Age Differences in Reaction Times and a Neurophysiological Marker of Cholinergic Activity*

Marielle Young-Bernier,[1,2] Annick N. Tanguay,[1,2] François Tremblay,[1,2,3,4] and Patrick S. R. Davidson[1,2,4]

RÉSUMÉ

La détérioration du système cholinergique lors du vieillissement normal semble contribuer au déclin de l'attention avec l'âge. Nous avons examiné l'effet potentiel de l'âge sur la performance au « Attention Network Test » (ANT) ainsi que sur la variabilité intra-individuelle dans la vitesse des réponses à une tâche go/no-go et à une tâche de temps de réaction (TR) à choix multiples chez un groupe de jeunes adultes et de personnes âgées en santé. Nous avons ensuite examiné si un marqueur neurophysiologique de l'activité cholinergique dérivé de la stimulation magnétique transcrânienne (i.e., inhibition afférente à courte latence; IACL) était associé à la performance. Les personnes âgées montraient un ralentissement au ANT ainsi qu'une plus grande variabilité intra-individuelle que les jeunes adultes à la tâche de TR à choix multiples, mais il n'y avait pas de différence liée à l'âge dans les scores reflétant les réseaux attentionnels du ANT (vigilance, orientation aux stimuli et contrôle exécutif). Les niveaux de IACL étaient diminués chez les personnes âgées, mais ils n'étaient pas associés à la performance. Il est possible que des relations entre le marqueur de l'activité cholinergique et l'attention émergent seulement en cas de déficits de neurotransmission sévères. D'autres mécanismes corticaux pourraient aussi être plus fortement associés aux fonctions liées à l'attention.

ABSTRACT

The deterioration of the cholinergic system in aging is hypothesized to contribute to age-related declines in attention. We investigated potential age differences in performance on the Attention Network Test (ANT) and intra-individual variability in speed (RT-IIV) on go/no-go and choice reaction time tasks in young and healthy older adults. We also asked whether short-latency afferent inhibition (SAI), a neurophysiological marker of central cholinergic activity obtained via transcranial magnetic stimulation, might be correlated with performance. Older adults were slower on the ANT and exhibited greater RT-IIV than young adults on the multiple choice RT task, but there were no age differences on the ANT network scores (alerting, orienting, and executive control). SAI was diminished in older adults, but it was not significantly correlated with performance. It may only be in cases of severe cholinergic dysfunction that relations with attention emerge. Other brain mechanisms may also be stronger predictors of functions relating to attention.

[1] School of Psychology, University of Ottawa

[2] Bruyère Research Institute, University of Ottawa

[3] School of Rehabilitation Sciences, University of Ottawa

[4] Heart and Stroke Foundation Canadian Partnership for Stroke Recovery, University of Ottawa

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La correspondance et les demandes de tirés-à-part doivent être adressées à: / Correspondence and requests for offprints should be sent to:
Marielle Young-Bernier, PhD
School of Psychology
University of Ottawa
136 Jean-Jacques Lussier
Ottawa, ON K1N 6N5
(myoun006@uottawa.ca)
or
Patrick Davidson, PhD
School of Psychology
University of Ottawa
136 Jean-Jacques Lussier
Ottawa, ON K1N 6N5
(patrick.davidson@uottawa.ca)

The cholinergic system supports many cognitive functions, including aspects of attention, likely at least in part through its role in facilitating the detection of relevant sensory cues while filtering out irrelevant information (i.e., increasing the signal-to-noise ratio; Furey, 2011; Hasselmo & Sarter, 2011; Sarter, Hasselmo, Bruno, & Givens, 2005). As such, the deterioration of the cholinergic system in aging (e.g., Dumas & Newhouse, 2011) is hypothesized to be associated with declines in attention.

