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Understanding Ageing

An Evaluation of Research Designs for Assessing the Interdependence of Ageing-Related Changes

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Ageing · Methodology · Cognition

Abstract
Background: Cross-sectional studies of samples varying widely in age have found moderate to high levels of shared age-related variance among measures of cognitive and physiological capabilities, leading researchers to posit common factors or common causal influences for diverse age-related phenomenon. ***Objective:*** The influence of population average changes with age on cross-sectional estimates of association has not been widely appreciated in developmental and ageing research. Covariances among age-related variables in cross-sectional studies are highly confounded in regards to inferences about associations among rates of change within individuals since covariances can result from a number of sources including average population age-related differences (fixed age effects) in addition to initial individual differences and individual differences in rates of ageing (random age effects). Analysis of narrow age-cohort samples may provide a superior analytical basis for testing hypotheses regarding associations between rates of change in cross-sectional studies. ***Conclusions:*** The use of age-heterogeneous cross-sectional designs for evaluating interdependence of ageing-related processes is discouraged since associations will not necessarily reflect individual-level correlated rates of change. Typical cross-sectional studies do not provide sufficient evidence for the interdependence of ageing-related changes and should not serve as the basis for theories and hypotheses of ageing. Reanalyzing existing cross-sectional studies using a sequential narrow-age cohort approach provides a useful alternative for evaluating associations between ageing-related changes. Longitudinal designs, however, provide a much stronger basis for inference regarding associations between rates of ageing within individuals.

Many age-related differences are evident when comparing young and old individuals. For example, age-related differences are observed, on average, in memory and reasoning, immune function, forced expiratory volume, number of teeth, and muscle strength across people varying in age. Investigations that aim to understand 'ageing' often focus on associations between such time-dependent processes and emphasize particular questions. Are the causal pathways of cognitive ageing few or many? What are the prior causes of these changes? Are the causes proximal or distal to the outcome? Are ageing-related changes different across different people? To what degree are ageing-related changes independent of one another? This paper is concerned with these questions and how different study designs and analytic methods may lead to quite different conclusions regarding the dimensionality and structure of aging-related changes and of predictors and concomitants of such changes.

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Most gerontological theories, certainly most cognitive ageing theories, are based on cross-sectional data of samples varying broadly in age. A focus of many of these studies is on the amount of shared age-related variance and on which variables account best for the individual differences in other types of functioning. Indeed, analyses of cross-sectional data have clearly demonstrated that the covariance between chronological age and cognitive variables (e.g., memory and speed) is rarely unique. This lack of unique age-related covariance among cognitive variables has been interpreted as a demonstration that single or common factor ageing theories are sufficient to account for cognitive age effects. Although the partitioning of variance is a general paradigm in cognitive aging research, two hypotheses in particular, the general slowing hypothesis [1, 2] and the 'common cause' sensory-cognitive link hypothesis [3, 4], have emphasized that a large proportion of age-related variance in varieties of cognitive function is accounted for by measures of processing speed and sensory ability (e.g. visual and auditory acuity), respectively. Although few would consider aging to be a simple and general process for all types of functioning, the evaluation of common and specific age associations among age-related processes are emphasized in research on cognitive aging and usually involve cross-sectional research designs and variance partitioning approaches [5–9]. In general, however, large proportions of shared age-related variance among diverse variables are found in such studies although there have been reports of unique proportions of age-related variance for particular variables [10–12].

This interpretation regarding the high degree of commonality among ageing processes relies on the complex assumption that shared age covariance at cross-section (of a sample varying in age) reflects correlated ageing-related change – that rates of ageing within individuals are associated. This assumption is complex because there are at least several ways in which ageing-related change can be associated. First, ageing-related variables can be related in terms of magnitudes and patterns of population average change. This type of association is indexed by fixed age effects, which indicates the average population change over time. A second type of association refers to individual differences in rates of change within the population. This association is indexed by random age effects, expressed as deviations in rate of change from the population average change, which determine whether individuals who decline rapidly on one variable also tend to decline rapidly on another variable. Third, systematic change can be correlated within individuals over time. This type of change reflects whether, for a given individual, the amount of change in one variable over a given temporal interval correlates with the amount of change in a second variable over that same interval. Stated simply and assuming a strong association between speed and memory, if a person experiences relatively little slowing between the ages of 70 and 75, but much slowing between 75 and 80, then they should also experience little memory loss during the first interval relative to the second [13]. This type of change or fluctuation in performance can also be assessed at much shorter intervals to indicate the extent to which processes systematically covary, perhaps influenced by environmental or health-related events, and thus provide information regarding systems of variables and associated common influences. While each type of correlated change is relevant for ageing theories in general, and cognitive ageing theory in particular, we describe serious limitations regarding the use of cross-sectional designs for understanding correlated rates of change and discuss designs that provide a much stronger basis for understanding ageing.

The central point of this paper is that cross-sectional analyses of age-heterogeneous samples are more informative about population-level mean trends than associations between rates of ageing, and therefore provide a weak basis for examining the interdependence of ageing-related changes within individuals. We show that estimates of covariance in cross-sectional samples are confounded with covariance related to average age trends, which alone will produce positive correlations between variables even if the true correlation between rates of change across processes is zero or negative. This simple fact, that virtually any variable that is associated with chronological age – that exhibits age differences on average – will result in a positively biased association, poses a major problem for theories and empirical findings based on cross-sectional data. Indeed, cross-sectional studies of this type are inclined to find large proportions of shared age-related variance and that common factor models of diverse age-related variables fit the data quite well. Unfortunately, findings of commonalities or common factors may not reflect anything substantive about the causal dimensionality of age effects, but rather, these common factor solutions are, at least in part, simply detecting the passage of time and that older individuals perform, on average, differently than younger individuals. That a variable exhibits a particular pattern and magnitude of change with age is important to know, but we would not want to base theory or hypotheses on the simple fact that a set of variables change over time.

