YALE JOURNAL OF BIOLOGY AND MEDICINE 92 (2019), pp.37-51.

REVIEW

A Review on the Trajectory of Attentional Mechanisms in Aging and the Alzheimer's Disease Continuum through the Attention Network Test

Ian M. McDonough[a,*], Meagan M. Wood[b], and William S. Miller, Jr.[a]

[a]*Department of Psychology, The University of Alabama, Tuscaloosa, AL;* [b]*Department of Psychology, Mississippi University for Women, Columbus, MS*

Multiple domains of cognition are known to decline in both normal aging and in the trajectory towards Alzheimer's disease (AD†). While declines in episodic memory are most well-known in both normal aging and AD, some of these memory differences might stem from early deteriorations in attention that have consequences for later memory. Further complicating the matter is that attention is a multifaceted construct that might be differentially affected in normal aging and AD. According to cognitive neuroscience models of attention, three types of attention networks exist: alerting, orienting, and executive. Efficiency of these three networks can be captured using the Attention Network Test (ANT). We reviewed the literature investigating differences in attention networks using the ANT as a function of normal aging and the AD trajectory, which included people at risk for AD, preclinical stages of AD, mild cognitive impairment, and those diagnosed with AD. We found that normal aging and the AD trajectory evidenced different patterns of attentional declines. Whereas normal aging was most consistently associated with impairments in alerting, early phases of the AD trajectory were most consistently associated with impairments in executive attention, and later phases of the AD trajectory were mixed. The mixed results with AD are largely attributed to small sample sizes and confounding effects of general slowing. These findings highlight key gaps in the literature linking different phases of AD while also highlighting the usefulness of the ANT to distinguish normal aging from the AD trajectory, especially in the earliest phases of the disease process.

*To whom all correspondence should be addressed: Ian M. McDonough, Department of Psychology, The University of Alabama, Box 870348, Tuscaloosa, AL 35487, USA; Tel: 205-737-3442, E-mail: immcdonough@ua.edu.

†Abbreviations: AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; ANT, attention Network; Test; ANT-I, attention Network Test with Interactions; APOE, apolipoprotein E; DBP, diastolic blood pressure; fMRI, functional magnetic resonance imaging; HC, healthy controls; LBD, Lewy bodies dementia; MCI, mild cognitive impairment; nvMCI, patients with mild cognitive impairment without subcortical vascular damage; RT, reaction time; SBP, systolic blood pressure; SVM, support vector machine; svMCI, subcortical vascular damage.

Keywords: Aging, Alerting, Attention Network Test, Alzheimer's Disease, Executive Function, Mild Cognitive Impairment

Author Contributions: Manuscript ideas and outline was developed by IMM; Writing was conducted by IMM, MMW, and WM.

Copyright © 2019

INTRODUCTION

Maintaining visual attention is critical to select and process information in one's environment for everyday tasks like driving, cooking, and caring for others [1-3]. Information that is attended to and processed also is more likely to be remembered. In this way, memory encoding can be viewed as a byproduct of attention and its associated processes. Given the well-characterized declines in episodic memory in aging and Alzheimer's disease (AD), it is unclear to what extent these declines stem from differences in attention rather than (or in addition to) processes occurring during memory retrieval. Recent perspectives in cognitive neuroscience suggest that attention can be characterized by at least three different classes: alerting, orienting, and executive [4,5]. These three classes of attention may decline differently in normative aging compared with pathological aging, as in AD. Here, we review studies using the Attention Network Test (ANT) [4] that intentionally measure these classes of attention in a single task across the aging and AD spectrum: risk for AD, preclinical AD, mild cognitive impairment (MCI), and diagnosed AD. We note that other modern models with their own associated paradigms exist to study attention including, but not limited to, the computational Theory of Visual Attention [6], Cowan's framework on Attention and Memory [7], and the theory of Threaded Cognition [8]. We chose to focus on the ANT in this review because it assesses multiple classes of attention and has been the most widely used model to study attention across the aging and AD spectrum, thus providing the clearest comparisons across normative and pathological aging trajectories.

THEORIES OF VISUAL ATTENTION

Attention often is viewed as a process similar to a spotlight in the dark. Only a few selected objects can be viewed at a time, but we have volitional control to move the spotlight around and view different objects in our surrounding. We also can direct the spotlight near or far depending on our motivations and goals. This metaphor, however, ignores critical elements of attention, including the fact that exogenous sources can take control of or capture our attention, and the fact that attention can wane over time. Additionally, the metaphor does not allow for processes like aging or dementia to alter how the spotlight works (except perhaps in the fading of batteries that culminates in complete dysfunction).

Posner and colleagues have proposed a cognitive neuroscience perspective of attention that consists of three functionally interrelated, but anatomically distinct, attentional networks: alerting, orienting, and executive control. Alerting is the process by which one initiates and sustains an aroused attentional state to prepare for an upcoming event or stimulus and is driven by the neurotransmitter norepinephrine via the thalamus, frontal cortex, and parietal cortex [4,9]. Orienting is the process by which attention is spatially shifted to select an object and is driven by the neurotransmitter acetylcholine via the lateral parietal cortex and the frontal eye fields [10]. Executive attention is the process by which one monitors and resolves conflicts among competing thoughts, feelings, or responses [11]. Executive attention is driven by dopamine via the anterior cingulate and lateral prefrontal cortex [4].

THE ATTENTION NETWORK TEST

The ANT is designed to test the three attentional networks in one procedure (Figure 1) [4,5]. Participants spend approximately 30 minutes determining whether the center arrow points left or right. Sometimes before a trial, a cue in the form of an asterisk above or below a central fixation point alerts participants of an upcoming arrow (single cue), whereas other times a cue appears both above and below a central fixation point (double-cue), and yet other times no cue appears (no cue). When the arrow appears, it can be above or below the focal point and can be accompanied by flankers (distracting arrows) that are in the same direction as the center arrow (congruent) or a different direction as the center arrow (incongruent). Response times (RTs) are then measured for trials that contain combinations of these manipulations and difference scores are calculated to estimate the efficiency of each network. Generally, one condition offers a type of low-level baseline of attention and a second condition either facilitates attention (leading to faster RTs as is the case for alerting and orienting) or interferes with attention (leading to slower RTs as is the case for executive attention). Thus, the larger the difference score, the more facilitation or interference can be inferred. The task can be easily implemented with a wide range of participants, including older adults and those with neurocognitive disorders, thereby keeping accuracy at a very high level.

