Integrating Health into Cognitive Aging: Toward a Preventive Cognitive Neuroscience of Aging

Avron Spiro III1,2,3 and Christopher B. Brady1,4,5

1Massachusetts Veterans Epidemiology Research and Information Center, VA Boston Healthcare System, Massachusetts, 2Department of Epidemiology, Boston University School of Public Health, Massachusetts.
3Department of Psychiatry, 4Department of Neurology, and 5Department of Behavioral Neuroscience, Boston University School of Medicine, Massachusetts.

Objectives. We argue that age is a descriptive, and not explanatory, variable and consequently cannot account for the cognitive changes that often occur with aging. Once age is removed from consideration, other truly causal explanations for “cognitive aging” must be identified. We argue that health and disease represent an important class of explanatory variables for age-related cognitive changes.

Methods/Results. We make this argument first by reviewing the prevalence of risk factors, disability, and subclinical and frank disease in the elderly population. We emphasize that the complexity of health effects rivals that of age on cognition while noting that most studies of cognitive aging rarely consider this complexity fully. We then consider in more detail the “vascular hypothesis,” which proposes that vascular diseases (e.g., stroke, heart disease) and their risk factors (e.g., hypertension) can explain aspects of cognitive decline in aging through their impact on circulatory and brain functions. Clinical implications of this hypothesis suggest that treatment of vascular risk factors might well reduce the incidence or severity of dementia syndromes.

Discussion. We conclude with a brief summary of approaches to further integrate aspects of health and disease into the study of “cognitive aging.”

Key Words: Alzheimer’s disease—Cardiovascular disease—Cognition—Epidemiology—Health.

INTEGRATING HEALTH INTO COGNITIVE AGING

In this article, we present the following argument. First, age is not an explanatory variable; thus, it alone cannot account for “cognitive aging” or the frequently observed declines in cognitive functions that occur as people age. Second, if age is no longer an acceptable explanation, we suggest health be considered in its place. We offer several reasons why health is a viable candidate, including the increase of chronic diseases and debilitating conditions that occur among older persons and offer an overview of medical and epidemiological evidence linking health to cognitive decline. Finally, we suggest some ways in which to pursue the health–cognition link in future studies. In conclusion, we agree with Finch’s statement, “The era is ending when cognitive aging could be honestly studied without considering the detailed medical history of each individual (Finch, 2009, p. 518, emphasis in original).”

AGE IS DESCRIPTIVE, NOT EXPLANATORY

Forty years ago, Wohlwill (1970) proposed a radical revision of the role of age in developmental research, suggesting that it was better viewed as a dependent rather than an independent variable. That is, age is an axis for describing changes in behavior rather than a mechanism for explaining them. In his words, age was “a dimension along which temporal changes in behavior are charted (p. 49, emphasis in original).” Wohlwill’s argument was based on the study of child development but is more broadly applicable. Peto and Doll (1997) argued that “There is no such thing as aging (p. 1030).” More recently, Kannel and Vasan (2009) argued that age is not a cause of heart disease but rather a marker for the accumulation of influences across a lifetime.

These authors all agree that age is not a causal variable but is instead a temporal axis along which various exposures and disease processes operate. What we claim, based on these arguments, is that the simple fact of aging (i.e., growing older with time) is not a meaningful explanation for why one might experience cognitive decline, impairment, or dementia. The fact that age may be a strong and robust predictor of dementia, for example, says little; using age as an explanation “is merely a cloak for our ignorance (Wohlwill, 1970, p. 50).”

PSYCHOLOGICAL EXPLANATIONS FOR COGNITIVE AGING

Most current psychological accounts of cognitive “aging” suggest that other psychological or behavioral processes account for changes (usually, declines) observed with aging (cf. Craik & Salthouse, 2008; Dixon, Bäckman, & Nilsson, 2004; Hofer & Alwin, 2008). These include sensory declines (Baltes & Lindenberger, 1997), decreased inhibition (Hasher & Zacks, 1988), resource reduction (general slowing; working memory limitations; e.g., Hasher & Zacks, 1988; Salthouse, 1991), and declines in executive functioning (West, 1996). However, these accounts seem limited in that
they generally leave open the question of what accounts for
decline with age in the proposed explanatory process. That is,
if declines in speed or sensory function account for cog-
nitive declines with age, then what in turn accounts for de-
clinies in these variables?