In gerontological research, time is an intrinsic aspect of the processes under study and can be seen as having an effect both at the population level (known as the fixed effect or average trend) and at the individual level (deviations from this average trend). In cross-sectional studies, these two types of effects cannot be easily disentangled and so the major problem resides in deriving inferential statements regarding common and specific effects related to age or aging from information about population average changes (age differences in cross-sectional studies). Indeed, this is the major issue emphasized here – how the population average, and deviations about the population average effects, are an aspect of both cross-sectional and longitudinal studies.

The problem is one of aggregation and in developmental and aging research, the aggregation is based on time or age. In cross-sectional models focusing on time-dependent variables, age is a between individual effect. In the sections below, we demonstrate how covariances result, at least in part, from the aggregation of average age-based differences and therefore, results in a mixture of between and within-individual effects. The problem associated with aggregation of this type is well known in particular areas of science and statistics, though the cautions in regard to developmental or aging phenomena have not influenced research practices [14–18]. That correlations may result from mean differences in individuals of different ages is closely related to the ecological fallacy [19, 20], Simpson's paradox [21–24], and Lord's paradox [25–27], where the essential problem results from aggregating or pooling data across groups. In 1903, Yule [24] referred to this problem as an 'illusory association', the result of an improper mixture of distinct groups where differences in the variables to be correlated were both associated with group status (e.g. different proportions or means of the attributes observed across sex groups). Yule described similar problems in relation to sampling over time, referred to as the time-correlation problem [28, 29]. Other critical developments of these ideas for gerontologists includes differential selection of a population over time which result in estimates of population dynamics that may not reflect individual characteristics or patterns of change [30] and the establishment of measurement invariance across groups and time [31]. We should also note that there are more general concerns regarding the utility of variance partitioning for understanding the relative importance of variables [9, 32, 33] although these issues will not be dealt with here.

The second major point is that an alternative cross-sectional design – the analysis of narrow-age cohorts (i.e. samples of individuals of the same or nearly the same chronological age) – can inform about the second type of correlated change in that the covariance between two variables in the population at a given age is a function of both the covariances between initial level and covariance between rates of aging (random age effects). The narrow-age cohort design has been used to evaluate whether increasing covariance between age-related processes is observed as a function of correlated rates of ageing [14, 15] and has formed the basis for several gerontological studies [34]. As to the third type of correlated change, there is no cross-sectional design that can inform about correlated change that occurs within individuals. Only the direct observation of change in individuals within longitudinal studies can provide the necessary data to infer association at the intraindividual level [35].

In emphasizing confounds related to population average rates of change in age-heterogeneous cross-sectional samples [16, 17], we do not at all dismiss or undervalue other, better-known measurement and analysis issues that are pertinent to developmental and aging research designs (e.g. no direct inference of within-individual change, selection and mortality, age-period-cohort confounds, disparate time spans) [36–38]. The issue of attrition, due to mortality or other causes, is a major problem in both cross-sectional and longitudinal designs and this has led to new developments in statistical methods to obtain better inferences of change under reasonable assumptions regarding the attrition process [39, 40]. While attrition is usually regarded as a problem for longitudinal studies, it is arguably a greater problem for cross-sectional designs because the selection process is unobserved – individuals of different ages are not random samples of the population of individuals of younger ages [30, 41] – and there is no opportunity to acquire information regarding the causes or magnitude of differential selection over time within such single occasion studies. Information regarding the selection process (i.e. attrition, mortality) may, however, be observed in longitudinal studies and because it is observed, it must be dealt with. In cross-sectional studies, however, attrition is generally ignored since no information is available and this is also an issue for longitudinal studies that begin with an age-heterogeneous sample. Retest effects are a major source of bias in deriving inferences regarding longitudinal change within individuals and a recurrent problem. Cohort effects may also lead to alterations in means and covariances, particularly in age-heterogeneous samples, and lead to generalizability issues when relying on narrow age-cohort samples. While we do not describe further the differential impact of these

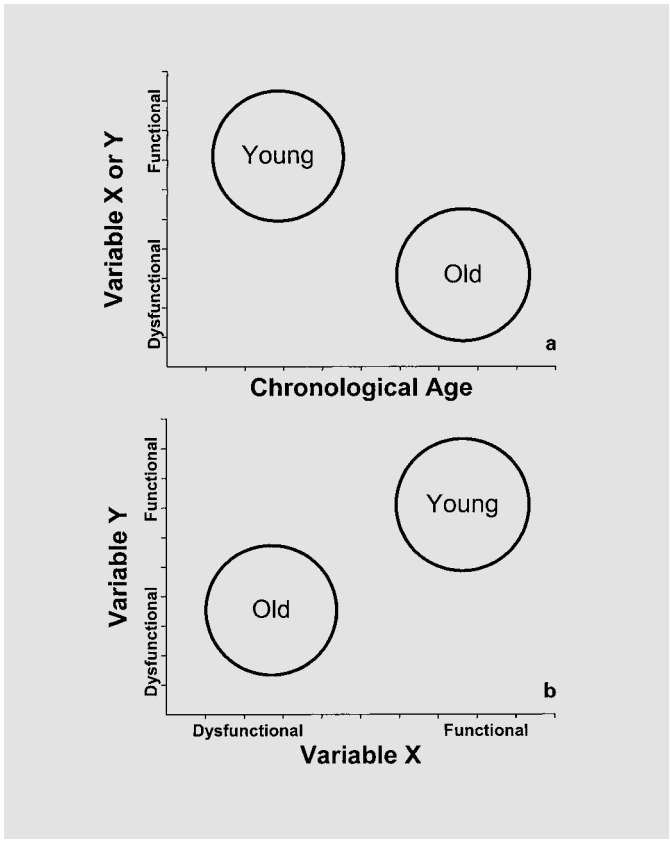

Fig. 1. Demonstration of how average population-level age-related differences (fixed effects) will influence the association between two age-dependent variables.

