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An Evaluation of Analytical Approaches for Understanding Change in Cognition in the Context of Aging and Health

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Objectives. In this article, we discuss the importance of studying the relationship between health and cognitive function, and some of the methods with which this relationship has been studied.

Methods. We consider the challenges involved, in particular operationalization of the health construct and causal inference in the context of observational data. We contrast the approaches taken, and review the questions addressed: whether health and cognition are associated, whether changes in health are associated with changes in cognition, and the degree of interdependency among their respective trajectories.

Results. A variety of approaches for understanding the association between cognition and health in aging individuals have been used. Much of the literature on cognitive change and health has relied on methods that are based at least in part on the reorganization of between-person differences (e.g., cross-lag analysis) rather than relying more fully on analysis of within-person change and joint analysis of individual differences in within-person change in cognition and health.

Discussion. We make the case for focusing on the interdependency between within-person changes in health and cognition and suggest methods that would support this.

FOR many years, cognitive aging research has focused on primarily "healthy" older adults and has relied on the assumption that health factors could be ignored for purposes of understanding aging-related causes of change. More recently, there has been increased interest in examining the impact of physical health on cognitive function in understanding aging-related change (e.g., Spiro & Brady, 2008). The impetus has been to better understand the contribution of pathology to changes in cognition, but also to understand more about normative changes in cognition. Understanding the role of health in late life changes in cognitive function is important for research on cognitive aging, as changes resulting from declines in health, which might be remediated or prevented, would otherwise be inappropriately attributed to normative aging-related change (i.e., development) and assumed to be less amenable to intervention. Interest in these associations operates at two levels—interest in whether health and cognition are associated (i.e., pathological aging), and interest in age-related change in cognitive function after accounting for poor health within individuals and in the population (i.e., normative aging). Multiple reports have linked various aspects of cognitive function with particular indices of physical health in older adulthood (for reviews, see Hendrie et al., 2006; Plassman et al., 2010; Spiro & Brady, 2008). Research into the links between health and cognition can provide valuable information from both a public health and a personal well-being perspective. It is worth considering the ways in which study of the link between aspects of health and cognition has been approached, and the questions the various methods address.

Our aim here was to examine the ways in which researchers have approached particular questions of aging-related changes in cognition and health. In reviewing the variety of questions and statistical analyses that have been applied to typical longitudinal studies of aging (i.e., multiple occasions, relatively equally and widely spaced over multiple years), we highlight issues in the implementation of a number of these approaches and encourage the use of methods addressing associations between changes in physical and cognitive health, and explicitly separating lifelong between-person differences from within-person changes. Mental health and socioeconomic factors are, no doubt, additional factors influencing both physical and cognitive health, but they will not explicitly be discussed here.

For simplicity, this article considers the study of health influences on cognition, but the comments and suggestions made here apply equally for the opposite direction, mutual influence, and alternate outcomes and predictors. In studying associations between changes in health and cognition (or any two variables), questions appear at three basic levels: whether the two constructs are associated (each measured at a single, though not necessarily the same, point in time), whether occasion to occasion change in the constructs is associated (using data from two points in time for

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each variable), and whether trajectories of change in two constructs are associated. In addition to these main types of associations, many variations also appear, with status in one predicting subsequent change in the other, change in one predicting status in the other, and with status and change themselves defined in a rich variety of ways. We first review several of the challenges in studying the associations between cognition and health. We next summarize questions relating to health and cognition according to these three main levels, with greater emphasis on association among trajectories of change, which is likely to provide the best characterizations of within-person change. Where possible, we refer to examples from the literature on health and cognitive function based on an extensive search for longitudinal work on these topics. Where examples linking health and cognition were not found, we cite work implementing the method in alternate domains. Finally, we consider future directions for progress in this area.

Challenges for Understanding Associations between Cognition and Health

Measuring "Health"

Although it may appear straightforward to state that "health" influences cognition, measuring "health" for this purpose may be anything but straightforward, and with specificity, comes much greater complexity. The World Health Organization (WHO) definition, "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO, 1948) has essentially not changed since 1948, but little progress has been made toward operationalizing this definition for research purposes. Narrowing to include only physical well-being, this definition is still awkwardly broad and difficult to implement.

Characterizing an individual's health involves measurement complexity along multiple dimensions: type of measurement (e.g., assays, physiology, diagnosis, self-report of symptoms, and self-rating of health), breadth of measurement (e.g., cardio- and cerebrovascular, metabolic, immunologic, musculoskeletal), chronicity, severity, comorbidity, treatment, and adherence (Spiro & Brady, 2008). Determining whether someone is healthy, or in which areas they are less than healthy, requires consideration of a very long list of possible diseases and comorbidities. Efforts to address this complexity have ranged from simple self-report of global health, to including single or multiple diagnoses, to developing indices such as biological age (e.g., MacDonald, DeCarlo, & Dixon, forthcoming; Wahlin, MacDonald, deFrias, Nilsson, & Dixon, 2006) or frailty (e.g., Karunananthan, Wolfson, Bergmann, Béland, & Hogan, 2009; Searle, Mitnitski, Gahbauer, Gill, & Rockwood, 2008). The influence of different conditions on cognition may be through different mechanisms (e.g., neuropathology, pain, fatigue), yet their impact may appear similar. Health-related change may co-occur with cognitive changes (e.g., stroke) or may precede such changes by many years (e.g., hypertension); formal diagnosis of health conditions is not always tightly linked with onset of either symptoms or underlying pathology. Finally, although medications can also have negative consequences on cognition, particularly in older adults (e.g., Bressler, 1993), for some fraction of the population, diagnosis brings treatment that may reduce the impact or progression of the pathology: for example, a person with diagnosed, controlled diabetes may be healthier than a person with undiagnosed uncontrolled symptoms.