Cognitive neuroscience (Cabeza, Nyberg, & Park, 2005;
Reuter-Lorenz & Park, 2010) has begun to identify poten-
tial neurological substrates for some cognitive changes with
age. In part, by positing brain changes that account for cog-
nitive changes, this approach has begun to move beyond the
focus on a single level or category of explanation, that is,
other behavioral processes. Cognitive neuroscience also
seems to recognize that single-level theories are insufficient
and that multiple levels (e.g., genetic, physiological, behav-
ioral, social) are required for any comprehensive account of
cognitive change. However, much about brain changes re-
 mains to be explained; we cannot ignore the fact that the
aging brain is encased in an aging body. If there is no
“cognitive aging,” there can likewise be no “brain aging”—
something else is required to explain these age-related
changes in mind, brain, and body.

We note that cognition (1) can be considered from differ-
ent perspectives (e.g., psychometric, neuropsychological)
and (2) is clearly multidimensional whether one considers
psychometric abilities or neuropsychological functions.
Furthermore, not all aspects of cognition decline nor does
it seem to “all go together when it goes” (Rabbitt, 1993).
Some aspects of cognition increase across adulthood,
whereas others begin to decline after adolescence (cf.
Salthouse, 2009 and related commentary; Schaie, 2005).
Finally, there is a good deal of variability among persons in
how and when cognitive domains change with age, and
within persons, there is evidence of plasticity (i.e., some old
dogs can learn new tricks).

Health as a Potential Explanation for
Cognitive Aging

What Is Health?

When we use the term “health,” we also include disease;
we view these as ends of a continuum which we choose to
refer to by the term “health.” We can define health in terms
of various dimensions and modes of measurement. For ex-
ample, among dimensions (or levels) of health, consider the
following (Spiro 2001, 2007; Spiro & Brady, 2008):

1. tissue alterations (e.g., atherosclerosis, carcinoma),
2. laboratory assays or physiological parameters (e.g., glu-
cose, cholesterol),
3. records produced by physiologic measuring equipment
   (e.g., electrocardiogram, functional neuroimaging),
4. clinical judgments (e.g., physician diagnoses),
5. self-reports, and
   a. diagnoses (e.g., My doctor told me I’ve had a stroke)
   b. observable symptoms (e.g., rash, lumps)
6. self-ratings
   a. global items (e.g., How would you rate your health?)
   b. multidimensional measures (e.g., SF-36; [Ware &
      Sherbourne, 1992]).

Other aspects of health include the complete lack thereof,
often known as mortality. For persons closer to the disease
rather than health end of the continuum, we must acknowl-
dge and assess the treatment of various diseases, condi-
tions, and symptoms, including the use of medications or
supplements, surgery, anesthesia, or radiation and chem-
otherapy, most of which are likely to affect the brain and its
mind in one way or another.

To some extent, each of these levels is related to an
assessment mode, ranging from laboratory or recording
equipment, through expert judgment, to self-reports or rat-
ings made by the individual. Also, with increasing use of
electronic health records, population registries, etc., admin-
istrative data include a good deal of health information and
can be considered an additional measurement category.

When we consider the intersection of health dimensions
and measurement sources, we find that some information
can only be obtained from selected sources. For example,
laboratory assays and physiological measures are obtained
by recording devices (e.g., a sphygmomanometer for blood
pressure), but the results can be recorded in administrative
data or reported to a physician who then informs the patient
who could in turn self-report the results to an interviewer.
Self-reports or ratings of symptoms or of health status can
only be provided by a patient. Some measures of health can
be reported by an observer or informant, but more “objective”
in the sense of observable health measures show better
agreement between patient and observer (or administrative
data) than do subjective symptoms (e.g., Miller et al., 2008;
Okuda et al., 2004). Thus, if relying on an observer, it is
more reliable to have them assess observable behaviors
rather than subjective symptoms or feelings.

Health of the Elderly

The elderly (those aged 65 years and older) have a num-
ber of health issues. These include elevations in numerous
risk factors for disease; higher prevalence of diseases
(whether chronic, acute, or subclinical); poor diagnosis,
treatment, and control of diseases; sensory limitations; and
widespread use of medications.

