Only Time will Tell: Cross-sectional Studies Offer no Solution to the Age-Brain-Cognition Triangle—Comment on Salthouse (2011)

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Abstract

Salthouse (2011) critically reviewed cross-sectional and longitudinal relations among adult *a*ge, *b*rain structure, and *c*ognition (ABC), and identified problems in interpretation of the extant literature. His review, however, misses several important points. First, there is enough disparity among the measures of brain structure and cognitive performance to question the uniformity of B and C vertices of the ABC triangle. Second, age differences and age changes in brain and cognition are often nonlinear. Third, variances and correlations among measures of brain and cognition frequently vary with age. Fourth, cross-sectional comparisons among competing models of ABC associations cannot disambiguate competing hypotheses about the structure and the range of directed and reciprocal relations between changes in brain and behavior. Based on these observations, we offer the following conclusions. First, individual differences among younger adults are not useful for understanding the aging of brain and behavior. Second, only multivariate longitudinal studies, age-comparative experimental interventions, and a combination of the two will deliver us from the predicaments of the ABC triangle described by Salthouse (2011). Mediation models of cross-sectional data represent age-related differences in target variables but fail to approximate time-dependent relations, and thus do not elucidate the dimensions and dynamics of cognitive aging.

Keywords

brain; aging; cognition; longitudinal; mediation

> "…the science which investigates causes is more instructive than one which does not, for it is those who tell us the causes of any particular thing who instruct us."
>
> Aristotle, Metaphysics, Book 1, 982a.

That much we know: With advancing age, the mammalian brain undergoes profound structural changes (for a review, see Raz & Kennedy, 2009). The brain changes are accompanied by declines in cognitive performance that may be delayed by several decades (de Frias et al., 2007; Salthouse et al., 2010; Small et al., 2011). Numerous cross-sectional investigations show that the brains of older adults look and act differently from those of their

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younger counterparts (Hedden & Gabrieli, 2004; Lindenberger, Burzynska, & Nagel, in press; Raz, 2000), and that multiple measures of cognitive performance in many domains favor younger adults (Horn & Cattell, 1967, Salthouse, 1996).

Based on such knowledge, it is natural to hypothesize meaningful relationships among age (A), brain (B), and cognition (C), and cognitive aging researchers have been working hard to elucidate these connections for the past two decades. In his review, Salthouse (2011) turns strong and harsh light onto the assembled findings. He forgoes the nuances and illuminates an imbalance in the directionality assigned to the paths connecting the three nodes of the ABC triangle. In relation to the BC link, he sees little empirical justification for favoring one direction over the other. He also notes that the AB link may sometimes be absent altogether. In noting these empirical and conceptual flaws, Salthouse provides the researchers of cognitive aging with a much-needed reality check. Indeed, the days of simple linear truths such as "bigger = better" and "the brain mediates between age and cognition" are over. Bigger brain volumes derived from MRI scans may reflect less than salubrious events, and the number of studies revealing negative associations between regional brain volumes and performance, although still not large, is growing steadily (Guatam et al., 2011; Salat et al, 2002; Van Petten et al., 2004;). As for associations between B and C, the assumption that brain changes influence changes in cognition is highly plausible but not exclusive. The effect of the brain on cognition may be reciprocated, either through direct effects of training (e.g., Draganski et al., 2006), even in older adults (Lövdén et al., 2010, in press), or via twice- or trice-removed causes such as lifestyle, nutrition, and health maintenance decisions mediated by cognitive factors (e.g., Hertzog, Kramer, Wilson, & Lindenberger, 2009). Finally, some of the BC relations may lack directionality and be better understood as different manifestations of the influences exerted by other variables, not specified in the models. Salthouse's valuable message to those of us who are trying to navigate the deceptively simple yet devilishly complex terrain of cognitive neuroscience of aging is: The things are not as bad as you think; they are much worse.