and other sources of bias in cross-sectional and longitudinal studies, these influences clearly impact the designs we describe below. Our emphasis is on the examination of an underappreciated source of covariance in cross-sectional studies – the influence of average population age differences or mean trends.

In the following sections, we describe in detail the problem of estimating associations between processes using typical cross-sectional designs, and, in particular, the confound in the covariance related to average population trends. We examine the alternative narrow age-cohort approach to cross-sectional designs and demonstrate how information regarding correlated random age effects can be recovered, and, therefore, why we may observe the process of dedifferentiation across samples differing in age. Finally, we describe briefly the implications for experimental ageing research and the utility of longitudinal designs that permit a stronger basis for inference regarding the association between ageing-related change.

Inference from Age-Heterogeneous Cross-Sectional Designs

In addition to other reasons for differences between cross-sectional and longitudinal results focusing on developmental and ageing processes, associational analysis of individuals varying broadly in age emphasizes population-level mean change in addition to individual variation about the population mean. Analyses of correlated change in longitudinal studies are based on detrended individual differences in change (expressed as deviations about the population trend) and so may result in a less-biased estimate of association between change in processes because the fixed effects are not a component of the covariance. Indeed, age-heterogeneous cross-sectional analysis may provide little useful information regarding the interdependence of within-person changes than is known in terms of mean differences or correlation with chronological age.

Association Due to Population Average Trends

Results from cross-sectional analysis provide very weak evidence for associated 'rates of change' since moderate-to-high associations will arise even when the ageing-related changes are completely independent within individuals. A simple example demonstrating how associations may arise from mean trends is provided in figure 1a, which displays two variables (X and Y) that exhibit mean differences across age groups. To simplify the diagram, only two groups are shown but a continuum of age groups could be present. Note that the association between X and Y within age groups is assumed to be zero and that there is no association between rates of change within the population. All that is present is population average change across chronological age. Under such circumstances, figure 1b shows that the association between variables X and Y may be quite high and result exclusively from mean differences across age groups. This was described by Yule in 1903 [24, p 134]; 'if two separate records, for each of which the correlation is zero, be pooled together, a spurious correlation will necessarily be created unless the mean of one of the variables, at least, be the same in the two cases'.

Hofer and Flaherty [16] show analytically how associations between time-dependent variables are at least partly and may be entirely due to mean trends in cross-sectional data and provide a demonstration of this using simulated data. A distinction between fixed age and random age effects, terminology common to longitudinal modeling, to denote population average change and systematic indi-

vidual-level rate of change expressed as deviations from the population average is shown. Assume a sample of individuals followed continuously over their lifespan such that each individual has a complete distribution of scores on two processes, X and Y, as a function of their initial level and rate of change over time. Parameters subscripted by i refer to the random effects (deviations from population means). An individual's score at any particular age (t) is a function of the population average intercept or level (L_x, L_y), deviation from population average intercept (L_{xi}, L_{yi}), population average rate of change or slope (S_x, S_y), deviation from population average rate of change (S_{xi}, S_{yi}), and other sources of systematic and random variance (e_{xi}, e_{yi}) which are assumed to be normally distributed and independent.

$$x_{it} = L_x + L_{xi} + S_x t + S_{xi} t + e_{xi}$$
$$y_{it} = L_y + L_{yi} + S_y t + S_{yi} t + e_{yi} \quad (1)$$

In the typical cross-sectional study, a sample of one measurement at time t from each individual is obtained so that a broad range of ages is represented. In age-heterogeneous cross-sectional samples, the individual scores contain information on both the fixed and random effects of the individual trajectories. This can be seen by inserting the age of each individual in the above equations giving the individual scores at time t.

Equation 3 shows the covariance between two time-dependent processes, X and Y, which is the result of substituting equation 1 into the formula for a covariance shown as equation 2,

$$Cov(X,Y) = E[(X - \mu_x)(Y - \mu_y)] \quad (2)$$

and

$$Cov(X,Y) = E\{[(L_x + L_{xi} + S_x t_i + S_{xi} t_i + e_{xi}) - E(L_x + L_{xi} + S_x t_i + S_{xi} t_i + e_{xi})]$$
$$[(L_y + L_{yi} + S_y t_i + S_{yi} t_i + e_{yi}) - E(L_y + L_{yi} + S_y t_i + S_{yi} t_i + e_{yi})]\}, \quad (3)$$

where t_i denotes an individual i's age at time t.