The Attention Network Test ([ANT]; Fan, McCandliss, Sommer, Raz, & Posner, 2002) has been used widely to study three putative attention networks: The *alerting* network underlies the maintenance of an alert state, the *orienting* network involves the selection of sensory information to guide attention to particular stimuli, whereas the *executive control* network corresponds to the detection and resolution of conflicts. Though interactions between these networks have been described (e.g., Wang et al., 2014), they may rely on at least partially dissociable neuroanatomical networks and neurotransmitter systems (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Petersen & Posner, 2012). A highly cited study with rhesus monkeys using a task similar to the ANT suggested that the cholinergic system might be especially important for orienting (Davidson & Marrocco, 2000). However, evidence from human experiments only partially supports this suggestion, as the administration of cholinergic antagonists reduces brain activity in regions supporting the orienting and executive control networks but only disrupts performance on the latter (Thienel, Kellermann, et al., 2009; Thienel, Voss, et al., 2009). Additionally, administration of nicotine (a cholinergic agonist) to non-smokers appears not to affect alerting or executive control on the ANT, but may paradoxically have mild detrimental effects on orienting (Kleykamp, Jennings, Blank, & Eissenberg, 2005; Wignall & de Wit, 2011).

In contrast, effects of normal aging on the ANT have been found often in alerting, rarely in orienting, and inconsistently in executive control (Gamboz, Zamarian, & Cavallero, 2010; Jennings, Dagenbach, Engle, & Funke, 2007; Knight & Mather, 2013; Mahoney, Verghese, Goldin, Lipton, & Holtzer, 2010; Westlye, Grydeland, Walhovd, & Fjell, 2011; Zhou, Fan, Lee, Wang, & Wang, 2011). A similar (but more extreme) pattern of deficits on the ANT has been described in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD), a cholinergic form of dementia (Fernandez-Duque & Black, 2006; Martella et al., 2014; Van Dam et al., 2013). MCI patients with vascular damage, likely involving decreased cholinergic integrity, have also been reported to exhibit reduced orienting on the ANT (Fernandez et al., 2011).

Attentional control can also be examined through intra-individual variability in reaction times ([RT-IIV]; MacDonald, Li, & Backman, 2009). RT-IIV appears to increase in normal aging, and increases further still in MCI and AD (Duchek et al., 2009; Dykiert, Der, Starr, & Deary, 2012; Phillips, Rogers, Haworth, Bayer, & Tales, 2013). This increased variability has been ascribed in part to changes in neurotransmission at the cortical level, with dopamine having garnered the most interest (MacDonald et al., 2009). However, given the role of acetylcholine (ACh) in increasing the signal-to-noise ratio, the deterioration of the cholinergic system in aging has also been hypothesized to contribute to the greater variability seen in normal aging and may well underlie the additional declines seen in MCI and AD (MacDonald, Nyberg, & Backman, 2006).

The Present Study

Here, we examined performance on three attentional tasks in young and older adults. On the ANT, for the reasons we have outlined, we expected age differences in the alerting and possibly also the executive control network scores. On the two other RT tasks (a 4-choice

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RT and a go/no-go task), we predicted that older adults would display greater RT-IIV than their younger counterparts, especially on the former due to its greater difficulty (Dykiert et al., 2012).

We also examined the relationship between performance on the behavioral tests and a marker of central cholinergic activity derived from transcranial magnetic stimulation (TMS). When paired with afferent nerve stimulation at an interval of approximately 20 ms (Tokimura et al., 2000), TMS of the motor cortex leads to the inhibition of the motor evoked potential (MEP) which is referred to as *short-latency afferent inhibition* (SAI). The level of afferent inhibition, as reflected in the modulation of MEP amplitudes, is dependent on cholinergic modulation of intra-cortical excitability in the motor cortex through the activation of $GABA_A$ receptors (Di Lazzaro et al., 2002). We have previously demonstrated that SAI is significantly reduced in normal aging when MEPs are evoked using a constant intensity approach (Young-Bernier, Davidson, & Tremblay, 2012). In addition, we found that age-related variations in SAI level were more strongly associated with differences in memory and motor speed (i.e., RTs) than with executive functions (Young-Bernier, Davidson, et al., 2012; Young-Bernier, Kamil, Tremblay, & Davidson, 2012). However, few studies have examined the relationship between SAI and attentional processes in normal aging. As we have outlined, the literature is discordant as to the specific role(s) of the cholinergic system in alerting, orienting, and executive control. We asked whether central cholinergic activity, as indexed by SAI, would be associated with any of the three attention networks from the ANT (i.e., alerting, orienting, and executive control). Given ACh's possible role in modulating intra-individual variability in speeded performance (MacDonald et al., 2006), it seemed reasonable to predict that SAI would be associated with RT-IIV.