Alerting is assessed by the impact of a *temporal signal* on attention that should enable better attention and faster responding. The estimate of alerting is calculated by subtracting RTs in the double-cue condition (*i.e.*, pre-arrow warning) from the no-cue condition. A larger difference score is indicative of better alerting abilities because people are better able to take advantage of the temporal warning cues [4,5]. Orienting is assessed by the impact of a *spatial signal* on attention that should enable better attention and faster responding. The estimate of orienting is calculated by subtracting RTs in the single spatial cue condition (*i.e.*, cue above or below the center that indicates valid information as to where the arrow

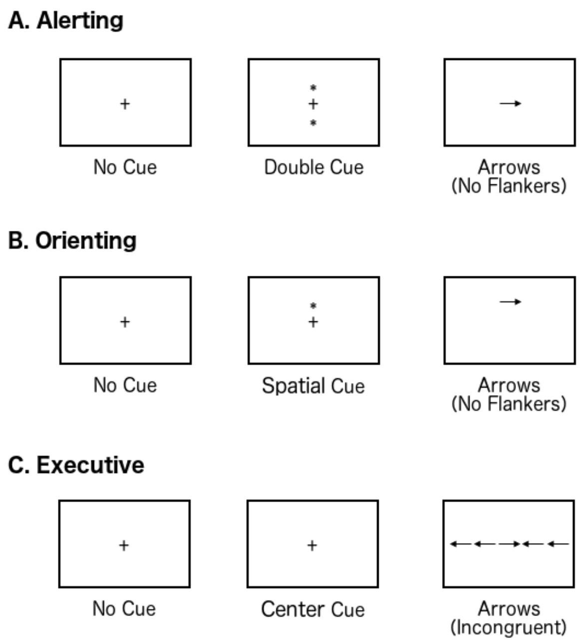

Figure 1. Schematic of Attention Network Test. Panel A illustrates an alerting trial with a neutral arrow (*i.e.*, no flankers). Alerting is calculated by subtracting response times in the double-cue condition from the no-cue condition. Panel B illustrates an orienting trial with a top spatial cue and a neutral arrow. Orienting is calculated by subtracting response times in the single spatial cue condition from the no cue condition. Panel C illustrates an executive trial with incongruent flankers. In the actual paradigm, these different trials are systematically combined so that all combinations of trials are possible. Executive attention is calculated by subtracting response times in the congruent flanker condition (not shown) from the incongruent flanker condition.

might appear) from the no cue (or sometimes the invalid cue) condition. A larger difference score is indicative of better orienting abilities because people are better able to take advantage of the spatial warning cues [4,5]. Lastly, executive attention is assessed by the time it takes to resolve conflicting sources of information due to the flankers that should impair attention and slow down responding. The estimate of executive attention is calculated by subtracting RTs in the congruent flanker condition (*i.e.*, outside arrows match the center arrow) from the incongruent flanker condition (*i.e.*, outside arrows do not match the center arrow). A smaller difference score is indicative of better executive attention because people are less impaired by the distracting, conflicting information [4,5].

In an older adult sample, Mahoney *et al*. [12] found high independence among the three measures. The correlations between alerting and executive attention were near zero (r = -.07) as were the correlations between orienting and executive attention (r = -.05). However, the correlations between alerting and orienting were significant (r = -0.27), which was attributed to the overlapping nature of spatial and alerting cues [4]. Additionally, Ishigami *et al*. [13] found that each measure was reliable using split-half correlations in a variant of the ANT (ANT-I).

ANT PERFORMANCE IN NORMAL AGING

Fernandez-Duque and Black [14] were one of the first to investigate the effects of aging and AD on ANT performance. They found that older adults showed a larger alerting effect (*i.e.*, larger difference scores) than younger adults. Notably, these authors also corrected for general age-related slowing in their analyses. Because older adults often respond slower across all conditions, this general age-related slowly can artificially create larger difference scores in one group compared to another [15-17]. They implemented this correction using proportion scores that were calculated by dividing the mean RTs in each condition for each participant by their overall RT. Fernandez-Duque and Black [14] argued that older adults might have some difficulty sustaining their attention in the trials and, as a result, may have benefited more from cues than younger adults. No age differences were found in orienting or executive attention. Although this study was one of the earliest studies to use the ANT to test for age differences, the sample sizes were quite small (n = 13 per group).

Contrarily, Jennings and colleagues [18] used a larger sample of cognitively normal older adults (N = 63). Using raw difference scores (as is traditional in most ANT studies in young adults), older adults had smaller alerting effects than younger adults, and thus did not benefit as much from alerting. Like Fernandez-Duque and Black [14], Jennings *et al*. [18] also corrected for general age-related slowing but did so by transforming the raw response times into z-scores and re-conducting the analyses. These new transformed scores showed the same age effects. Interestingly, these alerting effects were in the opposite direction as the smaller study conducted by Fernandez-Duque and Black [14]. These researchers argued that any age differences seen in alerting across studies may be due to differences in methodology such as the duration of the presentation or the persistence of the warning cues. Jennings and colleagues [18] argued that when the duration of the cues is increased, an increase in older adults' alerting also can be seen. However, when the duration of the cues is closer to 100 milliseconds, larger age differences might occur. Jennings *et al*. [18] also found a larger executive attention effect in older adults than younger adults, suggesting that older adults were more distracted by the incongruent flankers than young adults. However, when these scores were transformed to correct for general age-related slowing, they no longer showed significant age differences. No age differences were found for orienting.

Later, Gamboz and colleagues [19] found similar results using a similar sample size (N = 65), but in a low educated sample (mean education = 11 years). They found that when raw scores were used, older adults showed a smaller alerting effect (*i.e.*, less benefit from the double cue versus no cue), a larger orienting effect (*i.e.*, more benefit from the spatial cue versus the central cue), and a larger executive effect (*i.e.*, more conflict from the incongruent versus the congruent cue) than younger adults. However, after transforming the scores using the proportion method, only the smaller alerting effect in older adults compared with young adults remained. A similar pattern of transformed versus raw effects were found by others [20-22], providing additional evidence of smaller alerting effects in older adults than younger adults. Gamboz and colleagues [19] argued that the contradictory results found by Fernandez-Duque and Black [14] might be due to the more salient (*i.e.*, bigger and brighter) warning cues compared to those used in other studies [18,19] or due to differences in duration (*e.g.*, 500 milliseconds vs. 100 milliseconds).

In a study conducted by Zhou and colleagues [23], the efficiency of the attentional networks was examined among young, middle-aged, and older Chinese adults. They discovered that older adults had significantly smaller alerting effects than young and middle-aged adults, suggesting an impairment in alerting only during old age. Large executive attention effects (worse performance) also increased from young to middle-aged to old age. In contrast, there were no significant age differences in orienting. These effects remained after correcting for general slowing using proportion scores. While these age differences resemble other findings for alerting, they contrast many of the previous null results for executive attention. Not only were these age differences in executive attention roughly twice as large as the alerting effects, but they were discovered in participants in as early as middle age.

Westlye *et al*. [24] also found age differences while investigating the neuroanatomical correlates of the ANT in a large sample (N = 128). After correcting for age-related slowing using the proportion method, they found smaller alerting effects (*i.e.*, poorer alerting) with older age and smaller executive attention effects (*i.e.*, better executive attention) with older age. This executive attention effect was about half the size of the alerting effect and in the opposite direction than expected. However, using the same age-related slowing corrections, Young-Bernier *et al*. [25] found the age-related effects to be in the same direction, supporting the Westlye *et al*. [24] study.

Another large study (N = 263) [26] used an ANT-like task that measured orienting and executive attention in a lifespan sample from ages 6 to 88 years old. From early adulthood to old age, they found very stable orienting effects, suggesting that this attention type does not differ in adulthood. They did, however, find larger executive attention effects from middle-age to older-age, suggesting an impairment in this attention ability after about age 67. While these authors found that mean RTs (an indication of general slowing) differed with age and were correlated with both orienting and executive attention effects, they did not recalculate their analyses while controlling for these slowing effects. Thus, despite the large sample size, it is not clear whether these aging effects would remain after controlling for general slowing.