The message of Salthouse's (2011) review is clear, but by forgoing the examination of details and entertaining a bird's eye view of the extant literature, he obscures the fact that the reviewed studies vary substantially in the ways they assess brain integrity. A cornucopia of methods, such as manual measures of regional volumes, estimation of local density and volume of gray and white matter derived from voxel-based morphometry, regional estimates of cortical thickness, semi-quantitative ratings of white matter hyperintensities (WMH) burden, measures of WMH volume, and indices of white matter organization derived from diffusion properties were, at least conceptually, lumped together. Although Salthouse (2011) considers volume, WMH, and diffusion-based measures separately, he ignores significant differences among measurement methods within each domain. Methodological considerations and empirical evidence militate against the indiscriminate cataloguing of diverse indicators under B. The analyses of MRI data generate multiple indices of brain integrity that are not only weakly correlated (Kennedy et al., 2009; Ziegler et al., 2010) but differ in strength of their associations with age. For instance, age explains four times greater share of variance in WMH volumes than in WMH ratings (van den Heuvel et al., 2006); cortical thickness, volume, and cortical surface area appear quite independent and tap into different structural aspects of aging brain (Lemaitre et al., 2010); individual differences in cortical thickness and volume stem from distinct genetic sources (Panizzon et al., 2009). Thus, B is not composed of uniform brain measures as Salthouse presumes it to be.

We have similar reservations about the treatment of the C vertex of the ABC triangle. An important problem in the extant ABC literature is that most of the reviewed studies address the issue with manifest variables (scores on cognitive tests or tasks) instead of latent variables (constructs based on multiple measures). A strong, often implicit assumption

underlying this approach is that every cognitive test or task measures something specific and that its score reflects the integrity of a unique piece of brain circuitry. The likelihood of such a one-to-one mapping is very low. Often, it is a good idea to aggregate measures into meaningful constructs before exploring BC associations (Little et al., 1999; McArdle, 2009; Salthouse, 1991, 1996). Thus, ABC vertices are considerably fuzzier than Salthouse (2011) would have it, and regrettably, this fuzziness was not addressed (or even mentioned) in the article.

Three Questions

Whereas we applaud the general objective of Salthouse (2011) to gain further insight into the nature of ABC relations, we want to elaborate on three issues, on which our views on how to approach this objective differ from his. The differences between approaches are more a matter of a degree than of kind. Nonetheless, we believe that these differences lead to divergent judgments about what can be learned about ABC relations from evidence that is restricted to samples of younger adults, findings from cross-sectional research designs, or both. Below, we discuss these issues, and comment on the consequences of the noted discrepancies between approaches.

Do Declines in Brain and Cognition Follow Linear Trajectories?

Salthouse (2011) suggests that linear age trends generally offer a viable approximation to mean age differences and mean age changes in brain and behavior. For instance, based on analyses of his own data, he notes that "[a]dditional analyses revealed that the quadratic age relations … were not significantly different from zero … To summarize, nearly linear age-related declines in both cross-sectional and longitudinal comparisons have been reported in several major cognitive abilities" (pp. 2–3).

In contrast to this view, we remind that nonlinear age trends in both B and C have been reported in studies with one or more suitable design characteristics such as large sample size, large age range, and longitudinal observations (for a similar view, see Nilsson et al., 2009). With respect to cognition, several studies have noted nonlinear age differences and age changes in one or more cognitive tests and abilities (e.g., de Frias et al., 2007; Lindenberger & Ghisletta, 2009; Rönnlund et al., 2005; Schaie, 1996). In the Betula study data, for instance, longitudinal average decline as been found to be greater in the older age groups than in the younger age groups defying the notion of linearity (e.g., Nilsson et al., 2004; de Frias et al. 2007).

Studies on age differences and age changes in brain structure also have documented a sizeable amount of nonlinearity (e.g., Raz et al., 2005; Raz et al., 2010). For instance, in a five-year longitudinal study of 72 individuals aged 20 to 77 years at baseline, we examined age-related differences and changes in 12 brain regions (Raz et al., 2005). We observed a highly differential pattern of regional age-related shrinkage. Although age-related shrinkage observed in the prefrontal cortex was linear, declines in the hippocampal and the prefrontal white matter volumes increased with age. Moreover, late-onset age-related increase in shrinkage was observed in the entorhinal cortex (EC), a region that showed no shrinkage in the younger and the middle-age participants. In the hippocampus, both linear and quadratic trends in age-related shrinkage were limited to hypertensive participants, which highlights the importance of accounting for modifiers of age-related change. Notably, the extent of EC shrinkage was associated with memory performance and fluid intelligence at baseline (Rodrigue & Raz, 2004; Raz et al., 2008). Thus, in contrast to Salthouse (2011) assertion, aging of brain and cognition is characterized by a substantial degree of nonlinearity. The causes of these nonlinearities are unclear, but our findings suggest that age-related changes

in brain and cognition may vary as a function of age and may stem from the influence of age-related modifiers, such as elevated vascular risk.