Risk factors are elevated among older people, as Table 1
shows. High blood pressure is the norm among men and af-
flicts about half of women. About half are physically inac-
tive and over two thirds are overweight. Over half of men
and a third of women are current drinkers.

Table 2 shows that many elders have a variety of diseases
or conditions, including heart disease (a third of men and a
In addition to the high prevalence of disease and impairment, many elderly are unaware that they have chronic conditions such as hypertension or diabetes (McDonald, Hertz, Unger, & Lustik, 2009). Among the roughly three quarters who are aware, a third to half do not receive treatment; among those treated, only half have their condition under control (see Table 3).

Subclinical diseases are common among the elderly. Among those with no history of cardiovascular disease (CVD), 37% had subclinical CVD. Among those without known prior strokes, 28% had magnetic resonance imaging indications of silent infarcts. Silent infarcts are 10–20 times more prevalent than are clinical strokes (Black, Gao, & Bilbao, 2009) and are associated with greater risk of subsequent clinical stroke (Chaves, Kuller, O’Leary, Manolio, & Newmark, 2004) as well as with impaired cognition (Vermeer, Longstreth, & Koudstaal, 2007).

Medication use is also common among elders, with 89% reporting at least some use (Safran et al., 2005). Among those taking medications, the average number is 4.7. Despite this, many do not follow their medication regimen for a variety of reasons including cost, adverse side effects, or the mistaken belief that their condition has improved.

Data such as these suggest that there is a great deal of disease and impairment, often unrecognized or inadequately treated, among the elderly. If a sample is recruited, screened for good health, and those with disease are excluded, then that sample likely would no longer be representative of the elderly population nor would the sample be as healthy as the investigator might suppose given the burden of subclinical disease. If a representative sample of elderly is selected, then health status is likely to vary among persons, and this should be carefully considered. Thus, to truly understand the health of a sample requires a careful and thorough assessment. However, as noted some years ago, health screening in cognitive aging research is largely reliant on self-reports (Poon, Krauss, & Bowles, 1984; Christensen, Moyle, Arisman, & Kern, 1992). Although some have made efforts to assess health more thoroughly, many studies continue to rely on self-ratings of health, whereas others ignore health completely.

The value of self-reported health (in contrast to self-ratings) rests on several events (1) that the participant has been told by a medical provider that they have a condition, (2) they can recall the diagnosis, and (3) they are willing to report it to researchers. Although self-reports can provide reliable and valid information regarding health, they require a specific approach (e.g., a checklist asking about physician diagnoses; Christensen et al., 1992) rather than asking for self-ratings of general health. Self-reports of chronic diseases with objective symptoms or ongoing management issues are more likely to agree with medical records than are asymptomatic diseases that do not require ongoing management (e.g., Miller et al., 2008; Okura, Urban, Mahoney, Jacobsen, & Rodenheffer, 2004). As noted previously, self-reports are neither comprehensive nor reliable and can be especially misleading among those who are unaware that they have a disease or condition. And sometimes participants fail to report the presence of a disease (e.g., hypertension or diabetes) because its being treated (whether or not

<table>
<thead>
<tr>
<th>Disease or condition</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>37</td>
<td>26</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>Stroke</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>Arthritis</td>
<td>43</td>
<td>54</td>
</tr>
<tr>
<td>Impairment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trouble hearing</td>
<td>48</td>
<td>35</td>
</tr>
<tr>
<td>Trouble seeing</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Global rating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fair/poor self-rated health</td>
<td>26</td>
<td>26</td>
</tr>
</tbody>
</table>

Table 2. Prevalence of Selected Health Indicators Among U.S. Adults Aged 65+ Years (percent)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current drinker</td>
<td>54</td>
<td>36</td>
</tr>
<tr>
<td>Former drinker</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>Lifetime abstainer</td>
<td>19</td>
<td>42</td>
</tr>
<tr>
<td>5 or more drinks/day</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Physically inactive</td>
<td>47/52</td>
<td>49/64</td>
</tr>
<tr>
<td>Overweight</td>
<td>78/66</td>
<td>70/63</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>71/80</td>
<td>41/55</td>
</tr>
</tbody>
</table>

Table 1. Prevalence of Risk Factors Among U.S. Adults Aged 65+ Years (percent)