Methods

Thirty-three young (22.4± 3.2 years; 20 females) and 31 healthy older adults (70.2 ± 4.9 years; 18 females) were recruited for this study. The sample size was determined to allow detection of large-size effects ($1 - \beta \approx 0.80$) in age-group differences in both SAI (Young-Bernier, Davidson, et al., 2012) and behavioral performance on the ANT (e.g., Jennings et al., 2007; Zhou et al., 2011). Estimated power to detect large correlations ($\rho = 0.5$) between the behavioral and TMS data for $n = 31$ was 0.84. Prior to participation, subjects were screened for psychiatric or neurological disorders and contraindications to TMS. Older adults were also screened with the Montreal Cognitive Assessment ([MoCA]; Nasreddine et al., 2005). Although some seniors scored below the recommended cutoff of 26 points ($n = 10$, MoCA scores of 23–25), they were deemed eligible for the study based on the interview and published evidence that this cutoff may be too high (Rossetti, Lacritz, Cullum, & Weiner, 2011). Participants' medication schedules were not altered for testing, with many older adults taking drugs related to vascular health (i.e., drugs to lower hypertension and cholesterol). None of the participants were taking neuroactive drugs such as neuroleptics; however, one young and one older adult were taking antidepressants, but their TMS data were within normal limits. Results from five additional young adults and one older adult were discarded due to incomplete data. The Research Ethics Boards of the University of Ottawa and the Bruyère Research Institute approved the study procedure in accordance with the principles of the Declaration of Helsinki. Participants provided written consent and received a minimal honorarium for their participation.

ANT Testing

Participants completed the Attention Network Test (ANT; JAVA version) on a 17-inch color computer screen following the parameters described by Fan et al. (2002). Participants were instructed to quickly indicate the direction (right or left) of a target arrow on the screen. The target was either preceded by no cue or a central, double, or spatial cue (i.e., asterisk). On some trials, the target arrow was flanked between 4 arrows that were pointing in the same (congruent) or opposite (incongruent) direction. Each participant completed a practice session of 24 trials (with auditory feedback on performance) followed by 3 blocks of 96 trials (no feedback).

Median RTs on the valid trials were averaged across the 3 blocks to reduce the effect of outliers and inherent skew in RTs. Performance on the ANT was examined using both the median RTs for each cue and flanker condition and the attention network scores. With regard to these scores, we followed the methodology recently suggested by Wang et al. (2014) to compute "purer" attention network scores and diminish the possible influence of irrelevant cues or flankers and inter-network interactions when calculating network scores. This method also accounts for slowing with age by adjusting each score by the relevant baseline RT. The ANT networks scores (expressed in terms of percentage) were thus computed as follows using the median RTs:

$$\text{Alerting} = (RT_{\text{double-cue congruent}} - RT_{\text{no-cue congruent}}) / RT_{\text{no-cue congruent}}$$

$$\text{Orienting} = (RT_{\text{spatial-cue congruent}} - RT_{\text{center-cue congruent}}) / RT_{\text{center-cue congruent}}$$

$$\text{Executive control} = (RT_{\text{no-cue incongruent}} - RT_{\text{no-cue congruent}}) / RT_{\text{no-cue congruent}}$$

RT Testing

Participants also completed 20 trials each of a go/no-go and 4-choice RT task on a Multi-Operational Apparatus

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for Reaction Time (MOART) panel (Lafayette Instrument Life Sciences, http://www.lafayettelifesciences.com). For go/no-go, participants were asked to release a key with their dominant index finger in response to a go-cue (green light) but withhold responses to a no-go cue (red light). In the choice RT task, they were instructed to place four fingers (index and middle finger of both hands) over keys and to release the appropriate key in response to a go-cue that appeared on top of one finger. Performance was derived from the PsymSoft II software (Lafayette Instrument Life Sciences). For the go/no-go task, mean RTs and standard deviations were computed for each participant by averaging their performance on correct go-cue trials (mean number of correct go trials = 15 ± 2; accuracy for go and no-go trials = 97%). Similarly, only correct trials on the choice RT task (mean number of correct trials = 17.7 ± 1.6, accuracy = 89%) were used to compute the mean RT and standard deviation values for each participant. Coefficients of variation were also derived for each participant (CV = *SD*/mean RT) to examine IIV while adjusting for general slowing with age.