In summary, when examining the effects of normal aging on the ANT, common themes did arise (see Table 1). Studies using larger samples and shorter cue time lengths create conditions under which older adults show less benefit from cues meant to enhance alerting than young adults. On the other hand, most of the studies found no significant age differences for orienting and executive attention within the ANT after accounting for generalized age-related slowing. For those studies that did find age differences in executive attention, a study by Mahoney *et al*. [12] might partially account for some of the conflicting findings. They compared young-old adults (70 to 79 years old) with old-old adults (80+ years old) and found that greater age was associated with a larger executive attention effect (*i.e.*, greater susceptibility for distraction from the flanking cues) even when controlling for general slowing (for similar findings, see also [27]).

Table 1. Summary of Attention Network Test Studies

First Author	Year	Participants (N, Type, Mean Age)	Findings	Notable Limitations
Festa-Martino	2004	15 YA (*M* = 18.3) 19 OA (*M* = 77.1) 18 AD (*M* = 79.4)	- After correcting for age-related slowing, YA larger alerting effects than OA and AD. - OA had larger alerting effects than AD. - AD had larger orienting than YA and OA.	- Small sample sizes
Fernandez-Duque	2006	13 YA (*M* = 19.8) 13 OA (*M* = 72.5) 13 AD (*M* = 74.7)	- After correcting for age-related slowing, OA had larger alerting effect than YA. - After correcting for age-related slowing, AD exhibited poorer executive attention than OA.	- Small sample sizes
Tales	2006	15 OA (*M* = 74.6) 15 AD (*M* = 72.9)	- AD had a larger orienting effect than OA.	- Small sample sizes - Did not investigate executive attention. - Baseline response times were not controlled.
Jennings	2007	60 YA (*M* = 19.2) 63 OA (*M* = 69.1)	- After correcting for age-related slowing, OA had smaller alerting effects than YA.	
Gamboz	2010	70 YA (*M* = 25.8) 65 OA (*M* = 67.9)	- After correcting for age-related slowing, OA had smaller alerting effects than YA.	
Lv	2010	42 MCI (*M* = 68.5) 45 OA (*M* = 64.8)	- Direct comparisons revealed no differences between amnestic MCI and OA on any of the tasks. - Support vector machine analysis was able to differentiate between amnestic MCI and OA.	- The combination of a) using a non-linear support vector machine, b) including age in the analysis, and c) finding no mean differences between groups for any of the individual measures complicates the interpretation of these findings. - Baseline response times were not controlled.
Mahoney	2010	184 OA (*M* = 80.41)	- After controlling for general slowing, higher blood pressure was associated with better executive attention.	
Waszak	2010	263 Age Range 6-88 (no mean age reported)	- Executive attention increased from MA to OA.	- Did not investigate alerting. - Did not correct for age-related slowing.
Westlye	2010	268 Age Range 20-84 (*M* = 48.5)	- After correcting for age-related slowing, OA had smaller alerting and executive attention effects than YA. - The same brain regions that atrophy in AD were also associated with individual differences in executive attention and alerting.	

Fernández	2011	34 MCI (*M* = 69.8) 19 OA (*M* = 70.3)	- Subcortical vascular MCI showed smaller orienting effects than non-subcortical vascular MCI and OA.	- Small sample sizes when breaking up MCI groups.
Zhou	2011	30 YA (*M* = 27.8) 30 MA (*M* = 51.2) 30 OA (*M* = 70.9)	- After correcting for age-related slowing, OA had smaller alerting effects than YA and MA. - After correcting for age-related slowing, executive attention effects increased from YA to MA to OA.	
Deiber	2013	20 YA (*M* = 25.5) 28 OA (*M* = 64.9)	- After correcting for age-related slowing, OA had larger orienting effects than YA.	- Small sample sizes
Gaudet	2013	19 CE (*M* = 64) 16 OA (*M* = 62)	- OA who recently suffered a cardiac event had poorer executive attention than those without such event. - Greater impairments in executive attention were associated with poorer driving in a driving simulator.	- Small sample sizes - Baseline response times were not controlled.
Knight	2013	27 YA (*M* = 21.37) 32 OA (*M* = 73.34)	- When tested in the morning, YA had greater alerting effects than OA after correcting for age-related slowing. - When tested in the evening, no age differences in alerting were found even after correcting for age-related slowing.	- Small sample sizes
van Dam	2013	19 MCI (*M* = 77.6) 15 OA (*M* = 74.6)	- The amnestic MCI group had larger executive attention effects than OA. - The amnestic MCI group had increased brain activity using fMRI in the parietal cortex than OA for the alerting and orienting tasks. - The amnestic MCI group had decreased brain activity in the anterior cingulate cortex, medial prefrontal cortex, and lateral prefrontal cortex than OA for the executive attention task.	- Small sample sizes. - Baseline response times were not controlled.
Gamble	2014	26 YA (*M* = 20.54) 30 OA (*M* = 69.10)	- Viewing nature, but not urban, pictures significantly improved executive attention in both OA and YA. - No age differences or interactions with age were found.	- Small sample sizes - Did not correct for age-related slowing.
Martella	2014	20 MCI (*M* = 66.5) 18 OA (*M* = 66.6)	- OA had larger executive attention effects than MCI. - MCI showed lower vigilance than OA.	- Small sample sizes - Baseline response times were not controlled.

Firbank	2015	23 OA (*M* = 76.3) 23 AD (*M* = 75.8) 32 LBD (*M* = 75.0)	- LBD had smaller executive attention than OA. - AD failed to deactivate parietal brain regions in executive attention task compared with OA and LBD.	- Small sample sizes - Baseline response times were not controlled.
Young-Bernier	2015	33 YA (*M* = 22.4) 31 OA (*M* = 70.2)	- After correcting for age-related slowing, OA had smaller alerting and executive attention effects than YA. - Follow-up analyses accounting for inter-network interactions when calculating the ANT network score, however, revealed no significant age differences.	
Zhang	2015	12 MCI (*M* = 69.3) 16 AD (*M* = 69.9) 15 OA (*M* = 67.8)	- OA had better executive attention than amnestic MCI. - Dorsal and ventral attentional networks were more functionally connected to each other in amnestic MCI than OA. - Correlations were found with connectivity for all three attentional networks within the amnestic MCI group. - AD performed worse on all three attentional networks than OA. - AD had decreased connectivity within the dorsal attentional network and the ventral attentional networks.	- Small sample sizes - Baseline response times were not controlled.
Kaufman	2016	19 YA (*M* = 22.9) 16 OA (*M* = 64.8)	- After controlling for age-related slowing, YA had greater alerting than OA. - Alerting cues led to a greater posterior N1 response using ERP in YA than OA.	- Small sample sizes
Lu, Chan *et al*.	2016	137 OA (*M* = 71.5) 36 AD (*M* = 73.4) 31 VD (*M* = 73.5)	- After correcting for age related slowing, those with AD and VD showed larger executive attention effects than OA.	- AD group had unusually high levels of cognitive functioning (Chinese MMSE = 27.22)
Lu, Fung *et al*.	2016	145 OA Age Range 65-80 (*M* = 72.41)	- After correcting for age-related slowing, increasing age within the OA was associated with greater executive attention.	
Williams	2016	24 YA (*M* = 21.6) 24 OA (*M* = 65.1)	- After controlling for age-related slowing, OA showed reduced alerting than YA. - N2 and P3 responses using ERP were larger in YA than OA.	- Small sample sizes

Notes. YA = Young Adults; MA = Cognitively Normal Middle-Aged Adults; OA = Cognitively Normal Older Adults; MCI = Older Adults with Mild Cognitive Impairment; AD = Older Adults with Alzheimer's Disease; LBD = Older Adults with Lewy Body Dementia; VD = Older Adults with Vascular Disease; CE = Older Adults with Recent History of a Cardiac Event; MMSE = Mini-Mental Status Exam.