<table>
<thead>
<tr>
<th>Disease, U.S. Adults Aged 65+ Years (percent)</th>
<th>Hypertension</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>71</td>
<td>21</td>
</tr>
<tr>
<td>Awareness</td>
<td>76</td>
<td>71</td>
</tr>
<tr>
<td>Treatment</td>
<td>69</td>
<td>51</td>
</tr>
<tr>
<td>Control (among treated)</td>
<td>49</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 3. Prevalence, Awareness, and Management of Chronic Disease, U.S. Adults Aged 65+ Years (percent)

Note: Data from Federal Interagency Forum on Aging-Related Statistics (2008).
the treatment actually controls the condition) and they consider themselves “cured.” Although it is easy to assess health by asking respondents to provide reports or ratings, self-reports can be inaccurate, for example, when they result in misclassification of diseased (but as yet undiagnosed) persons as healthy. As the data presented above suggest, many elderly have conditions or diseases that have not been diagnosed or which they otherwise fail to report. It is unclear whether it would be better to forgo reliance on self-reports or to use them while recognizing the possibility that they are subject to classification error.

**WHY SHOULD WE CONSIDER HEALTH IN COGNITIVE AGING?**

What are the consequences of failing to assess health in cognitive aging research and what are the implications for cognitive aging theory? First and foremost, failure to assess health means that it cannot be a potential explanation for cognitive changes, and other variables must be considered. In other words, health becomes a “hidden variable,” one which despite being unmeasured, likely has an influence on the outcome. Failing to measure health or measuring it poorly can lead to ignoring a source of variability among persons, and misattributing this variability to measured variables (e.g., age, gender, education, race) that are correlated with health. Thus, the effects of these variables on the outcomes are misspecified by the omission of health measures; if health is present but measured poorly (e.g., with self-ratings), then its effects on the outcome are also likely misspecified (Mauro, 1990).

Given that health and age are often related and that age is usually measured in cognitive aging studies whereas health is not, some of the variance in cognition that is actually due to health can be misattributed to age. Thus, when health is either omitted or measured poorly, the role of age in cognitive change can be overestimated (e.g., Mauro, 1990). As Box (1979) noted, “all models are wrong, but some are useful (p. 204).” Arguably, theoretical and statistical models that omit important explanatory variables are not useful; in fact, they may be worse than wrong because they are misleading. As Mark Twain said, “It ain’t what you don’t know that gets you into trouble. It’s what you know for sure that just ain’t so.”

By failing to consider health, many studies have accumulated a good deal of data that likely overestimate the role of age in cognitive change while ignoring the likely role of health. Thus, what we think we “know” about age as an explanation for cognitive changes may well have gotten us into trouble by ignoring health, aspects of which are potentially modifiable. Whether one should include age (or other temporal metrics) in an analytic model is debatable. Including it can help account for some of the residual variance in cognitive outcomes, but the key question is whether or not age plays a theoretical role in the underlying explanatory model of cognition (Shmueli, 2010).

When health is assessed, even perfunctorily using self-reports or self-ratings, one can use these measures in a variety of ways. For example, self-reports can be used to exclude certain participants (e.g., those who report a history of stroke, recent anesthesia, psychiatric disorders) or self-ratings can characterize the “health” of a sample (e.g., Salthouse, 2009). Another use for health information is to include it in a statistical model to adjust for the fact that some people are healthier than others and to take such differences into account in predicting their cognitive performance (e.g., Van Dijk, Van Gerven, Van Bokel, Van der Elst, & Jolles, 2008). However, to the extent that self-reported health information is used, it is likely to misestimate the true effects of health and lead to an overemphasis on the effects of other covariates (e.g., age) on the outcomes.

A final use for health is to consider it as an explanation for differences in cognitive performance. There are at least two ways in which this can be done. Many studies have compared the performance of those with and without a given disease (Waldstein & Elias, 2001). For example, Albert and colleagues (2009) compared performance on word retrieval tasks between those with and without hypertension or type 2 diabetes (and also examined the impact of diagnosis, treatment, and control of these conditions on the outcomes). Alternatively, one can model explicitly the effects of various diseases on cognitive performance (Spiro & Brady, 2008). This requires some sophistication in characterizing diseases because one can consider prevalent or incident disease, disease severity, or the effects of treatments for a given disease (e.g., classes of medication for treating hypertension can affect different cognitive parameters; Shah et al., 2009). One can examine individual diseases or create an index such as a count of the number of diseases/conditions reported (Svedberg, Gatz, & Pedersen, 2009) or a latent variable (MacDonald, Dixon, Cohen, & Hazlitt, 2004) and examine the association between this measure and cognitive outcomes.