Equation 4 shows the expansion of the covariance of the fixed and random effects for Level and Slope after substituting the mean of the X and Y processes and omitting terms with expectations of zero (which includes terms involving error). Given that this is a cross-sectional sampling of individuals varying in age, a single measurement associated with a particular age location is sampled from an individual's trajectory. We use the notation t_i to represent individual i's age at time t. Equation 4 demonstrates that the covariation between two variables from a cross-sectional sampling scheme is a function of the fixed effects indicating population average change in addition to covariance related to initial individual differences (covariance between intercepts), covariation between rates of change (random effects), and covariance between intercepts and rates of change.

$$Cov(X,Y) = E(L_{xi}L_{yi} + L_{xi}S_y t_i + L_{xi}S_{yi}t_i + S_x t_i L_{yi} + S_x t_i S_y t_i + S_x t_i S_{yi} t_i - S_x t_i S_y \bar{t} + S_{xi} t_i L_{yi} + S_{xi} t_i S_y t_i + S_{xi} t_i S_{yi} t_i - S_{xi} t_i S_y \bar{t} - S_x \bar{t} S_y t_i - S_x \bar{t} S_{yi} t_i + S_x \bar{t} S_y \bar{t} \quad (4)$$

To use an extreme example, suppose we have two processes that exhibit systematic average change over time within a population. Assume, however, that these two processes are completely independent and therefore have no association with one another in terms of individual differences in either initial level or rate of change. This is the condition shown in figure 1 where there is no association between processes within particular age groups but where both processes exhibit mean differences across age. With only fixed effects present in the expected covariance, equation 4 simplifies to

$$Cov(X,Y) = S_x S_y Var(t_i). \quad (5)$$

Equation 5 demonstrates that covariation will result from simple linear trends in cross-sectional samples varying in age. This covariation will be a product of the squared age of the individual multiplied by the rates of change in processes X and Y (centered at the average age of the sample). This presents a fundamental problem when evidence from cross-sectional designs is used to evaluate the interdependency of process. Associations produced by simple mean age trends in the population should not be taken as evidence for a common causal ageing mechanism or common process change within individuals over time. Cross-sectional designs based on broad age samples are the most confounded in terms of sources of covariation, in contrast to other designs, since associations between time-dependent processes may arise from trends in mean level in addition to correlated rates of change and initial individual differences. We should note that this expectation is based on a simple linear model and that curvilinear change and the additional influences on such study designs cited above will necessarily compound the complexity of the expected covariance in actual data.

The problem of mean trends in producing spurious associations between uncorrelated processes has been known for nearly a century. For example, in regards to sampling across time it is important to detrend to evaluate associations between processes, otherwise mean-induced autocorrelations will arise. One of the problems with cross-sectional sampling of age (time) is that with coincident measurements obtained at an arbitrary occasion in time (i.e. age), we do not know the previous values

of these measurements. Because we do not have a history on each individual from such sampling, we cannot detrend the individuals' scores to evaluate patterns of covariation that are separate from the average population age-change trajectories, a problem further compounded by unknown sample selection over time. What is observed in the cross-sectional covariance is the between-individual effects – the covariances that arise from the mean levels of functioning at each age represented in the sample.

Inference from Age-Homogeneous Cross-Sectional Designs

An alternative analysis of cross-sectional data focuses on associations between variables in samples that do not vary significantly in chronological age. A less-utilized cross-sectional design, the narrow age-cohort (NAC) sample may be more suitable for deriving inferences regarding the interdependence of ageing-related change. NAC sampling designs, particularly sequential comparison of narrow age-cohorts (SNAC), provide stronger evidence for disassociation of ageing effects than age-heterogeneous cross-sectional studies.

The NAC design is based on the idea that there are individual differences in rates of ageing and that, given sufficient time, the rank ordering of individuals at cross-section (e.g. age 75) will increasingly reflect the rank ordering of individual rates of ageing-related change. If ageing has a common effect on different processes (i.e. the rates of ageing are associated), moderate and increasing correlations across systems of variables should be observed.

In the NAC and SNAC designs, the fixed effects are constant within age group and do not contribute to the cross-products. Note also that since the age within NAC groups is constant, t is not subscripted and represents a fixed age effect. Hofer and Flaherty [16] derive the covariance of two time-dependent processes as a function of the random effects of initial level and rate of change. Covariance terms containing fixed age effects are constant, means of the random effects terms are zero, and terms involving error all drop from the model leaving us with the general case for covariance within a single age group,

$$Cov(X,Y) = Cov(L_{xi}L_{yi}) + [t]Cov(L_{xi}S_{yi}) + [t]Cov(S_{xi}L_{yi}) + [t^2]Cov(S_{xi}S_{yi}). \quad (6)$$

The key concept motivating the NAC design is that the rank order across individuals of the same age will become more and more informative regarding the associations between aging-related rates of change and that average population change (fixed age effects) will not enter into the estimate of association. Equation 6 demonstrates how the covariance of any single NAC, representing a single slice of time, will be a function of covariance between Level and Slopes ($[t]Cov(L_{xi}S_{yi})$, $[t]Cov(S_{xi}L_{yi})$), initial Level covariance ($Cov(L_{xi}L_{yi})$) and, most importantly, covariance related to rates of change ($[t^2]Cov\ (S_{xi}S_{yi})$). Equation 7 shows that as time increases, the effect of the covariance between the rates of change in the processes increases quadratically,

$$\begin{aligned}
&t \rightarrow Cov(X,Y) = \\
&Cov(L_{xi}L_{yi}) + [t]Cov(L_{xi}S_{yi}) + [t]Cov(S_{xi}L_{yi}) + [t^2]Cov(S_{xi}S_{yi}) \\
&1 \rightarrow Cov(X,Y) = \\
&Cov(L_{xi}L_{yi}) + [1]Cov(L_{xi}S_{yi}) + [1]Cov(S_{xi}L_{yi}) + [1]Cov(S_{xi}S_{yi}) \\
&2 \rightarrow Cov(X,Y) = \\
&Cov(L_{xi}L_{yi}) + [2]Cov(L_{xi}S_{yi}) + [2]Cov(S_{xi}L_{yi}) + [4]Cov(S_{xi}S_{yi}) \quad (7) \\
&3 \rightarrow Cov(X,Y) = \\
&Cov(L_{xi}L_{yi}) + [3]Cov(L_{xi}S_{yi}) + [3]Cov(S_{xi}L_{yi}) + [9]Cov(S_{xi}S_{yi}) \\
&4 \rightarrow Cov(X,Y) = \\
&Cov(L_{xi}L_{yi}) + [4]Cov(L_{xi}S_{yi}) + [4]Cov(S_{xi}L_{yi}) + [16]Cov(S_{xi}S_{yi})
\end{aligned}$$