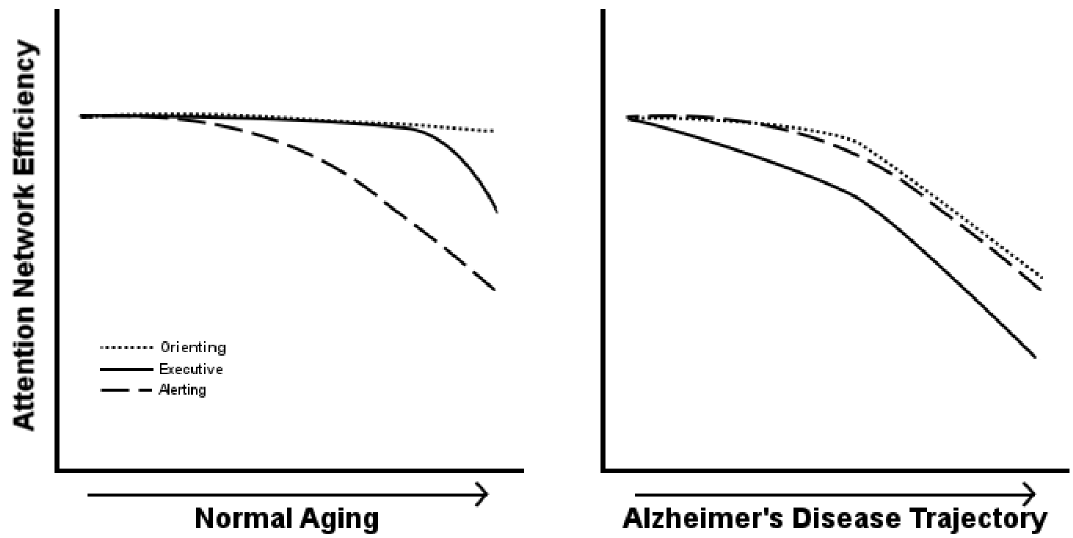

Figure 2. Summary of findings for trends in normal aging (left) and the AD trajectory (right). In normal aging, alerting gradually decreases with age, executive attention declines only in very old age, and orienting is stable. In early phases of the AD trajectory (*i.e.*, normal older adults at risk for AD, preclinical AD, and amnestic mild cognitive impairment), executive attention declines above beyond normal age-related declines in attention. In later phases of the AD trajectory (*i.e.*, diagnosed AD), orienting declines at a similar rate as alerting. Because the likelihood of a diagnosis of AD increases with old age, we use the age-related alerting effect as a reference line. AD = Alzheimer's disease.

No differences in these two old age groups were found for alerting or orienting. Thus, these studies [12,27] suggest that although alerting may become altered with normal aging earlier on (60 to 70 year-olds), executive attention might become altered later in life (*i.e.*, 80+ year-olds). This pattern is summarized in the left panel of Figure 2.

At the same time, not all studies have found age differences across any of the measures [28]. For example, Young-Bernier *et al*. [25] found that when they corrected for interactions between the purportedly independent networks, no age differences were found. Knight and Mather [21] also found that time of day impacted the degree of age differences. No age differences were found when testing participants in the evening, but age differences in alerting were found if participants were tested in the morning. In addition, one study found differences in neither alerting nor executive attention, but rather in orienting; older adults exhibited larger (*i.e.*, more beneficial) effects of orienting than younger adults, even when correcting for age-related slowing [29]. No one factor can explain the few studies that deviate from these trends. One other important aspect to consider in "normal" aging studies is that many of them likely unintentionally include some participants in preclinical stages of AD that will convert to AD in subsequent years. The preclinical AD stage is characterized by a slow accumulation of AD pathology (*i.e.*, beta-amyloid plaques and tau neurofibrillary tangles) leading to neurodegeneration that can impact cognitive performance [30-32]. Without biomarkers of this preclinical stage or longitudinal measures of function, many older adult studies are at risk for including a subset of those on the trajectory towards AD.

ANT PERFORMANCE IN OLDER ADULTS WITH AD RISK

Various factors other than chronological age have been established that predict the likelihood of converting to late onset AD, including having a family history of AD and the *APOE* E4 gene [33,34]. While these risk factors have the most specific links with AD, we could not find any studies that have investigated the ANT as a function of these risk factors. However, epidemiological studies have identified many other factors that increase one's risk for AD [35], albeit with considerably lower public awareness [36]. For example, a recent systematic review [37] documented nearly a dozen modifiable risk factors for AD including hypertension, high cholesterol, obesity, level of cognitive activity, diabetes, smoking, coronary heart disease, depression, low consumption of a Mediterranean diet, and high alcohol intake. We found two studies that fell into one of these categories.

Gaudet *et al*. [38] investigated performance in the ANT in older adults who had recently suffered a cardiac event (including myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, or angina) and older adults who had not experienced such an event. The cardiac group had marginally higher levels of hypertension and lower education levels compared to the control group—both posing additional risk for AD. Despite the relatively high risk for AD in the cardiac group, no differences in the ANT performance measures were found. However, when controlling for some confounding effects (*i.e.*, age, sex, education, hypertension, and diabetes), the cardiac group had poorer executive attention than the control group. Although age-related slowing was not explicitly accounted for, the authors did control for age (a proxy for age-related slowing) and no differences were found in mean RTs, suggesting a low likelihood that general slowing accounted for these differences. Interestingly, greater impairments in executive attention were also associated with poorer driving in a driving simulator, attesting to the real-world importance of impairments on this measure. Though in this case, mean RTs also were associated with poorer driving, thus potentially explaining the executive attention effect on driving.

Abnormal blood pressure (both hypertension or hypotension) also increases the risk for a host of cardiovascular diseases and future cognitive decline [39-42]. Some studies have indicated that higher blood pressure in mid-life and lower blood pressure in later life both predict future dementia [43,44]. Using data from the Einstein Aging Study, Mahoney and colleagues [12] investigated how abnormal blood pressure levels impact performance in the ANT in a sample of cognitively normal older adults. When controlling for general slowing by including overall RT in their regression analyses, higher blood pressure (SBP > 120 mmHg and DBP > 80 mmHg) was associated with better executive attention (*i.e.*, participants were less likely to be impacted by the distracting flankers, thus resulting in smaller difference scores). No differences were found for the effects of blood pressure on alerting or orienting. Given that some studies have suggested that higher blood pressure in old age might actually be protective, perhaps the benefits of high blood pressure for executive attention are consistent with this idea.

In summary, a paucity of studies has investigated relevant risk factors for AD using the ANT. Of the two studies reviewed, both point to alterations in executive attention. Nevertheless, strong conclusions cannot be made as to whether risks for AD in older adults lead to subtle deficits in the attention networks.

ANT PERFORMANCE IN PRECLINICAL AD

Preclinical stages of AD are associated with biological changes in the brain—such as the accumulation of beta-amyloid, tau neurofibrillary tangles, and declines in cortical thickness—even when cognition is within normal ranges [32]. Recent neuroimaging research has provided evidence that cortical thickness can be used as a proxy of neurodegeneration in preclinical AD. Specifically, Dickerson *et al*. [45] has established a set of nine brain regions, dubbed AD Signature Regions, that are negatively associated with beta-amyloid and decrease as severity of AD symptoms worsen.