What we argue for is something more than these approaches. We implore investigators to consider health not as a nuisance or a covariate to be adjusted nor as descriptive variable used to select or characterize a sample in cognitive aging research. Rather, we urge investigators to view health as a key explanatory domain in cognitive aging theory. That is, differences in health can account for differences in cognitive functions among, and within, people over time. Furthermore, different diseases can affect different cognitive functions, as can different treatments of a given condition. We need to move the study of cognitive aging from describing the health of a sample, beyond identifying and assessing potential health risk factors, to developing theories about the causal pathways through which different aspects of health affect cognitive changes (Kuller, 2006; Kuller & Lopez, 2008).

This can best be done by forging interdisciplinary collaborations with physicians, epidemiologists, and others trained in assessing health and disease (e.g., Spiro & Brady, 2008).
THE VASCULAR HYPOTHESIS OF COGNITIVE AGING

To this end, we offer both a general and a specific hypothesis about the role of health in cognitive aging. The general hypothesis is that diseases in their various aspects (e.g., incidence, severity, rate of progression, treatment) account for a substantial portion of the variation among people in the cognitive declines that occur with aging. The corollary of this general hypothesis is that by preventing, reducing, or treating diseases or by slowing their progression, we could reduce the extent and rate of these declines.

The specific hypothesis, the “vascular hypothesis” (Casserly & Topol, 2004; de la Torre, 2002, 2004; Kuller, 2006; O’Brien et al., 2003; Raz & Rodrigue, 2006; Spiro & Brady, 2008), is that vascular diseases, as well as vascular risk factors, affect the brain as well as the heart; through their effects on the brain, specific cognitive functions are affected. The corollary of this hypothesis is that prevention and treatment of vascular diseases could reduce the magnitude of cognitive declines with aging. Vascular diseases include stroke, myocardial infarctions, and atherosclerosis; vascular risk factors include physiological parameters such as elevated levels of blood pressure, glucose, and cholesterol; behavioral factors such as alcohol and tobacco consumption, lack of activity (cognitive, physical, social), and obesity; and genetic factors such as apolipoprotein E (APOE).

We recognize, but do not consider here, the role of pathophysiologic mechanisms that could explain vascular as well as other diseases and indeed aging itself, such as lipid metabolism, inflammation, and oxidative stress (Casserly & Topol, 2004; Hughes & Ganguli, 2009; Napoli & Palinski, 2005; Roriz-Filho et al., 2009). Enhancing our understanding of these and related mechanisms underlying multiple disease processes will clearly enhance our ability to diagnose, prevent, and treat cognitive declines, but (1) we are a long way from understanding these mechanisms and (2) observational epidemiological studies are not the optimal way to study them.

In the past decade, a growing body of research suggests that Alzheimer’s disease (AD) is a vascular disease (Casserly & Topol, 2004; de la Torre, 2002; Launer, 2002). If true, this might explain why there is a good deal of overlap between cases of Alzheimer’s and vascular dementias despite differing diagnostic criteria, and why treatments for AD have been less than successful because they may have targeted correlates rather than causes of AD. If AD is vascular in origin, it provides a rationale for detecting and treating vascular disease earlier in life (de la Torre, 2010), with a dual objective of preventing brain as well as heart disease.

If the vascular hypothesis of cognitive aging is correct, then we should consider three questions about the relations between health and cognition:

1. Do vascular risk factors predict cognitive outcomes (including decline, impairment, and dementia)?
2. Does treatment or control of vascular risk factors reduce cognitive decline?
3. Does prevention of vascular disease prevent or slow cognitive decline?