The major feature of the NAC design is that, as time elapses, the magnitude of the covariance becomes increasingly due to the covariance associated with rates of change relative to the other sources of covariance. Therefore, in older samples of individuals, more time will have transpired and this will increase the contribution to the covariance of NAC samples that reflects individual differences in rates of ageing. In the analysis of a single age-cohort sample, associations between variables may be due to 'initial' individual differences as well as to common rates of ageing. We make the assumption that intraindividual change due to 'ageing' overwhelms any initial (early adulthood) individual differences in functioning. It would be only in the unusual case where the observed association among variables is attenuated because of the cancellation of initial individual differences with correlated rates of change (e.g. negative correlation of initial individual differences with positive correlation between rates of change) that no association in older age-cohort groups would be observed. Sequential narrow age-cohort (SNAC) samples permit evaluation of increases or decreases in covariation across age (or other group status variables), as shown in figure 2, and permit distinction between initial individual differences and common rates of ageing as the key sources of covariation between processes. The key concept is that the rank ordering (e.g. NAC covariance) will indicate the interdependence between rates of ageing to increasing degrees in samples where the developmental and ageing processes have influenced the rates of change from the initial values.

This SNAC approach is related to the analysis of differentiation and dedifferentiation in that changes in the covariation among variables or factor structure are assessed across sequential narrow age-cohort groups [42, 43]. What is described here is the statistical mechanism by which covariational evidence for dedifferentiation (and differentiation in childhood) might arise [16]. In NAC and SNAC designs, only the outcomes of time-dependent processes are observed and time is treated as the continua over which a process unfolds. As shown above, the covariances among outcome variables carry information regarding the correlated change over time within individuals.

These methods might be usefully applied to understanding the interdependence resulting from other forms of time-dependent processes, such as span to death as in the terminal decline hypothesis, changes in health status, or changes in cognitive functioning during the preclinical phase of dementia that occurs prior to clinical diagnosis. Additionally, changes in covariance structures can be evaluated across time within the same individuals using data from longitudinal studies. We must also be clear that the analytical expectations described above predict increasing or decreasing covariances in narrow age-cohort samples if selection (i.e. mortality), cohort, and other effects are negligible. Cross-sectional designs remain highly confounded, with age, cohort, and time of measurement remaining difficult or impossible to disentangle and the influence of mortality and attrition expected to have differential effects on results for particular outcome variables and across different age-cohort samples. Of course, these are all problems for the typical, age-heterogeneous design as well. Narrow age-cohort designs are, nevertheless, less confounded than age-heterogeneous designs in that mean trends do not contribute to the covariance among processes.

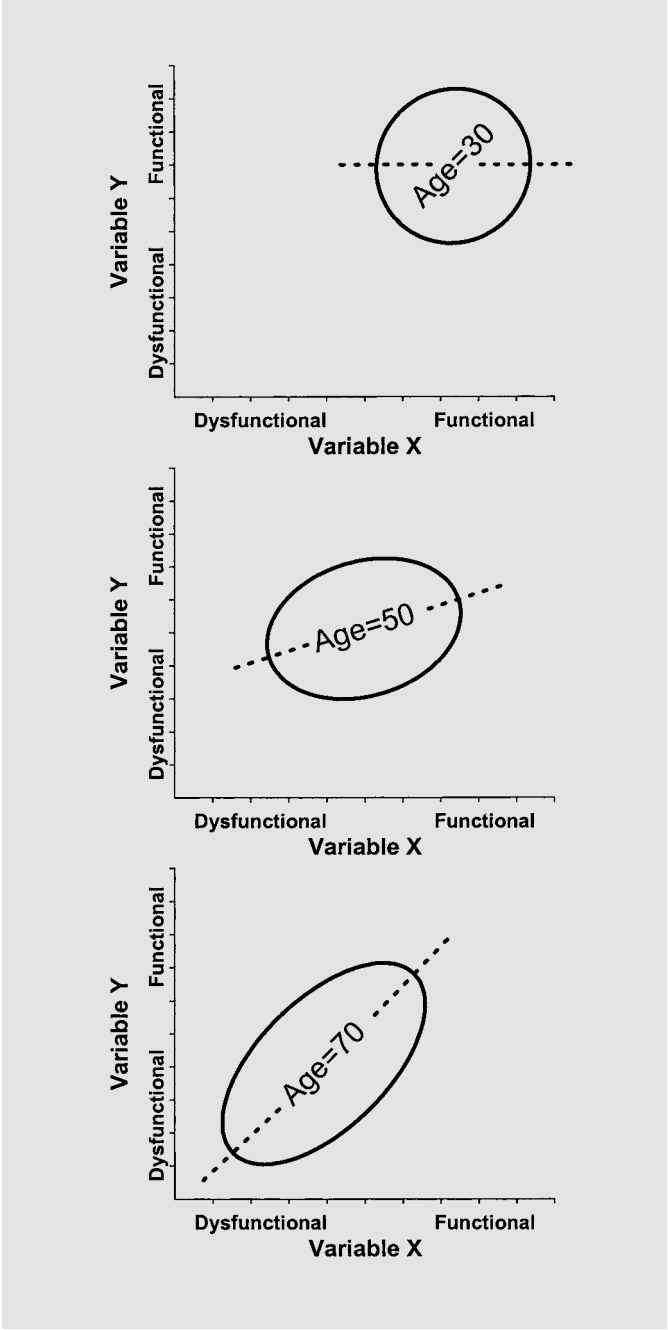

Fig. 2. Utility of the narrow age-cohort (NAC) design for demonstrating increasing covariances between outcomes due to common rates of ageing.