Although we could not find any studies that have correlated individual variability in beta-amyloid or tau and performance on the ANT, one study assessed the relationship between cortical thickness and ANT performance in a sample with a large age range [24]. In this study, some of the same regions associated with preclinical AD were also associated with aspects of the ANT. The most widespread effects were negative associations between the executive attention effect and cortical thickness. Of the regions found to be related to executive attention, the inferior parietal cortex, lateral superior temporal gyrus, and portions of the medial temporal lobe spatially overlapped with the AD Signature Regions. Negative associations also were found with individual variability in alerting performance, but only in the medial and lateral superior parietal lobe. Each of these regions overlap with the AD Signature Regions. No significant effects were found for orienting effects. To the extent that cortical thickness in the brain regions overlapping AD Signature Regions are causally related to executive attention and alerting, this finding suggests that those two classes of attention might be at risk to decline with the progression of AD.

ANT PERFORMANCE IN MCI

MCI has been commonly defined as the transitional state between normal age-related cognitive decline and the early stages of dementia [46-48]. The three most prevalent forms of MCI are single-domain amnestic MCI (aMCI), single-domain dysexecutive MCI, and multiple-domain amnestic MCI [49,50]. Furthermore, the high rate of conversion from aMCI to AD have led many researchers and clinicians to consider this category as the most likely precursory stage of AD [51].

In a study comparing healthy individuals and those with aMCI, van Dam and colleagues [52] found a difference in executive attention. Specifically, the executive effect was much larger in the aMCI group compared to the healthy control (HC) group, suggesting that participants with aMCI were more distracted by the incongruent trials than normal adults. No RT differences were found for alerting or orienting. They also found that there were differences within the neural networks responsible for each class of attention using the ANT during fMRI. The aMCI group showed increased brain activity when contrasting the effects of alerting in the left parietal cortex and when contrasting the effects of orienting in the bilateral parietal cortex. The authors argued that the increases in brain activity might be a form of neural compensation that allows this group to maintain their performance in alerting and orienting. In contrast to these increases in activation, decreased brain activity was found in the aMCI group compared with HCs for the executive attention contrast in the anterior cingulate cortex, medial prefrontal cortex, and lateral prefrontal cortex. These decreases in brain activity are consistent with the impaired executive attention performance found in this group. In this case, fundamental executive attention processes might be directly impaired, but different approaches or strategies might also exist between the groups that cause both differences in performance and brain activity [53].

Lv and colleagues [54] also investigated performance on the ANT in a group of cognitively normal adults and a group with aMCI. Unlike van Dam *et al*. [52], they did not find any behavioral differences in any of the attention networks when employing direct comparisons between the two groups. However, they were able to find differences between the two groups when using machine learning techniques (*i.e.*, support vector machine or SVM). The SVM technique used was a non-linear classifier that allowed patterns of multiple performance indices from the ANT to separate the two groups. The model that best separated the HC and aMCI groups included RT differences for the executive attention effect, RT differences for the orienting effect, accuracy differences between the incongruent versus the no cue condition (*i.e.*, executive attention), and the age of participants. While this finding suggests that both measures of executive attention and orienting (but not alerting) do differ between aMCI and HCs, the combination of a) using a non-linear SVM, b) including age in the analysis, and c) finding no mean differences between groups for any of the individual measures complicates the interpretation of these findings. One untested possibility is that age interacted with cognitive status to lead to ANT differences between groups. Despite these concerns, the pattern of results found by Lv *et al*. [54] is consistent with the neural findings of van Dam *et al*. [52] who found effects in these two networks but is inconsistent with the effects in normal aging in which only alerting is consistently impaired.

More recently, Zhang *et al*. [55] investigated ANT performance and functional connectivity in a group of normal older adults, people with aMCI, and AD patients. They tested the role that the dorsal attentional network (*e.g.*, intraparietal sulcus and frontal eye fields) and the ventral attentional network (*e.g.*, temporal parietal junction and ventral frontal cortex) play in early disease stages. Compared with the HC group, they found only behavioral differences indicative of poorer performance in executive attention, but it should be noted that their sample sizes were quite small (12 aMCI and 15 HCs). Interestingly, they found that the dorsal and ventral attentional networks were more connected to each other in the aMCI group than the HC group. The authors attributed this heightened functional connectivity to a possible compensatory reorganization or recruitment of cognitive resources as a result of subtle neurodegeneration occurring within attention neural systems. Lastly, regressions were conducted that correlated functional connectivity with the ANT RT measures while controlling for key variables such as age, education, and gray matter volume. They found correlations with connectivity for all three ANT RTs within the aMCI group. Larger alerting RT effects were associated with greater dorsal attention network connectivity and worse ventral attention connectivity; larger orienting RT effects were associated with greater dorsal attention network connectivity; greater executive attention RT effects were associated with both increases and decreases in connectivity with the dorsal attention network (depending on hemisphere). Consistent with other studies, aMCI appears to be characterized by deficits in executive attention. However, the functional connectivity results reveal a complicated interplay between dysfunction and compensation for multiple neural systems underlying attention.

Martella and colleagues [56] investigated a variant of the ANT task that not only investigated interactions among ANT measures, but also added an attentional vigilance component. Vigilance was defined as the ability to maintain a high level of alertness over the course of the task. The MCI subtypes consisted of six amnestic, six non-amnestic, and eight multiple-domain types. Collapsing across all MCI subtypes, they found that the executive attention effect was larger in the HC group than the MCI group, suggesting that the MCI group had better executive attention performance. Interestingly, this benefit was only found when an alerting cue was absent. Follow-up MCI subtype analyses suggested that the above pattern was most exaggerated in the multi-domain MCI group and smaller executive attention effects across both alerting conditions were found in aMCI and non-aMCI groups. The authors suggested that the alerting cue helped minimize the effect of the distracting flankers, but only in the MCI group. However, it is unclear why the alerting signal led to better executive attention than in the HCs. One possibility is that general slowing effects often found in groups of MCI participants (especially multi-domain MCI) may have exaggerated these group differences, although differences in general slowing were not taken into account to test this proposal. The vigilance analyses indicated that all of the MCI subtypes showed equally lower vigilance than HCs.

Other types of MCI also have been investigated using the ANT. Fernández and colleagues [57] examined attention deficits among MCI patients with subcortical vascular damage (svMCI), MCI patients without SVD (nvMCI), and HCs. Results indicated that the svMCI group showed smaller orienting effects compared with the nvMCI and HC groups when controlling for overall slowing using proportion scores and no group differences in the other domains. Fernández and colleagues [57] argued that the subcortical damage affects the cholinergic system, ultimately impairing the covert orienting system. This reduced orienting effect in the ANT, however, is different from the impaired effects in executive attention found in aMCI.

Overall, performance on the ANT appears to reveal different patterns depending on what types of neurodegeneration might be present. Neurodegeneration to subcortical structures appears to impair attention differently than either normal aging or aMCI. An important consideration is that the studies comparing MCI (of any subtype) to normal older adults often use smaller sample sizes (about 8 to 20 people per group). Nevertheless, the evidence appears to consistently implicate early executive attention deficits in aMCI. However, only one of these MCI studies controlled for group differences in general slowing [57]. Unfortunately, this was the one study that did not investigate aMCI, which is the subtype of MCI most likely to convert to AD. Thus, general slowing rather than executive attention remains a possible mechanism underlying these aMCI results.