TMS and Short Afferent Inhibition (SAI)

The procedures we used for TMS and measurement of SAI are similar to the ones described in our previous report (Young-Bernier, Davidson, et al., 2012). In this study, magnetic stimulation was delivered with a Magstim 200 stimulator (Magstim, http://www.magstim.com/) connected to a focal coil (70-mm loop diameter). The coil was manually held in place by the same experimenter (FT) for all participants and MEPs were recorded in the first dorsal interrosseus muscle (FDI) using small auto-adhesive surface electrodes (Ag/AgCl, Kendall Medi-Trace 130). Electromyographic signals were amplified (AB-621G bioelectric amplifier; Nihon Kohden America, http://www.nkusa.com/Monitoring/), digitized at a rate of 2 kHz (BNC-2090 terminal block; National Instruments, www.ni.com) and further relayed to a laboratory computer running custom software to control acquisition. The resting motor threshold (RMT) was determined using the maximum likelihood strategy for estimating motor thresholds (Awiszus, 2003) with the Motor Threshold Assessment Tool 2.0 software (available at http://www. clinicalresearcher.org/software.htm). Test TMS intensity was fixed at 120 per cent RMT for both unconditioned and conditioned trials. Conditioning afferent stimulation was produced by applying 200 μs electrical pulses (S88 stimulator, Grass Technologies, www.grasstechnologies.com/products/research.htmlS) on the median nerve 20 ms before TMS at an intensity just above the motor threshold to evoke a minimal visible twitch of the thenar muscles (Di Lazzaro et al., 2000; Tokimura et al., 2000). Unconditioned MEP amplitude in the FDI was first determined for each participant by eliciting 15 MEPs at rest (120% RMT). Following the same procedure, 15 MEPs were elicited at the conditioned 20 ms interval. Mean individual values for conditioned and unconditioned MEP responses were measured offline by averaging the amplitude of each trial. SAI was expressed as per cent of unconditioned responses (i.e., $^{MEP}_{Conditioned}$ / $MEP_{Unconditioned}$ × 100).

Statistical Analysis

Mixed analysis of variance (ANOVA) and independent *t*-tests were used to examine age group differences in SAI levels and cognitive performance. Pearson's correlations were used to examine associations between SAI levels and performance on the ANT and RT tasks. Statistical significance was set at $p = .05$. Statistical analyses were performed with SPSS software (IBM, http://www-01.ibm.com/software/analytics/spss/) and we used G*Power for power analyses (Faul, Erdfelder, Lang, & Buchner, 2007). Figures were prepared using GraphPad Prism (GraphPad, http://www.graphpad.com/).

Results

Age Differences in Performance on the ANT

Mean performance on the ANT and RT tasks is shown in Table 1. Mean accuracy was very high on the ANT (98%). A mixed 2 (young vs. older adults) × 4 (cue type) × 3 (flanker type) ANOVA on median RTs from the ANT revealed main effects of group ($F_{1, 62} = 125.55$, $p < .001$), cue ($F_{3, 186} = 142.66$, $p < .001$), and flanker type ($F_{2, 124} = 662.56$, $p < .001$). There was a significant flanker by group interaction ($F_{2, 124} = 25.09$, $p < .001$) and cue by flanker interaction ($F_{6, 372} = 13.71$, $p < .001$; see next paragraph). The cue by group interaction ($F_{3, 186} = 1.82$, $p > .05$) and the three-way interaction between cue, flanker, and group ($F_{6, 372} = 1.27$, $p > .05$) were not significant. The group by flanker interaction was still significant when including only congruent and incongruent flankers ($F_{1, 62} = 7.05$, $p = .01$) and was explained by a slightly stronger effect of incongruent flankers for older adults ($F_{1,30} = 388.86$, $p < .001$; $\eta_P^2 = .928$) compared to young adults ($F_{1,32} = 280.73$, $p < .001$, $\eta_P^2 = .898$). Indeed, when compared to the neutral condition, both the young and older adults were slowed down by approximately 100 ms when congruent flankers were present (i.e., in the 500 ms range versus the 400 ms range for young adults and 700 ms with congruent flankers versus 600 ms in the neutral condition for older adults), but the older adults were more affected by the incongruent flankers (in the 900 ms range versus the 600 ms range in the neutral condition) than the young adults (in the 600 ms range with incongruent flankers versus 400 ms in the neutral condition).