The epidemiological evidence for the first question seems quite clear, with numerous studies concluding that vascular risk factors predict cognitive decline, impairment, and dementia (see reviews by Duron & Hanon, 2008; Hughes & Ganguli, 2009; Kloppenborg, van den Berg, Kappelle, & Biessels, 2008; van den Berg, Kloppenborg, Kessels, Kappelle, & Biessels, 2009; Roriz-Filho et al., 2009). The vascular risk factors examined include three types: genetic factors (e.g., APOE), which can act as modifiers (Duron & Hanon, 2008); medical factors (e.g., diseases such as hypertension or diabetes, syndromes or conditions such as the metabolic syndrome, and physiological risk factors such as high lipids); and behavioral factors (e.g., health risk behaviors such as tobacco or alcohol use, obesity, poor diet, low physical, social or cognitive activity). Many of these are widely recognized as affecting vascular health and have long been known as risk factors for vascular dementia but are increasingly recognized as risk factors for AD (Breter, 2000; Casserly & Topol, 2004; de la Torre, 2004; Launer, 2002; Staessen, Richart, & Birkenhager, 2007).

For the second question, the evidence is less clear; although prospective observational studies suggest that individuals with treated vascular risk factors show less cognitive decline, impairment, or dementia, most randomized controlled trials (RCTs) fail to show treatment effects on cognition. For example, hypertension can affect cognitive functions by increasing risk of infarcts, transient ischemic attacks, strokes, and white matter hyperintensities; by reducing brain volume and blood flow; and by altering white matter pathways (Gorelick, 2005). Although a number of observational studies suggest that treatment for hypertension reduces some cognitive declines, the Cochrane Collaborative review of RCTs suggests there is “no convincing evidence” from trials of blood pressure lowering medications on reducing cognitive decline or dementia (McGuinness, Todd, Passmore, & Bullock, 2006).

Likewise, observational studies of diabetes show negative effects on cognitive outcomes related to severity and time since diagnosis (Kloppenborg et al., 2008; Roriz-Filho et al., 2009; van den Berg et al., 2009), but few RCTs have examined the impact of treating diabetes on cognition in the elderly. A Cochrane review of RCTs for diabetes concluded that “no studies were found to be appropriate” for review (Grimley Evans & Areosa Sastre, 2009), so no conclusions could be drawn whether treating it reduces cognitive decline or incidence of dementia. A similar situation exists with respect to use of statins for treating high cholesterol; observational studies show protective effects that are not found in RCTs (Haan, 2010; McGuinness, Craig, Bullock, & Passmore, 2009; Muangpaisan et al., 2010).

There are a number of reasons why observational studies and RCTs disagree (Coley et al., 2008). First, with the
exception of trials focused on AD, most RCTs consider cognition as a secondary outcome and instead are designed to evaluate the effects of an intervention on a disease outcome. Second, observational studies tend to enroll healthy participants in midlife and follow them as they develop chronic diseases, whereas trials often enroll older persons who have a disease, often at an advanced stage. Most trials allow the intervention only a short time (perhaps a few years) to have an impact, whereas many observational studies have found that risk factors measured in midlife predict cognitive outcomes 10 or 20 years later. Thus, most risk factors caused damage much earlier, whereas most RCTs are initiated too late in life to mitigate the damage. Third, RCTs focus on treating a single disease and usually enroll participants free from other chronic diseases; thus, they are highly selected and may be unrepresentative of the elderly in general who often have multiple diseases and conditions. On the other hand, RCTs do a better job than observational studies in minimizing pre-existing differences among groups by means of random assignment to conditions. They also control more fully the exposure or treatment in question, allowing more unambiguous inferences regarding its effects.

As for the third question, few studies have considered whether prevention of vascular diseases enhances cognitive outcomes. One limitation is that this approach requires a relatively long-term study that would identify persons at risk of CVD, attempt to prevent CVD (which typically takes years to manifest), and then determine whether cognitive outcomes are affected. Deschaintre, Richard, Leys, and Pasquier (2009) conducted an observational study in a French clinic of 301 consecutive patients with AD but free from CVD. They compared treatment of none, some, or all of several vascular risk factors (high blood pressure, dyslipidemia, diabetes, smoking, and atherosclerotic disease) and used random effects regression to examine change in Mini-Mental State Examination (MMSE) scores. Those who were treated for all vascular risk factors showed the least decline in MMSE scores over 30 months, whereas those not treated showed significantly greater decline. A similar study is underway by Richard and colleagues (2009) in the Netherlands.