Regression Partial of Chronological Age

From the perspective of the SNAC design, there is a loss of information when chronological age is partialed from associations in cross-sectional samples varying broadly in age. It is also the case that partialling for chronological age variance only partially removes true aging effects that result from covariance associated with the cumulative effects of correlated rates of change (equation 6 above [16]). In other words, the use of regression to control for variance associated with chronological age does not provide an estimate of the association that is independent of age but rather of the association at the average age of the sample. After controlling for age-related variance, the covariance will still provide information about the variation associated with true within-person change over time, as in the NAC covariance expectations above, as well as the static individual differences between the processes. Figure 3 shows that the regression partial of age-

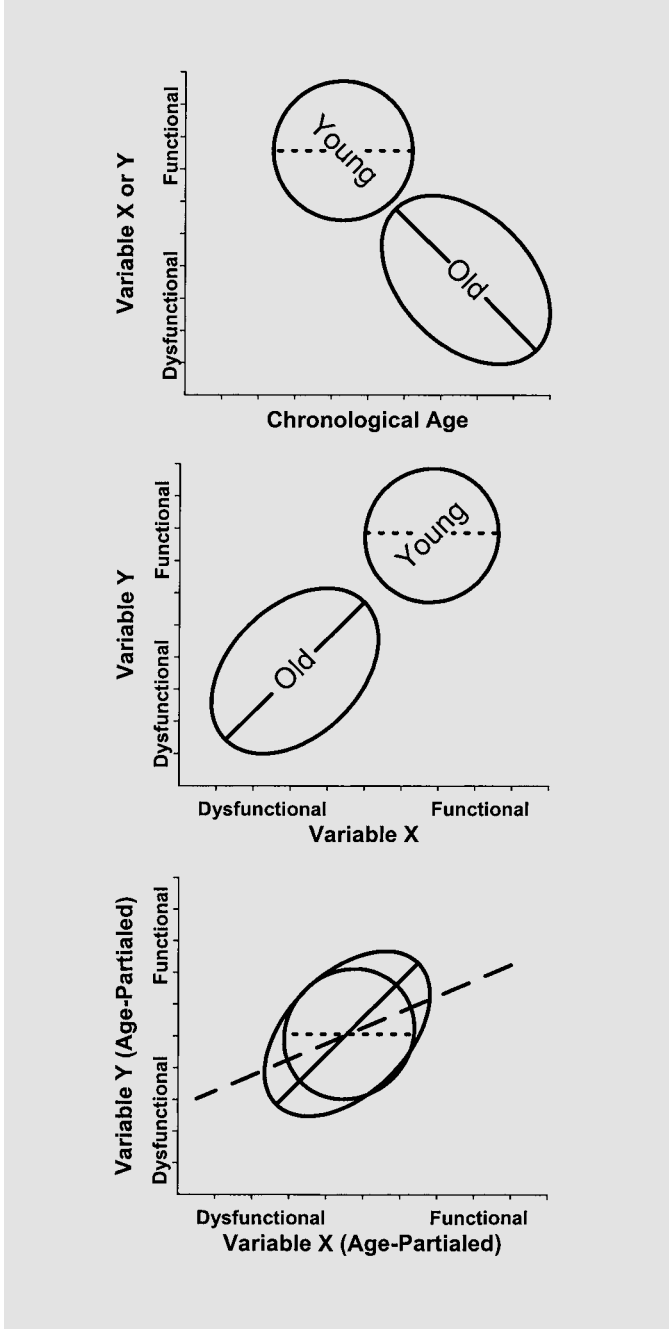

Fig. 3. Effect of regression partial of chronological age on association between two age-dependent variables.

related variance can be conceptualized as averaging covariance across SNAC samples – similar to a pooled between-group covariance with each age represented as a group. In this example, there is no association between X and Y in the young group and a moderate association in the old group. The aggregation across age groups, shown at the bottom of figure 3, removes mean differences in X and Y associated with chronological age and results in an average covariance between X and Y processes across SNAC samples, shown as the long dashed line. The age-partialed association may remain appreciable and due, at least in part, to the average common ageing influences but also to initial individual differences that are present across the age range of the sample. As we described earlier, the SNAC design is useful in that the change in covariation (increasing or decreasing interdependence) may be evaluated.

Inference from Longitudinal Designs

The study of ageing is the study of change. The study of change requires that the same individual be followed over time and longitudinal designs are necessary for clear assessment of the interdependence of age-related processes [35]. In longitudinal analyses, the random effects can be separately estimated from the fixed effects such that estimates of association between rates of change are 'detrended' from the population average change. However, longitudinal studies necessarily begin as cross-sectional studies, based on either age-heterogeneous or age-homogeneous sampling designs, and have similar limitations to those described above.