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Table 1: Mean (standard deviation) short afferent inhibition (SAI) level (% MEPcond/MEPuncond) and performance (ms) on the Attention Network Test and the reaction time tasks in the two age groups

		Young Adults	Older Adults	Cohen's *d*
Short Afferent Inhibition (SAI)		20.43 (13.12)	74.83 (80.31)	0.95
Attention Network Test				
Flanker	*Cue*			
Congruent	No	556.39 (74.76)	787.10 (86.71)	2.85
	Center	531.06 (82.97)	762.71 (72.56)	2.97
	Double	523.64 (67.55)	751.35 (88.73)	2.89
	Spatial	496.03 (63.22)	711.32 (84.92)	2.88
Incongruent	No	673.30 (111.93)	926.65 (102.23)	2.36
	Center	669.03 (97.29)	927.84 (108.81)	2.51
	Double	659.70 (98.67)	918.87 (107.12)	2.52
	Spatial	603.24 (92.19)	851.39 (106.40)	2.49
Neutral	No	524.67 (63.40)	685.84 (81.43)	2.21
	Center	477.36 (66.98)	665.71 (77.88)	2.59
	Double	474.27 (68.66)	647.32 (79.97)	2.32
	Spatial	452.00 (62.97)	621.06 (78.65)	2.37
Network Effects (% relative to relevant baseline)				
Alerting		–5.73 (4.76)	–4.44 (5.53)	0.25
Orienting		–6.10 (5.62)	–6.78 (5.93)	0.12
Executive Control		20.89 (8.95)	17.85 (5.74)	0.40
Reaction Times Tasks				
Choice	Mean	420.21 (55.19)	582.11 (127.38)	1.65
	Standard deviation	92.87 (44.08)	181.25 (87.79)	1.27
	Coefficient of variation	0.22 (0.09)	0.30 (0.10)	0.84
Go/No-go	Mean	381.02 (88.58)	461.85 (65.95)	1.04
	Standard deviation	76.52 (35.26)	92.20 (33.31)	0.46
	Coefficient of variation	0.20 (0.08)	0.20 (0.06)	0.00

Main effects of cue and flanker and cue by flanker interactions were still present when both age groups were examined individually ($p < .001$).

To further explore the cue by flanker interaction, we performed two 2 × 2 ANOVAs to examine the influence of alerting (no cue versus double cue) and orienting (center versus spatial cue) on the flankers (congruent versus incongruent flanker). Both ANOVAs showed main effects of cue type ($F_{1, 63} > 29.48$, $p < .01$) and flanker type ($F_{1, 63} > 455.58$, $p < .01$). Not surprisingly, RTs were faster with the double cues and spatial cues than when no cues were provided, while performance was slower with incongruent than congruent flankers. More specifically, the greatest benefit from the alerting cue was present when flankers were congruent and conflict resolution was therefore not required, than with incongruent flankers. In contrast, the spatial cue was of greatest benefit when the flankers were incongruent than congruent (for similar results, see Gamboz et al., 2010; Jennings et al., 2007).

Age differences in ANT network scores were examined using the traditional computation method, but using median RTs (Fan et al., 2002). This method revealed significant age-group differences for the orienting and executive control effect, with older adults showing greater benefit from the spatial cue ($t_{62} = 2.22$, $p = .03$) but being more slowed by incongruent flankers than young adults ($t_{62} = 2.66$, $p = .01$). There were no age differences on the alerting network. However, a different pattern of results emerged when RTs were adjusted for relevant baseline to account for slowing with age (Westlye et al., 2011). In this case, we found significant age-group differences for alerting and executive control network scores with older adults showing less benefit from alerting cues ($t_{62} = 2.05$, $p = .04$) but, surprisingly, being less affected by incongruent flankers than young adults ($t_{62} = 2.13$, $p = .04$). There were no age differences on the orienting network. (Additional information on these analyses can be made available upon request.)