Are Variances and Covariances in Brain and Cognition Age-Invariant?

In addition to crowning linearity as a presumably sufficient descriptor of brain and cognitive aging, Salthouse (2011) asserts that the magnitude of individual differences generally does not vary as a function of adult age. For instance, summarizing the data from projects by Salthouse (2010a, 2010b, 2010c) and Rönnlund et al. (2005 and Rönnlund et al. (2006), he concludes the following: "Although age-related increases in between-person variability are sometimes found (e.g., Rabbitt, 1993) … this is not the case in these data" (p. 2). Salthouse proceeds to generalize that "…this finding is not specific to these two projects because nearly constant between-person variability has been found in cognitive variables from different standardized test batteries …" He notes that his summary of results indicates "that not only is the magnitude of variability considerable in both the levels (cross-sectional) and the changes (longitudinal) in cognitive performance, but that variability does not inevitably increase with advancing age." He further asserts: "there is no statistical reason why correlations involving cognitive variables would necessarily be weaker among young adults than among middle-aged or old adults" (pp. 2–3).

We believe that for methodological as well as empirical reasons, the claim that variances and covariances in measures of brain and cognition in adults do not depend on age is difficult to defend, and probably factually incorrect. First, assuming age-related stability of variances and covariances over the adult life span is tantamount to acceptance of the null hypothesis. Before making such a claim, one needs to ascertain the statistical power of detecting the differences in targeted outcomes. Monte Carlo simulations and formal analysis have demonstrated that the power to detect group differences in variances and covariances of change in typical longitudinal panel designs is distressingly low (Hertzog et al., 2006, 2008; Oertzen et al., 2010), especially if the reliability of the measures is not close to perfect.

Second, empirical investigations conducted with appropriate statistical tools revealed significant age differences in variances and covariances of cognitive and brain measures. In the realm of cognition, individual differences in rates of change for memory and verbal fluency were not reliably different from zero among the younger participants but emerged in the older age groups (e.g., de Frias et al., 2005). Similarly, relations between means and variances vary reliably between groups of younger and older adults as well as between individuals within age groups (Schmiedek et al., 2009).

Age-related increments in individual differences in B and C reveal heterogeneity of individual trajectories of aging, and may affect covariances within and between cognitive and brain-related variables. In fact, several studies found that correlations among multiple cognitive variables are higher among the older adults than in the younger age groups (de Frias et al., 2007; Baltes & Lindenberger, 1997). As for age differences in BC relations, associations between hippocampal volume and age may be not reliably observed among the young but emerge in the older age range (Raz et al., 1998; Van Petten, 2004), and correlations between cortical thickness and executive functions can be larger in older than in younger adults (Burzynska et al., in press)

In summary, contrary to the assertion of Salthouse (2011), failure to detect reliable differences in variances or covariances in level and change may tell us more about the lack of statistical power than about their presence or absence. The identification of such differences with appropriate statistical tools in samples of sufficient size supports the claim

that individual differences in brain and behavior increase with advancing adult age (Lindenberger, Burzynska, & Nagel, in press).

Does Falsification of a Cross-Sectional Mediation Model Constrain the Search Space of Longitudinal Relations between Brain and Cognition?

We agree with Salthouse's (2011) statement that longitudinal data are to be preferred to cross-sectional evidence for testing associations between changes in brain and cognition. At the same time, Salthouse (2011) argues that comparing competing models of ABC relations on the basis of cross-sectional data would help to reduce the number of viable causal models that can then be followed up by longitudinal evidence. For instance, he writes "… it is important to emphasize that the results of these types of statistical control analyses do not provide a direct test of causal relations, and instead merely provide an opportunity for implications of particular hypotheses of causal relations to be disconfirmed. However, because alternative models can often be postulated to account for relations among the variables, confidence in the plausibility of the hypothesized model can be increased if the data are found to be inconsistent with alternative models of the relations" (p. 5).