ANT PERFORMANCE IN AD

As mentioned above, Fernandez-Duque and Black [14] reviewed the ANT among younger adults, normally aging older adults, and adults with AD. Patients with AD exhibited poorer executive attention (*i.e.*, longer RT difference scores) compared with normal older adults even after controlling for general slowing. No differences were found for alerting and orienting.

Tales and colleagues [58] also conducted one of the earliest AD studies to investigate alerting and orienting but used a task similar to the ANT without the executive attention component (*i.e.*, no distracting flankers). Compared with HCs, they found that AD patients had a larger orienting effect than healthy older adults. The AD patients had similar alerting effects to HCs. Their findings contradict others who used a similar (non-ANT) task to investigate alerting and orienting [59] and found significant alerting differences between AD patients and HCs. However, no correction for general slowing was calculated and the sample sizes also were quite small (n = 15 per group).

Firbank *et al*. [60] compared performance on the ANT between normal older adults and two dementia groups: AD and a combined group of dementia with Lewy Bodies and with Parkinson's disease (referred to collectively as the LBD group). No differences in performance were found between the AD and HCs across any of the ANT measures. These null results could have been due to small sample sizes (n = 23 people per group), or due to the fact that overall slowing masked potential group effects. Indeed, the mean RTs across all trials were fastest in HCs, followed by the AD group, and slowest in the LBD group. The only difference found was a smaller executive attention effect in the LBD group compared with the HCs. The LBD group also had the largest sample size (n = 32), further suggesting that the comparison with the AD group may have had limited power. Although behavioral effects were not found between the AD and HC groups, fMRI differences during the ANT were found for the executive attention contrast. Whereas the HC group (and the LBD group) showed greater deactivation in parietal brain regions in the incongruent trials relative to the congruent trials, AD patients exhibited no such deactivation. This failure to deactivate these brain regions might impair the efficient allocation of attention [61].

Research conducted by Lu and colleagues [62] examined the ANT in a large sample (N = 204) of Chinese older adults with AD, vascular disease, and HCs. They discovered that both those with AD and vascular disease had larger (*i.e.*, poorer) executive attention effects than HCs, even when correcting for general slowing using proportion scores. Individuals with AD and vascular disease had similar alerting and orienting effects to the HCs. No significant relationships were found between the attention network components and other cognitive functions that they measured.

As mentioned in the previous section, Zhang *et al*. [55] investigated ANT performance and functional connectivity in the dorsal and ventral attentional networks. They found that AD patients performed worse on all three attentional networks than HCs. For functional connectivity, AD patients had decreased connectivity within several regions of the dorsal attentional network and the ventral attentional network, even after correcting for multiple comparisons. They found that larger alerting RT effects were associated with decreases in both the dorsal and ventral attentional networks and that larger orienting RT effects and executive attention RT effects were associated with decreases in the dorsal attentional networks. However, Zhang *et al*. [55] did not control for general slowing effects.

Overall, the findings for studies investigating ANT differences in AD were quite mixed; two of the six studies found differences in alerting, two of the six studies found differences in orienting, and three of the six found differences in executive attention (not including the fMRI effects). Most of the studies reviewed in this section had small sample sizes and did not consistently correct for general slowing effects, potentially impacting the interpretation of the results. Patients with AD also might be taking a variety of medications, which may differ by sample, thus impacting the results. Given that one study found no differences in any of the attention networks [60] in AD and another study found all three attention networks to differ in AD [55], another possibility is that different severity levels (*i.e.*, mild, moderate, severe) of AD might impact the number of attention networks impaired. The latter study [55] that found all three attention networks to differ in AD also was the only one that included patients with severe AD (mean Mini-Mental Status Exam score = 13.1). Additional studies with larger sample sizes and corrections for general age-related slowing are needed to make confident claims regarding ANT differences in AD.

CONCLUDING REMARKS

The present review clearly indicated that the majority of studies using the ANT or variants of the ANT have focused on normal aging rather than the AD trajectory. This large body of research in normal aging revealed the importance of accounting for general slowing effects when measuring different attention networks because many of the significant group effects found for the raw scores disappeared after such corrections were made. Both before and after corrections, many of the studies reviewed revealed that the benefits of temporal alerting cues diminished in old age.

These studies also hinted at an impaired executive attention effect, possibly limited to very old age. Given the prominence of theories indicating frontal lobe dysfunction in normal aging [63-67], the weakness of these executive attention effects is somewhat surprising. Two lines of evidence provide more reason to expect declines earlier in the lifespan in executive attention. First, one large scale cross-sectional study using 48,537 participants across the adult lifespan suggested that working memory measures peaked as early as the 30's [68]. Second, Redick and Engle [69] found that working memory capacity was associated with executive attention performance in the ANT (but not alerting or orienting). Of the 14 studies to investigate age-effects, six of the studies found effects of executive attention: four found impaired executive attention and two found improvements with older age. Thus, even within the studies that found normal aging effects of executive attention, the direction of the effect was not consistent, preventing us from confidently concluding that executive attention strongly declines with normal aging.

While some studies have suggested that both the alerting and executive attention networks share common brain areas of activation [70,71], the present review suggests that subtle differences likely exist in the brain regions that decline with age that are also associated with these two networks. Alternatively, older adults might be able to successfully compensate for age-related declines in executive attention [72-74], whereas alerting requires fundamental processes in which no compensatory process is readily available. This idea is consistent with age-related declines in the ability to initiate and sustain attention akin to the notion of proactive cognitive control [75,76], therefore relying more on their reactions to stimuli after a conflict is detected, known as reactive control [22,29].

In contrast to the findings from normal aging studies, studies investigating early trajectories of AD more consistently implicated deficits in executive attention. Specifically, two studies investigating groups of older adults with cardiovascular issues implicated differences in executive attention [12,38]. Many of the studies investigating aMCI, the subtype most likely to convert to AD, also implicated differences in executive attention. In contrast, other subtypes of MCI that are less likely to convert to AD (*i.e.*, subcortical vascular MCI) did not show impairments in executive attention, strengthening the specificity of these effects.

In contrast to the rather consistent effects of possible early trajectories of AD, older adults diagnosed with AD showed a variety of patterns. Because AD is a neurodegenerative disease that ultimately will affect the entire brain and each attention network, one might predict that if executive attention began showing impairments in preclinical or prodromal phases of the disease, not only would these executive attention effects be more pronounced, but they also would expand to other attention networks. In contrast to this expectation, most of the AD studies found that only one of the attention networks differed from HCs and the one network that showed deficits was equally likely to be the alerting, orienting, or executive attention network. Unlike the normal aging studies, the lessons of using large samples and correcting for general slowing were rarely passed on to the AD studies, thus limiting the conclusions that can be drawn from the AD studies. Nevertheless, given the strong trends for deficits in executive attention leading up to an AD diagnosis, it is likely that at least executive attention is selectively impaired in early phases of the disease (see right panel of Figure 2).

Two key implications can be taken from these findings. First, differences in attentional networks in AD suggest that the hallmark memory impairments likely originate, at least in part, to attentional declines that impact memory encoding in AD. Second, the different patterns of attentional impairments between normal aging and AD suggest that the ANT can be used to differentiate which older adults might be on a "normal" trajectory and which might be on a "pathological" trajectory. However, these implications should be considered within the context of limitations of the ANT. First, the alerting network has the lowest reliability of the three networks (13]). To improve reliability, the number of trials in the ANT could be increased [77]. The ANT also uses difference scores, which have been criticized for reducing reliability [77]. While this is true in some situations, it is not clear why this general notion would selectively apply to alerting and orienting, but not to the same degree as executive attention. Using RT measures (rather than accuracy) also might introduce additional error or variability [77], especially in older adults or patients with AD who show an increase in response time variability compared with younger adults [78]. Other paradigms that rely on accuracy of whole or partial reporting of visually presented objects can offer reliable and alternative measures of attention including one's perceptual threshold, visual processing speed, and tonic alertness [79]. Note that these other measures of attention do not correlate with the ANT measures [77], suggesting that they measure complementary aspects of attention and do not replace the three classes of attention in the ANT.