As discussed in the Methods section, to further examine age differences in performance, we followed the methodology proposed by Wang et al. (2014) because it reduces the possible influence of inter-network interactions when calculating the ANT network scores. Thus, three additional mixed ANOVAs (2 × 2) were performed on the median RTs to examine the effect of age (young vs. older adults) on the relevant cue/flanker conditions for each attention network (i.e., alerting: $RT_{\text{double-cue congruent}}$ and $RT_{\text{no-cue congruent}}$; orienting:

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$RT_{spatial\text{-}cue\ congruent}$ and $RT_{center\text{-}cue\ congruent}$; executive control: $RT_{no\text{-}cue\ incongruent}$ and $RT_{no\text{-}cue\ congruent}$). All these ANOVAs revealed main effects of age group and cue or flanker type, but group by cue/flanker interactions were non-significant ($p > .09$). With regard to the network scores (computed according to Wang et al.; see Table 1), *t*-tests revealed no age-group differences when performance was adjusted for relevant baseline RTs to account for slowing with age ($p > .11$).

Age Differences in Performance on the RT Tasks

Regarding the RT tasks, young adults were significantly faster than the older adults and they exhibited less intra-individual variability on the choice task than the older adults ($t_{62} = -3.46$, $p = .001$). Go/no-go mean-adjusted RT-IIV was similar across both groups.

TMS and SAI

Data from one young adult were excluded from all analyses involving SAI due to abnormally poor MEP inhibition in response to afferent conditioning when compared to the other young adults (Grubb's test, $p < .01$, $z = 2.95$). Afferent conditioning led to a marked inhibition of MEP responses in young adults whereas older adults exhibited more variable responses, with many showing poor or even absent inhibition. Accordingly, SAI was significantly reduced in the older group compared to the young ($t_{61} = -3.78$, $p = .001$; see Table 1). Further analysis revealed that about half (17 of 31) of the participants in the older group exhibited abnormally low levels of SAI, corresponding to ≥ 2SD from the mean level observed in the young group (i.e., 46.7%). There were no age differences between the older adults displaying "abnormally" low levels of SAI ($n = 17$) and the seniors with "normal" SAI levels (i.e., within 2SD from the mean in young; $t_{29} = 1.40$, $p = .17$).

Correlation between SAI and Performance

When we performed an analysis across all individuals, SAI was significantly correlated with intra-individual variability in choice RTs ($r^2 = 0.10$, $p = .01$) and was marginally associated with mean speed on this task ($r^2 = 0.05$, $p = .08$). However, when we examined these correlations separately within each age group, they failed to obtain significance. SAI was also only weakly associated with performance on the three ANT network scores (computed according to Wang et al., 2014) and individual variability on the go/no-go RT task within both age groups ($r < .30$, $p > .05$; Figure 1).

We conducted an exploratory follow-up analysis to explore the possibility that only those seniors with "abnormal" SAI levels would differ from the young, but performance differences were not revealed beyond age-related changes on most tasks in three-group between-subjects ANOVAs examining performance on the ANT and RT-IIV in young adults, older adults with "abnormal" SAI levels (≥ 2SD SAI young adults; $n = 17$), and seniors with more efficient afferent inhibition (< 2SD SAI young adults; $n = 14$). Having said this, we did note that on choice RT-IIV, although the older adults with "normal" (coefficient of variation;