TOWARD A PREVENTIVE COGNITIVE NEUROSCIENCE OF AGING

One clear implication of the vascular hypothesis is that a focus on vascular factors offers a pathway toward identifying those at risk for cognitive declines, who could benefit from early intervention (Kivipelto & Solomon, 2009; Sacco, 2007), which is largely lacking at this time with respect to Alzheimer’s dementia. The studies addressing the three questions posed above about the relations between health and cognition suggest that we have a good deal to learn from preventive cardiology, which has a long history of identifying at-risk patients, initiating treatment, and reducing the impact of disease. Given that similar risk factors are involved in both heart and brain disease, it would seem there is much we can learn from cardiology as we seek to reduce the impact of neurodegenerative brain disorders (including stroke and dementia) in aging persons in an increasingly aging society.

We should move from a focus on dementia as an event that begins with a diagnosis and consider it instead a possible end stage in a long pathophysiological process that begins in midlife with a “brain at risk” (Hachinski, 2007). We need to identify patients at risk of cognitive declines and then initiate treatment to reduce risk factors and hopefully delay the onset and progression of disease. Once a dementia diagnosis is given, it’s far too late for prevention and remediation is at best only partially successful. Preventive cardiology has clearly shown that early identification and risk reduction are key.

To be successful in risk identification, we should follow preventive cardiology, which has a history (Bitton & Gaziano, 2010) of developing cardiovascular risk indices (Cooney, Dudina, & Graham, 2009). These are based on measures generally available in clinical practice and have been used to identify and initiate treatment among those at risk of heart disease. One approach that cognitive aging researchers could adopt is to examine the relations between cardiovascular risk measures and cognitive outcomes. Thus, we (Brady, Spiro, McGlinchey-Berroth, Milberg, & Gaziano, 2001) and others (Llewellyn et al., 2008) have used the Framingham Stroke Risk Profile (FSRP; D’Agostino, Wolf, Belanger, & Kannel, 1994), which assesses 10-year risk of stroke, to predict cognitive function and found that those with higher FSRP scores have worse performance on some cognitive tasks. A second approach (Barnes et al., 2009; Kivipelto et al., 2006; Reitz et al., 2010) is to develop indices predicting risk of cognitive decline or dementia, but those currently available may be limited by their inclusion of measures that may be difficult to obtain in general practice (Barnes & Yaffe, 2009; Stephan, Kurth, Matthews, Brayne, & Dufouil, 2010). This may still prove a useful strategy, and its development should be encouraged; cardiovascular risk indices have been under development for over 40 years (Bitton & Gaziano, 2010).

Another lesson from preventive cardiology is that clear definition of the outcome is necessary; thus, it is important to specify the cognitive outcome under study, whether it is normal decline, impairment, or dementia. Whether these outcomes are distinct or are various points on the spectrum of the brain at risk (Hachinski, 2007) must be considered; this is one reason for growing interest in the notion of “vascular cognitive impairment” (O’Brien et al., 2003) to characterize this continuum and its likely causes. Hachinski (2008) goes so far as to claim “The concept of dementia is obsolete (p. 2172)”; he proposes to replace it with a focus on the continuum of cognitive impairment rather than on an arbitrary threshold that must be crossed to yield a diagnosis.
Such a revised view, he argues, would lead to earlier identification and treatment of persons at risk, rather than waiting until symptoms are present and its likely too late for prevention or remediation to be effective. A similar perspective has been adopted in the CVD domain by the Framingham Study, which has moved from assessing risk of specific CVD outcomes (e.g., coronary heart disease, stroke, hypertension) to considering general cardiovascular risk that combines these various conditions and allows estimation of “vascular age” (D’Agostino et al., 2008), which indicates how much earlier vascular disease appears in a case compared with a non-case. Does it make sense for cognitive agers to develop indices of general cognitive risk (rather than conversion to dementia for example) and consider assessing “cognitive age” as a basis for intervention? If the vascular hypothesis is correct, it would seem useful to pursue the analogy with work in cardiovascular risk estimation. Learning how to predict (which is not the same as to explain; Shmueli, 2010) vascular diseases in the heart (Vasan & Kannel, 2009) would seem to have implications for predicting vascular diseases in the brain. If prediction is successful, whether or not it provides explanatory value, it can lead to earlier identification of those at risk for cognitive declines who might benefit from reduction of vascular risk factors. Thus, treating the heart as well as the brain is likely to reduce morbidity and mortality and may reduce the current lifetime risk of stroke or dementia, which is estimated to be one in three (Seshadri & Wolf, 2007).

