participated in its design, helped with the statistical analyses and drafted the manuscript. All authors read and approved the final manuscript.

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