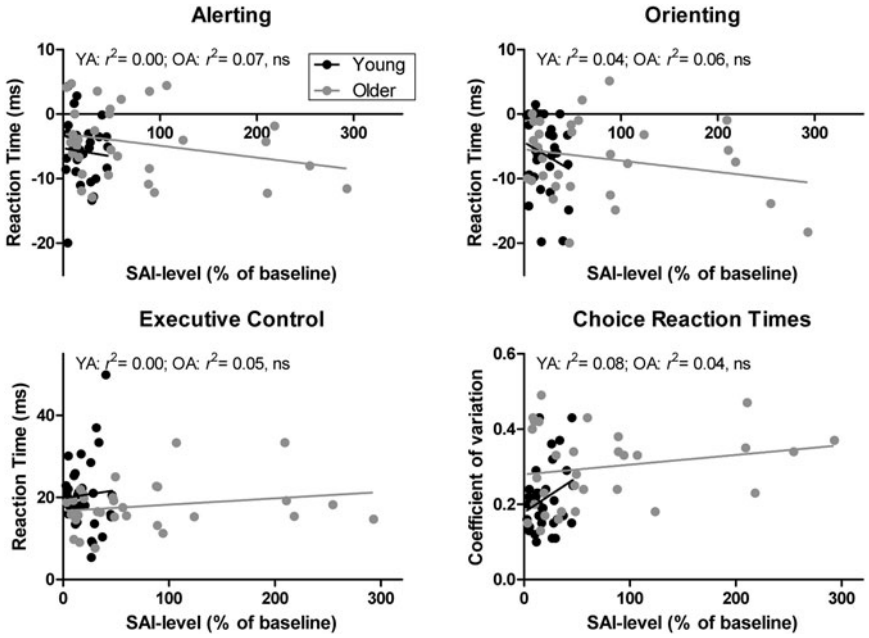

Figure 1: Associations between short-latency afferent inhibition (SAI) and performance on the Attention Network Test (ANT) and intra-individual variability (IIV) on the choice reaction time task in young adults (YA) and older adults (OA)

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[CV] M = 0.28 ± 0.13) and "abnormal" SAI (CV M = 0.31 ± 0.08) did not differ from one another ($t < 1, p > .05$, Cohen's d = 0.28), the seniors with "abnormal" SAI were further away from the young adults (CV M = 0.22 ± 0.09, Cohen's d = 1.06) on this score than were the seniors with "normal" SAI (Cohen's d = 0.54; Figure 2).

Discussion

Older adults were slower than young adults on all three tasks and exhibited greater RT-IIV than young adults on the choice RT task (although not on go/no-go). The latter finding is consistent with the suggestion of Dykiert et al. (2012) that older adults have greater difficulty sustaining their attention when tasks are relatively more demanding.

We also replicated our previous finding of reduced SAI in the older adults compared to the young (Young-Bernier, Davidson, et al., 2012), consistent with myriad other evidence of cholinergic decline in normal aging (e.g., Duzel et al., 2010; Grothe, Heinsen, & Teipel, 2012). However, there were no significant group differences on the ANT network scores after adjusting for general slowing with age (scores computed according to Wang et al., 2014), suggesting that at least some healthy older adults can benefit from simple environmental cues to the same level as young adults to improve their attention functions and that they have efficient executive and inhibitory control. This result is in contrast with previous reports of age effects on alerting and executive control on the ANT (Gamboz et al., 2010; Jennings et al., 2007; Knight & Mather, 2013; Mahoney et al., 2010; Westlye et al., 2011; Zhou et al., 2011) and may be attributed to our use of a computation method that reduced the possible influence of irrelevant cues or flankers and of inter-network interactions on the network scores (Wang et al., 2014). Indeed, we found that age differences on the network scores are largely dependent on the type of computation method used. When we followed the original method (i.e., Fan et al., 2002), we found that older adults benefited more from orienting cues than young adults but their performance was more affected by incongruent cues. However, when these network scores were adjusted for slowing with age (see Westlye et al., 2011), we found a significantly reduced alerting effect, but paradoxically increased executive control in older adults compared to young adults.

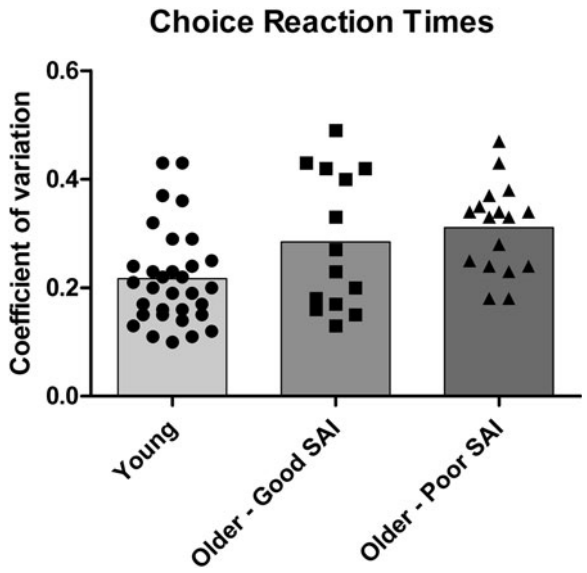

Figure 2: Association between short-latency afferent inhibition (SAI) and variability in choice reaction times in the young and older adults with "normal" (i.e., < 2SD SAI young adults) and "abnormal" SAI levels (i.e., ≥ 2SD SAI young adults)