Age-Heterogeneous Longitudinal Designs

Longitudinal studies do not provide sufficiently strong evidence for *definitive* statements about age-dependent causes and associated outcomes. Observing that time-dependent trajectories (rates of change) are associated is necessary but not sufficient to infer common causation. As described above, one reason that association in rates of change may be found is related to the fact that many longitudinal studies begin as cross-sectional samples of individuals varying broadly in age. In such studies, estimates of association between rates of change may be evaluated by fitting latent growth curves across occasions of measurement [44] and thus aggregating across individuals of different ages. Associations among time-dependent processes may arise due to different magnitudes of change, expressed in longitudinal analysis as deviations from the population average age trend (i.e. random effects), and result from age-defined periods of greater change (i.e. late adulthood versus middle adulthood). For example, in a longitudinal study that initially was comprised of a sample 50–80 years of age at the first occasion, estimates of

individual trajectories will show that 75-year-old individuals will exhibit greater change over the course of the study than 50-year-old individuals in many measured variables. Since these rates of change are expressed as deviations from population average change based on the entire age range of the sample, associations between 'rates of change' in these processes may be misleading in that they may not reflect truly coupled processes or mutually influenced processes *within* individuals but describe the probability for greater change or curvilinear change as a function of chronological age or events related to the age period of the individual. The caution raised here again focuses on the interpretation of associations between 'rate of change' since it would be confounded in age-heterogeneous studies with age-related population average change. This is definitely not to say that we regard the information regarding average rates of change in the population as unimportant. Understanding developmental and aging phenomena requires focus on both population average and individual differences about the average rate of change. We simply caution that the correlation among slopes (rates of change) within longitudinal modeling approaches may result from average age-dependent and nonlinear changes at the population level when such analyses are based on an aggregated sample composed of individuals of different ages.

Nevertheless, results from longitudinal studies do provide stronger evidence for coupled age processes than cross-sectional studies do. Longitudinal designs that begin with a relatively homogeneous age sample at the first occasion may permit a clearer interpretation of the associations in much the same way as the cross-sectional age-homogeneous designs do, generalizations across cohorts not withstanding.

Implications for Research on Aging

This critique focuses on the problem of how time-dependent processes might best be studied and is meant to encourage further discussion and use of optimal designs for understanding individual variation and covariation among developmental and ageing processes. Development and ageing occurs within individuals and although there are certainly commonalities to such changes, there is also evidence for many and varied influences on individual rates of ageing [44]. Clearly, changes within individuals contribute to average or population-level changes in function. However, the processes which contribute to or are an outcome of development and ageing may exhibit different magnitudes of effects within individuals, occur at different ages or periods, or have qualitatively different effects depending on subsequent or antecedent conditions. Research designs used to evaluate such associations among aging processes must be sensitive to the within-person processes and permit the separation of aging-related changes that occur on average from those that occur within the individual. In addition to longitudinal studies, experimental research designs and measurement intensive designs have demonstrated or potential utility in this regard.

Experimental Designs

The comparison of averages (fixed age effects) across age groups is the focus of the experimental approach and so is not influenced by the criticisms raised here. The experimental approach focuses on making inferences regarding the relative sensitivity of cognitive processes to ageing. Such approaches are valid when attempting to identify cognitive mechanisms that are fundamental to ageing. However, experimental procedures may be quite limited in finding broad or specific mechanisms that produce population-level age effects.

Measurement Intensive Longitudinal Designs

Long-term ageing effects can be gradual and enduring, decline abruptly, or fluctuate about a characteristic level with the potential for rebound to previous levels. In all these conditions, systematic fluctuation around an individual's characteristic trend will be confounded if single measurements or widely spaced measurements are obtained. A more sensitive *process-oriented* approach is the measurement intensive design, involving short-term measurement bursts, which permits estimates of covariation between different processes to be assessed over both short- and long-term intervals and permits stronger statements to be made regarding the effect of a common influence or dynamic across functions [46]. Numerous types of designs may be used that would greatly enhance statements regarding the interdependence of ageing processes and include measurement burst designs (permitting precise estimates of level and state variation) and measurement burst designs with factor indicators (permitting distinction between systematic state and random fluctuation). These designs are currently being implemented in a number of studies focused on both physiological and cognitive outcomes.

Summary and Conclusions

Theories and models of ageing should not be unduly influenced by the simple fact that age-related change occurs. This is the critical problem for theories and hypotheses that are based solely on cross-sectional studies of samples varying broadly in age. In this paper we sought to elaborate the analytical problems in analyzing associations of 'ageing-related' changes and to clarify the assumptions and interpretational basis for several commonly used approaches. The following points formed the basis of our discussion of optimal designs for understanding associations between ageing-related changes:

(1) Cross-sectional analysis of samples varying broadly in age will result in positively-biased estimates of association between processes that change with time. This results from the combination of fixed and random effects contributing to an individual's score.

(2) An alternative cross-sectional method based on examination of narrow age-cohort samples provides a useful approach for understanding the structure of ageing-related change. This is one method for 'detrending' the population-level effects within cross-sectional applications.

(3) Experimental ageing designs comparing young and old individuals are not susceptible to these problems because of their focus on population mean differences across age groups (fixed age effects).

(4) Longitudinal designs, particularly those involving intensive intraindividual measurements, provide direct information on within-individual change, variation, and covariation of ageing-related processes. Longitudinal designs, of course, present other challenges such as sample selection, attrition, and retest effects.