Alas, empirical findings and simulation research dash the hope of using cross-sectional findings in guiding longitudinal research. In a five-year longitudinal study, we observed all kinds of relations between longitudinal and cross-sectional estimates of change. For some brain regions (the prefrontal cortex), cross-sectional trend provided a good estimate of the rate of change; for others (caudate nucleus and cerebellum), the cross-sectional findings grossly underestimated the rate of shrinkage; and for still others (inferior parietal lobule), cross-sectional analyses missed reliable change revealed by longitudinal comparison (Raz et al., 2005).

In good agreement with this empirical evidence of diversity, formal analyses and Monte Carlo simulations have shown that the logic of using cross-sectional mediation models as an initial filter to weed out untenable assumptions about causal relations generally does not hold (e.g., Hofer et al., 2006; Lindenberger & Pötter, 1998; Lindenberger et al., 2011; Maxwell & Cole, 2007). The only exception emerges under highly restrictive conditions such as the "sequential ignorability assumption" (Imai et al., 2010), which is unlikely to be met in developmental research, in part for the reasons discussed above.

First, when a given cross-sectional mediation model fits the data well, then there is no guarantee that the lead-lag relations of the corresponding longitudinal changes mimic the cross-sectional model. In fact, as Maxwell and Cole (2007) demonstrate, the cross-sectional estimates are strongly biased for common models of change. Second, the situation is even worse: When a cross-sectional mediation does not fit the data, a corresponding longitudinal model may still hold. Thus, although a cross-sectional mediation model provides a summary description of age-related and other individual differences it dos not qualify as a viable first step toward delineating the temporal ordering and causal structure of brain-related and behavioral changes (Lindenberger et al., 2011; Maxwell & Cole, 2007).

In this context, proportions of "explained age-related variance" obtained with cross-sectional mediation created confusion among cognitive aging researchers, especially if these proportions turned out to be impressively large. At the risk of being redundant, we can state that finding, in cross-sectional mediation, that a brain variable accounts for 70%, 80%, or even 100% of the age-related variance in a cognitive variable leaves us with the following non-implications. The finding does not imply that changes in the brain variable correlate with changes in the cognitive variable, that change in the brain variable precede the change in the cognitive variable, or that changes in the brain variable cause changes in the cognitive variable. Furthermore, finding that the amount of age-related variance in a cognitive variable

associated with a brain variable derived from cross-sectional mediation is zero does *not* imply the lack of association between changes in the brain and changes in cognition. It also does not imply that changes in the brain variable do not precede changes in the cognitive variable, or that changes in the brain variable are functionally unrelated to changes in the cognitive variable. The only thing we can state with certainty about projecting from differences to change is that we do not know what is going on.

In summary, we agree that model comparisons based on cross-sectional data are useful for explaining concurrent individual differences in brain and cognition. However, in contrast to Salthouse (2011), we propose that the cross-sectional approach is generally unsuitable for constraining the search space of longitudinal relations and should not be used for this purpose.

Implications

We have identified several empirical and methodological issues about which we disagree with Salthouse (2011). Aggregation of studies of brain structure under the rubric of B is unwarranted, because of wide discrepancies in methods of measurement. Linear trends are insufficient to chart the aging of brain and cognition. Variances and covariances within and between brain-related and cognitive measures do change with adult age and tend to support the notion of heterogeneity in cognitive aging. Comparing different models of ABC relations based on cross-sectional data does not help in constraining the search for longitudinal relations between brain and cognition. Lumping together results from studies that use methods of discrepant reliability and validity jeopardizes meta-analytic interpretations of the findings.

Taken together, these claims have two important implications for the future study of brain-cognition relations in adulthood and old age. The first implication concerns the relative merit of studying samples of younger adults for understanding ABC relations. Indeed, if age trends were linear, if variances and covariances were age-invariant, and if cross-sectional models were effective devices for constraining the search space of longitudinal BC relations, then it would be reasonable to suggest that quite a lot about ABC relations aging can be learned by studying individual differences within samples of younger adults. If all three of these conditions were met, individual differences among younger adults would be likely to offer valid clues about individual differences that are driving age-related changes from early to late adulthood. However, given that the first two propositions are unlikely to be generally true and that that the third proposition has been formally shown to be wrong, a research strategy focusing on younger adults to understand cognitive aging is likely to systematically miss its target. Studying the young is not a valid proxy or a sufficient basis for understanding the brain basis of cognitive aging.