SUMMARY

In this article, we have argued that age is not a causal variable and cannot be viewed usefully as a basis for understanding cognitive changes. In its place, we suggest an enhanced consideration of health and disease. This emphasis on health is supported by growing evidence from the cognitive neuroscience of aging with its focus on understanding neural substrates of cognitive processes. Furthermore, prospective epidemiological studies indicate that there is substantial variability in health among older persons and that numerous aspects of health are associated with cognitive outcomes. Combined with neurological evidence, the “vascular hypothesis” suggests that vascular conditions are responsible for a substantial portion of cognitive decline, impairment, and dementia. If true, this suggests that there is much to learn from cardiovascular prevention that can be applied to the identification and treatment of risk factors for cognitive changes with age.

To implement a preventive science of cognitive aging, we need to reconsider the way we conduct our research. To identify predictive factors that alter cognitive outcomes, we must first clearly define the outcomes; the recent reconsiderations proposed by the DSM-5 workgroup on neurocognitive disorders and by National Institute on Aging and the Alzheimer’s association suggest that the criteria for dementia are in need of revision. Of more concern is the question of the etiology of dementia and whether Alzheimer’s is a vascular or a neurodegenerative disease. The introduction of mild cognitive impairment is an attempt to move the diagnosis of dementia earlier into life in order to begin treatment sooner. However, rather than creating a new diagnosis that can be given earlier, it may be more useful to consider Hachinski’s (2007) notion of the “brain at risk” and recognize that such risk begins long before symptoms may become evident. In this respect, there is much we can learn from the success of preventive cardiology in how to identify at-risk patients and how to treat them to reduce their risk of disease later in life. By clearly defining our outcomes, developing risk indices that predict these outcomes and by initiating treatment earlier in those identified at risk, we have an opportunity to develop a preventive science of cognitive aging and to reduce the growing burden of cognitive declines in aging. Obviously, we have failed to date in our attempts to cure AD.

A second requirement for implementing this preventive science is to enhance our measurement of health. Although self-report measures may be better than ignoring health completely, it is likely that their failure to adequately measure health leads to a substantial misunderstanding of the relative roles of age and health in cognitive change. As Finch (2009) claimed, our science should be mature enough to recognize that ignorance of the health of our samples is unacceptable. Although there may be other causes of cognitive changes than health, it seems clear that age per se does not play a causal role. Once we accept this as fact, then we can truly begin to understand the causes of cognitive changes and begin to prevent and treat them.

FUNDING

This paper was supported in part by Merit Review and Research Career Scientist awards from the Clinical Science Research and Development Service, U.S. Department of Veterans Affairs to the first author and by grants R01-AG014345 and R01-AG018436 from the National Institute on Aging.

ACKNOWLEDGMENTS

We thank Martin L. Albert, MD, PhD, J. Michael Gaziano, MD, MPH, and Pandel Vokonas, MD, for many useful discussions with us on these and related topics over the past few years. A. Spiro would like to thank the Center for Healthcare Evaluation at VA Palo Alto Healthcare System, Menlo Park, CA, and the Center for Advanced Study in the Behavioral Sciences, Stanford, CA, for their support while working on this paper. Versions of this paper have been presented at the conference on Cognition, Health & Aging: Integrating Cross-Disciplinary Perspectives. University Park, PA (October, 2009), at Georgia Institute of Technology (November 2009), and at the Meeting of the Integrative Analysis of Longitudinal Studies, Victoria, BC, Canada (June 2010).

CORRESPONDENCE

Correspondence should be addressed to Avron Spiro, PhD, MA VERIC (151IMAV), VA Boston Healthcare System, 150 South Huntington Avenue, Boston, MA 02130. E-mail: aspiro3@bu.edu.

REFERENCES


Kuller, L. H. (2006). Dementia epidemiology research: It is time to modify the focus of research. Journal of Gerontology: Medical Sciences, 61, 1314–1318.


and dementia in patients without apparent prior cerebrovascular disease. *Cochrane Database of Systematic Reviews* (2), CD004034.