Ageing occurs within individuals and it is at this level that theory must be evaluated. Although comparing individuals varying in age has long been considered a useful proxy for understanding within-individual ageing, the confounds associated with cross-sectional analysis seriously compromise any statement regarding associations between age-related variables and their shared or common influence. The concerns raised here in regards to the influence of mean trends are in addition to general concerns with the variance decomposition approach. In terms of model sufficiency, we must regard the typical cross-sectional design as confounded and potentially misleading regarding the commonality of ageing-related influences and outcomes. Cross-sectional designs will often lead to common factor explanations for influences that might be independent in terms of both causes and effects. Alternative models will fit the data equally well and all could be implausible. It is essential that methodological designs and analytical approaches be sensitive to causal multiplicity. Fundamentally, this is a question of the degree to which group-level processes can inform us of individual-level processes and is related to problems of aggregation and ergodicity, the assumption that all individuals are identical representations of one another. A major theme of the issues raised here is that understanding ageing – the dimensionality, structure, and causal pathways – will require multiple perspectives and designs sensitive to within-individual patterns of change.

Another problem associated with an emphasis on population-level effects is the relatively weak sensitivity to low prevalence rates within individuals. Different individuals, or subgroups of individuals, will exhibit different patterns and rates of change. For example, very strong influences such as preclinical dementia could account for most of the within-individual change in cognition prior to dementia diagnosis, which will only weakly be demonstrated in analysis across individuals and only weakly be related to chronological age [47]. In this way, it is possible for a variable to not exhibit large population mean changes but still account for a large proportion of within-individual ageing. Causal multiplicity of particular outcomes, when there are numerous weak ageing effects which cumulate over time, are not well described by many study designs. As we have shown, a very large number of causes that vary across subsets of people may appear as common effects due to the time dependencies of the processes. Typical cross-sectional approaches are insensitive to the multiplicity of ageing processes.

Nevertheless, the robustness of cross-sectional findings does require explanation. Why are processing speed and sensory acuity the 'best' predictors of age-related variance in varieties of cognitive functioning? Are variables that correlate most highly with chronological age (i.e. exhibit the greatest magnitude of age differences) the best predictors of age-related variance? There are numerous possibilities regarding why some behavioral and biological indicators of ageing are better predictors than others in cross-sectional studies and these reasons may include relative population mean change in the context of other predictors in the model, reliability, and the ratio of systematic inter-individual to intraindividual variability. However, it may be that the range of differences in these predictive associations is relatively narrow and the analytical explanations lie within a delimited range. In our view, attempts at such explanation are difficult since these associations are highly related to population mean trends. For example, an

explanation based on the relative ranking of correlations with chronological age is uninformative since the relative mean changes with age in a population may not be important for understanding common causal paths and outcomes of ageing-related change within individuals. Theoretical interpretations that focus on the relative degree of common and unique effects and that rely on empirical evidence from cross-sectional studies must be carefully considered.

The alternative design based on narrow age-cohort samples provides a useful approach to evaluating the structure of age-related changes. This approach treats covariances between individuals as the product of growth and decline, research topics known as differentiation and dedifferentiation. We have described analytically the effect of dedifferentiation in relation to ageing as the outcome of correlated individual differences in rates and patterns of change. In NAC population samples from three Nordic countries of individuals aged 75 years, Hofer et al. [14, 15] find no systematic evidence for the common-cause hypothesis. Few associations between sensory acuity, balance, and cognitive variables were observed and these could more parsimoniously be explained by general health and socioeconomic status (e.g. number of teeth was one of the strongest predictors of cognitive functioning) and peripheral sensory changes (cognitive tests requiring similar sensory functioning were more highly correlated). Using statistical simulations to provide examples of the analytical demonstration of mean-induced covariances, Hofer and Flaherty [16] show that the associations observed at any cross-section will increase with subsequent age samples and closely approximate the population values of the covariance between rates of change under the simulation conditions. This simulation demonstrated that the time-sampling frame is an important consideration regarding the strength of reorganization of individual differences based on associated rates of change and with different initial conditions. A strength of the NAC/SNAC approach is that it permits reanalysis of existing cross-sectional data and provides an alternative to the typical cross-sectional analyses of association that are confounded by population mean trends.

In summary, theories and hypotheses of ageing-related change in cognitive functioning have been based almost entirely on cross-sectional research designs. There are good reasons for this, though most of which are based on economy, of time and money. We would argue that these tradeoffs may not be cost-effective since such studies provide little basis for evaluating the interdependence between processes that change with age. Indeed, only weak evidence for correlated aging processes or outcomes can be derived from cross-sectional studies including shared age effects or that a common ageing factor is sufficient to account for all or most of the individual differences in cognitive change. Indeed, analyses focused on shared age effects or the magnitude of common to specific factor variances will reflect mean trends in the population and cannot permit strong inferences in regards to associations between rates of change and common influences on these changes.

This conclusion does not imply that a common factor theory is necessarily unlikely, only that support for such a theory cannot be obtained from analysis of age-related covariance in samples varying broadly in age. At present, we consider the case for common factor ageing theories as weak, given that the preponderance of supporting evidence comes from cross-sectional studies. Because of the methodological problems described here, theories, hypotheses, and empirical generalizations of ageing phenomenon that are based solely on cross-sectional samples varying broadly in age must be considered weak without alternative evidence. Clearly, cross-sectional designs will remain useful for describing important variables that exhibit age-related differences and for the development of measurement instruments for use across broad age spans or particular subgroups. Alternative cross-sectional designs (e.g. NAC, SNAC) are useful, but optimally, longitudinal designs will be used to evaluate associations between rates of ageing. This will lead to increased understanding of the structure of ageing, in terms of sequences and patterns of changes to the ageing body, brain, and behavior.

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