REFERENCES

1. Hoffman L, McDowd JM, Atchley P, Dubinsky R. The role of visual attention in predicting driving impairment in older adults. Psychol Aging. 2005;20(4):610.
2. Owsley C, McGwin G Jr. Association between visual attention and mobility in older adults. J Am Geriatr Soc. 2004;52(11):1901–6.
3. Wolfe JM. The Oxford Handbook of Attention. Oxford: Oxford University Press; 2014. pp. 35–44.
4. Fan J, McCandliss BD, Sommer T, Raz A, Posner MI. Testing the efficiency and independence of attentional networks. J Cogn Neurosci. 2002;14(3):340–7.
5. Posner MI, Rothbart MK. Research on attention networks as a model for the integration of psychological science. Annu Rev Psychol. 2007;58:1–23.
6. Bundesen C. A theory of visual attention. Psychol Rev. 1990;97(4):523–47.
7. Cowan N. Attention and memory: An integrated framework. Oxford University Press; 1998.
8. Salvucci DD, Taatgen NA. Threaded cognition: an integrated theory of concurrent multitasking. Psychol Rev. 2008;115(1):101–30.
9. Marrocco RT, Davidson MC. Neurochemistry of Attention. Cambridge: The MIT Press; 1998. pp. 35–50.
10. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci. 2002;3(3):201.
11. Duncan J, Seitz RJ, Kolodny J, Bor D, Herzog H, Ahmed A, et al. A neural basis for general intelligence. Science. 2000;289(5478):457–60.
12. Mahoney JR, Verghese J, Goldin Y, Lipton R, Holtzer R. Alerting, orienting, and executive attention in older adults. J Int Neuropsychol Soc. 2010;16(5):877–89.
13. Ishigami Y, Eskes GA, Tyndall AV, Longman RS, Drogos LL, Poulin MJ. The Attention Network Test-Interaction (ANT-I): reliability and validity in healthy older adults. Exp Brain Res. 2016;234(3):815–27.
14. Fernandez-Duque D, Black SE. Attentional networks in normal aging and Alzheimer's disease. Neuropsychology. 2006;20(2):133–43.
15. Bush L, Hess U, Wolford G. Transformations for within-subject designs: A Monte Carlo investigation. Psychol Bull. 1993;113(3):566–79.
16. Faust ME, Balota DA, Spieler DH, Ferraro FR. Individual differences in information processing rate and amount: implications for group differences in response latency. Psychol Bull. 1999;125(6):777–99.
17. Madden DJ, Whiting WL. Recent Advances in Psychology and Aging. Amsterdam: Elsevier; 2004. pp. 41–88.
18. Jennings JM, Dagenbach D, Engle CM, Funke LJ. Age-related changes and the attention network task: an examination of alerting, orienting, and executive function. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2007;14(4):353–67.
19. Gamboz N, Zamarian S, Cavallero C. Age-related differences in the attention network test (ANT). Exp Aging Res. 2010;36(3):287–305.
20. Kaufman DA, Sozda CN, Dotson VM, Perlstein WM. An event-related potential investigation of the effects of age on alerting, orienting, and executive function. Front Aging Neurosci. 2016;8:99.
21. Knight M, Mather M. Look out—it's your off-peak time of day! Time of day matters more for alerting than for orienting or executive attention. Exp Aging Res. 2013;39(3):305–21.
22. Williams RS, Biel AL, Wegier P, Lapp LK, Dyson BJ, Spaniol J. Age differences in the Attention Network Test: evidence from behavior and event-related potentials. Brain Cogn. 2016;102:65–79.
23. Zhou SS, Fan J, Lee TM, Wang CQ, Wang K. Age-related differences in attentional networks of alerting and executive control in young, middle-aged, and older Chinese adults. Brain Cogn. 2011;75(2):205–10.
24. Westlye LT, Grydeland H, Walhovd KB, Fjell AM. Associations between regional cortical thickness and attentional networks as measured by the attention network test. Cereb Cortex. 2010;21(2):345–56.
25. Young-Bernier M, Tanguay AN, Tremblay F, Davidson PS. Age differences in reaction times and a neurophysiological marker of cholinergic activity. Can J Aging. 2015;34(4):471–80.
26. Waszak F, Li SC, Hommel B. The development of attentional networks: cross-sectional findings from a life span sample. Dev Psychol. 2010;46(2):337.
27. Lu H, Fung AW, Chan SS, Lam LC. Disturbance of attention network functions in Chinese healthy older adults: an intra-individual perspective. Int Psychogeriatr. 2016;28(2):291–301.
28. Gamble KR, Howard JH Jr, Howard DV. Not just scenery: viewing nature pictures improves executive attention in older adults. Exp Aging Res. 2014;40(5):513–30.
29. Deiber MP, Ibañez V, Missonnier P, Rodriguez C, Giannakopoulos P. Age-associated modulations of cerebral oscillatory patterns related to attention control. Neuroimage. 2013;82:531–46.
30. Hedden T, Oh H, Younger AP, Patel TA. Meta-analysis of