The second implication is that the use of mediation analyses based on cross-sectional data, which is still common, should give way to longitudinal research designs. Longitudinal designs have some significant problems of their own, such as nonrandom attrition (e.g., Lindenberger et al., 2002) and practice effects (e.g., Rabbitt et al., 2004; Salthouse, 1996); we need to direct our energy towards alleviating them. In addition, there is the fundamental question of choosing the optimal time window (cf. Maxwell & Cole, 2007)—that is, deciding which sampling frequency faithfully captures the process of change in an observational study. The task of finding the correct sampling frequency is difficult enough for one variable (for discussion, see Raz et al., 2010), but it becomes increasingly complicated when the goal is to examine associations between two or more variables that change across time (e.g., B and C; cf. Boker, Molenaar, & Nesselroade, 2009). Salthouse (2011) acknowledges some of these problems and states the following: "in most cases a

temporal lag probably exists between the changes in two sets of variables, and analyses of lagged changes are only meaningful if the longitudinal interval between observations matches the interval between early change in the presumed causal variable and later change in the presumed effect variable…" (p. 5). However, his pessimism about "these types of lead-lag analyses" being unable to "eliminate the problem if the total observation interval, or the spacing of observations within the intervals, does not match the timing of critical events" (p. 5) is not entirely warranted, given the existence of a sampling rate that can reproduce any given quasi-periodic process. Whereas the general trend of the developmental process may be monotonic, there may be significant periodicity around that trend, because at any time, the system parameters, cognitive and neural, are likely to represent a dynamic equilibrium of multiple factors (e.g., Boker et al., 2009; Raz et al., 2010). There may be a reason for the optimistic expectation that with advancement of our knowledge about neurobiological processes underpinning cognition in general and age-related change therein, the true shapes of age trajectories in B and C, their between-person variation, and the range and direction of their interdependencies will emerge.

Particularly promising is the combination of longitudinal research design with intervention experiments (see Hertzog et al., 2009). Cognitive or fitness-related interventions attempt to alter brain functioning and boost cognitive performance. Hence, they provide more direct information on how changes in behavior are related to changes in the brain, including information about which brain mechanism support the maintenance of acquired skills over time.

Conclusions

Salthouse (2011) did the field a service by pointing out that focusing on one or two directed paths of the ABC triangle may lead to the unwarranted discounting of viable alternatives. We agree that all of us who have ever attempted a mediation analysis within the confines of a cross-sectional design (e.g., Lindenberger et al., 1993; Raz et al., 1998) need to be reminded of how perilous this enterprise is. What Salthouse's analysis revealed is important, but what it failed to emphasize is vital: even a perfect cross-sectional study is hopeless for the purpose of illuminating the causal structure of longitudinal change.

If cross-sectional designs are so hopeless, why do they remain so popular? Maxwell and Cole (2007) have asked that question and their answer was that "little is known about the practical consequences of using cross-sectional designs to study mediation… [and] if "differences between longitudinal and cross-sectional analyses of mediation are small in practice, researchers might be justified in continuing to study mediation with cross-sectional designs despite a theoretical disadvantage" (p. 24). Unfortunately, the bias in cross-sectional mediation analyses of change is so substantial (Maxwell & Cole, 2007) and the results so inconclusive (Lindenberger et al., 2011), that no practical reason can justify the continuation of business as usual.

We are not calling for abandonment of the cross-sectional studies of aging and development, as they provide valuable information about average age gradients, age differences in variances and covariances, and individual differences in general. However, the stated "primary question" of Salthouse's analysis—"the extent to which relations of age with measures of cognitive functioning are attributable to relations of age with measures of brain structure" (p. 1)—is unanswerable within the confines of cross-sectional design. We agree with Salthouse (2011) that comparing competing models is a powerful method in science. Unfortunately, continuing use of this method in cross-sectional studies of aging and development will only perpetuate wandering among the vertices of the ABC Bermuda

triangle, lest longitudinal assessments separated in time, experimental manipulation, or preferably both, elucidate its causal dynamics.

Acknowledgments

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