The absence of age differences in orienting on the ANT has been described consistently in previous studies, but given that aging involves clear deterioration of the cholinergic system (as evidenced in the present study by the age-related difference in SAI levels, commensurate with myriad other data; e.g., Duzel et al., 2010; Grothe et al., 2012), this observation is seemingly at odds with the idea that the cholinergic system influences orienting abilities (for further discussion, see following paragraphs).

Overall, the parallel age differences in SAI, ANT reaction times, and RT-IIV could be taken as evidence that cholinergic declines underlie older adults' reduced attentional functions. However, the case would have been stronger if we had found the expected correlations between SAI and performance within our older adults. This may have to do with statistical power. Our sample sizes were sufficient to detect the large age differences we observed in SAI, in RT-IIV on the choice task, and in RTs on the ANT (i.e., Cohen's d ranging from 0.84 to 2.97) and to detect large correlations between the neurophysiological and behavioral data. More subtle relationships, if indeed they exist, might be uncovered with more high-powered studies. The low to moderate reliability of the ANT network scores (Macleod et al., 2010) might also have impacted power and our ability to find age-related differences on this task or associations with SAI. As such, including a larger number of ANT trials to increase the reliability of the scores derived from this measure might be a direction for future studies (Ishigami & Klein, 2010). Similarly, increasing the number of RT trials could allow for more reliable measures of IIV, although previous studies have also examined RT IIV with a comparable number of trials to the tasks included here (e.g., Finkel & McGue, 2007; Hultsch, MacDonald, & Dixon, 2002).

Alternatively, a certain threshold in SAI may need to be reached before declines in cholinergic efficiency

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translate to detectable changes at the behavioral level (e.g., Robbins et al., 1997; Schliebs & Arendt, 2006). For example, although healthy older adults and even MCI patients are relatively unimpaired on the orienting index from the ANT, Fernandez et al. reported that MCI patients who also have significant subcortical vascular damage (likely involving decreased cholinergic integrity) exhibit impaired orienting on the ANT (Fernandez et al., 2011). It is therefore possible that we would have found stronger relationships between SAI and performance if we had included more older adults with substantial cholinergic declines (including patients with MCI and early AD). To add a further level of complexity to the possible association between SAI and cognitive performance, Nardone et al. (2012) recently showed that although SAI levels are correlated with performance on measures of attention/executive functions and verbal memory in patients with MCI, this marker of cholinergic activity is only reduced in amnestic multi-domain MCI but not in other MCI subtypes (i.e., single domain or non-amnestic multi-domain MCI). These results suggest that the disease process may need to be more advanced for SAI levels to be further reduced in patients with MCI when compared with healthy controls. Longitudinal studies in older adults and patients with MCI and AD will allow for a better understanding of the complex relationship between cholinergic and cognitive functions.

Another possibility is that the tasks used in this study may not have sufficiently taxed attentional resources to show strong associations between SAI and declining performance with age (Dumas & Newhouse, 2011; Sarter et al., 2005). Increasing the cognitive load – for example, by including a divided attention component (Sarter & Turchi, 2002) – may be a direction for future studies. Finally, declines in SAI levels may need to be associated with additional age-related changes, including microvascular damage and/or reduced dopaminergic activity, to show a relationship with attention (Backman, Nyberg, Lindenberger, Li, & Farde, 2006; Fernandez et al., 2011; MacDonald et al., 2009). In future studies, combining SAI, as a non-invasive marker of cholinergic activity, with neuroimaging and other methods, including perhaps eyeblink markers of dopaminergic activity (Lackner, Bowman, & Sabbagh, 2010), might provide a better understanding of how various anatomical, physiological, and neurotransmission changes interact to influence cognitive performance in normal aging.

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