amyloid cognition relations in cognitively normal older adults. Neurology. 2013;80(14):1341–8.
31. McDonough IM, Bischof GN, Kennedy KM, Rodrigue KM, Farrell ME, Park DC. Discrepancies between fluid and crystallized ability in healthy adults: a behavioral marker of preclinical Alzheimer's disease. Neurobiol Aging. 2016;46:68–75.
32. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):280–92.
33. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small G, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993;261(5123):921–3.
34. Slooter AJ, Cruts M, Kalmijn S, Hofman A, Breteler MM, Van Broeckhoven C, et al. Risk estimates of dementia by apolipoprotein E genotypes from a population-based incidence study: the Rotterdam Study. Arch Neurol. 1998;55(7):964–8.
35. Kaffashian S, Dugravot A, Elbaz A, Shipley MJ, Sabia S, Kivimäki M, et al. Predicting cognitive decline: A dementia risk score vs the Framingham vascular risk scores. Neurology. 2013;80(14):1300–6.
36. Farrow M. Dementia Risk Reduction: What Do Australian's Know? Alzheimer's Australia; 2007.
37. Deckers K, Boxtel MP, Schiepers OJ, Vugt M, Muñoz Sánchez JL, Anstey KJ, et al. Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. Int J Geriatr Psychiatry. 2015;30(3):234–46.
38. Gaudet J, Bélanger MF, Corriveau H, Mekary S, Hay D, Johnson MJ. Investigating the autonomic nervous system and cognitive functions as potential mediators of an association between cardiovascular disease and driving performance. Can J Physiol Pharmacol. 2013;91(5):346–52.
39. Duschek S, Matthia E, Schandry R. Essential hypotension is accompanied by deficits in attention and working memory. Behav Med. 2005;30(4):149–60.
40. Elias PK, Elias MF, Robbins MA, Budge MM. Blood pressure-related cognitive decline: does age make a difference? Hypertension. 2004;44(5):631–6.
41. Raz N, Rodrigue KM, Kennedy KM, Acker JD. Vascular health and longitudinal changes in brain and cognition in middle-aged and older adults. Neuropsychology. 2007;21(2):149.
42. Verghese J, Lipton RB, Hall CB, Kuslansky G, Katz MJ. Low blood pressure and the risk of dementia in very old individuals. Neurology. 2003;61(12):1667–72.
43. Gabin JM, Tambs K, Saltvedt I, Sund E, Holmen J. Association between blood pressure and Alzheimer disease measured up to 27 years prior to diagnosis: the HUNT Study. Alzheimers Res Ther. 2017;9(1):37.
44. Guo Z, Fratiglioni L, Winblad B, Viitanen M. Blood pressure and performance on the Mini-Mental State Examination in the very old: cross-sectional and longitudinal data from the Kungsholmen Project. Am J Epidemiol. 1997;145(12):1106–13.
45. Dickerson BC, Bakkour A, Salat DH, Feczko E, Pacheco J, Greve DN, et al. The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. Cereb Cortex. 2009;19(3):497–510.
46. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. Lancet. 2006;367(9518):1262–70.
47. Geslani DM, Tierney MC, Herrmann N, Szalai JP. Mild cognitive impairment: an operational definition and its conversion rate to Alzheimer's disease. Dement Geriatr Cogn Disord. 2005;19(5-6):383–9.
48. Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH, et al. Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol. 2001;58(3):397–405.
49. Missonnier P, Herrmann FR, Richiardi J, Rodriguez C, Deiber MP, Gold G, et al. Attention-related potentials allow for a highly accurate discrimination of mild cognitive impairment subtypes. Neurodegener Dis. 2013;12(2):59–70.
50. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment–beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med. 2004;256(3):240–6.
51. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):270–9.
52. Van Dam NT, Sano M, Mitsis EM, Grossman HT, Gu X, Park Y, et al. Functional neural correlates of attentional deficits in amnestic mild cognitive impairment. PLoS One. 2013;8(1):e54035.
53. Jeyakumar SL, Warriner EM, Raval VV, Ahmad SA. Balancing the need for reliability and time efficiency: Short forms of the Wechsler Adult Intelligence Scale-III. Educ Psychol Meas. 2004;64(1):71–87.
54. Lv S, Wang X, Cui Y, Jin J, Sun Y, Tang Y, et al. Application of attention network test and demographic information to detect mild cognitive impairment via combining feature selection with support vector machine. Comput Methods Programs Biomed. 2010;97(1):11–8.
55. Zhang Z, Zheng H, Liang K, Wang H, Kong S, Hu J, et al. Functional degeneration in dorsal and ventral attention systems in amnestic mild cognitive impairment and Alzheimer's disease: an fMRI study. Neurosci Lett. 2015;585:160–5.
56. Martella D, Manzaneres S, Campoy G, Roca J, Antunez C, Fuentes LJ. Phasic and tonic alerting in mild cognitive impairment: a preliminary study. Exp Gerontol. 2014;49:35–9.
57. Fernández PJ, Campoy G, Santos JM, Antequera MM, García-Sevilla J, Castillo A, et al. Is there a specific pattern of attention deficit in mild cognitive impairment with subcortical vascular features? Evidence from the Attention Network Test. Dement Geriatr Cogn Disord. 2011;31(4):268–75.

58. Tales A, Snowden RJ, Brown M, Wilcock G. Alerting and orienting in alzheimer's disease. Neuropsychology. 2006;20(6):752–6.
59. Festa-Martino E, Ott BR, Heindel WC. Interactions between phasic alerting and spatial orienting: effects of normal aging and Alzheimer's disease. Neuropsychology. 2004;18(2):258–68.
60. Firbank M, Kobeleva X, Cherry G, Killen A, Gallagher P, Burn DJ, et al. Neural correlates of attention-executive dysfunction in lewy body dementia and Alzheimers disease. Hum Brain Mapp. 2016;37(3):1254–70.
61. Leech R, Kamourieh S, Beckmann CF, Sharp DJ. Fractionating the default mode network: distinct contributions of the ventral and dorsal posterior cingulate cortex to cognitive control. J Neurosci. 2011;31(9):3217–24.
62. Lu H, Chan SS, Fung AW, Lam LC. Efficiency of attentional components in elderly with mild neurocognitive disorders shown by the attention network test. Dement Geriatr Cogn Disord. 2016;41(1-2):93–8.
63. Albert MS, Kaplan E. New directions in memory and aging: Proceedings of the George A. Talland Memorial Conference. Hillsdale, NJ: Lawrence Erlbaum Associates; 1980. p. 403-429.
64. Dempster FN. The rise and fall of the inhibitory mechanism: toward a unified theory of cognitive development and aging. Dev Rev. 1992;12(1):45–75.
65. Fuster JM. The prefrontal cortex: Anatomy, physiology and neuropsychology of the frontal lobe. New York: Raven; 1989.
66. Raz N, Gunning FM, Head D, Dupuis JH, McQuain J, Briggs SD, et al. Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. Cereb Cortex. 1997;7(3):268–82.
67. West RL. An application of prefrontal cortex function theory to cognitive aging. Psychol Bull. 1996;120(2):272–92.
68. Hartshorne JK, Germine LT. When does cognitive functioning peak? The asynchronous rise and fall of different cognitive abilities across the life span. Psychol Sci. 2015;26(4):433–43.
69. Redick TS, Engle RW. Working memory capacity and attention network test performance. Applied Cognitive Psychology: The Official Journal of the Society for Applied Research in Memory and Cognition. 2006;20(5):713–21.
70. Fan J, Gu X, Guise KG, Liu X, Fossella J, Wang H, et al. Testing the behavioral interaction and integration of attentional networks. Brain Cogn. 2009;70(2):209–20.
71. Fan J, Kolster R, Ghajar J, Suh M, Knight RT, Sarkar R, et al. Response anticipation and response conflict: an event-related potential and functional magnetic resonance imaging study. J Neurosci. 2007;27(9):2272–82.
72. Cabeza R, Anderson ND, Locantore JK, McIntosh AR. Aging gracefully: compensatory brain activity in high-performing older adults. Neuroimage. 2002;17(3):1394–402.
73. Park DC, McDonough IM. The dynamic aging mind: revelations from functional neuroimaging research. Perspect Psychol Sci. 2013;8(1):62–7.
74. Stern Y, Habeck C, Moeller J, Scarmeas N, Anderson KE, Hilton HJ, et al. Brain networks associated with cognitive reserve in healthy young and old adults. Cereb Cortex. 2005;15(4):394–402.
75. Braver TS. The variable nature of cognitive control: A dual mechanisms framework. Trends Cogn Sci. 2012;16(2):106–13.
76. Paxton JL, Barch DM, Racine CA, Braver TS. Cognitive control, goal maintenance, and prefrontal function in healthy aging. Cereb Cortex. 2007;18(5):1010–28.
77. Habekost T, Petersen A, Vangkilde S. Testing attention: comparing the ANT with TVA-based assessment. Behav Res Methods. 2014;46(1):81–94.
78. Hultsch DF, MacDonald SW, Dixon RA. Variability in reaction time performance of younger and older adults. J Gerontol B Psychol Sci Soc Sci. 2002 Mar;57(2):101–15.
79. Wiegand I, Petersen A, Bundesen C, Habekost T. Phasic alerting increases visual attention capacity in younger but not in older individuals. Vis Cogn. 2017;25(1-3):343–57.