A large portion of the research needed in the study of associations between health and cognition lies in developing workable definitions of health. In the meanwhile, focusing on the more prevalent conditions in older adults such as hypertension and diabetes (e.g., ; Hassing et al., 2004; Spiro & Brady, 2008) is likely to be the most fruitful, from the points of view of both public health impact and statistical power. Although comorbidity is likely to play an important role in cognitive change, integrating multiple individual conditions into feasible statistical models will be a challenge. Summary indices may be an effective way to represent the breadth of conditions a person might have, but they may lack the specificity that would permit theorizing regarding mechanisms. Use of summary indices in the context of measuring change may be problematic if there are situations in which a person is judged as having "recovered" from one illness and "gained" another: in this case, their summary score would not change, but relevant characteristics of their health profile may have altered significantly. A mix of these methods that considers comorbidity either within or across summarized groups of conditions believed to share common mechanisms of impact on cognition may provide a useful alternative. Such a balance of both strategies may help in the development of practical health indices.

Health Disparities

A well-known socioeconomic gradient in health, disease, and mortality has been linked to health behaviors, childhood and employment environments, and social supports (Marmot et al., 1991). These have also been implicated in cognitive decline (Brunner, 2005), and there have been efforts to link cognitive performance itself to changes in physical functioning (e.g., Jokela et al., 2010; Lubinski, 2009). Although much of this research has used cross-sectional or cross-lagged methodologies, it points to the need to incorporate the impact of socioeconomic status (SES) as another source of confounding in our models of health and cognition. This would involve including current or childhood SES as a control variable, considering its interaction with other predictors or risk factors, or constructing multigroup models and testing whether different pathways are relevant across different levels of SES.

Mortality Selection

Particularly in the study of older adulthood, missing occasions and dropout can be due to illness and death. Furthermore, individuals who died in midlife or earlier are no longer available to be sampled. The meaning and makeup of the population is in a constant state of flux. In attempting to study "aging," it would be ideal, though expensive and time consuming, to sample at an age young enough to precede the acceleration of these forces. In addition, both longitudinal data containing information regarding death dates and methods tailored to specific research questions (see Kurland, Johnson, Egleston, & Diehr, 2009) are required to adequately address the impact of mortality on research on aging, and to obtain estimates appropriate to the questions being asked. Finally, a portion of individuals may experience substantial declines in health related to imminent mortality. The relationship between measures of health and cognition made during the period immediately preceding death may represent a different process than during earlier stages of the life span.

Terminal Decline

Change and acceleration in change in cognitive functioning has been reported across a range of cognitive abilities associated with time to death. These observations, based on a variety of research designs and methods of analysis, provide evidence for "terminal decline" or "terminal drop" in cognitive functioning in proximity to end of life (for reviews see Berg, 1987; 1996; Bosworth & Siegler, 2002; Siegler, 1975; Small & Bäckman, 1999). However, they have been based primarily on between-person differences rather than test of acceleration of within-person rate of change (Piccinin, Muniz, Matthews & Johansson, in press). In addition, with some exceptions (e.g., Anstey, Mack, & von Sanden, 2006; Rabbitt et al., 2002), this research has been generally agnostic with regard to underlying health conditions and comorbidities that may differentially affect cognitive functioning before and during the terminal decline phase. Proximity to death may be a valid, though indirect, marker of overall health and vitality. Numerous studies have provided evidence for accelerated decline in a broad range of human abilities over a period immediately before death. Because of the potentially systemic changes related to dying, it is important to emphasize preterminal decline processes in understanding the effects of particular biological and health-related changes on cognitive impairment (e.g., Sliwinski, Stawski, Katz, Verghese, & Lipton, 2006).

Age Heterogeneity of Samples

In addressing the question of whether some of what is currently being treated as "aging-related" cognitive decline might instead be due to "health-related" declines, another significant challenge is the fact that decline in health (e.g., increasing comorbidity) is also more prevalent in later life. Given this situation where both predictor and outcome are related to age, it will be important, in any analysis of age heterogeneous samples, to include an indicator of age differences and to evaluate potential age-based interactions in associations between health and cognition. This permits evaluation of the impact of differences in health quality "given individuals of the same age". For example, Hertzog, Schaie, and Gribben (1978) found that when they included a "cohort" variable, separating their participants into two 14-year age groups, all longitudinal associations with cardiovascular disease disappeared except for psychomotor speed. It is possible, had statistical power been adequate to more finely delimit cohort, that this final association would also have been eliminated. In any case, age heterogeneity must be considered in both cross-sectional and longitudinal analysis.

It has often been stated that age is not an explanatory variable (e.g., Wohlwill, 1973), yet it is generally understood that it should be included in the analysis. An appropriate role for "age" may be as a control variable, so that associations among other variables of interest are less confounded with individual differences in chronological age. There is some risk, however, that controlling for age can induce a "horse racing" bias (Glymour, Weuve, & Chen, 2008; Peto, 1981)—serving as a proxy for prior decline. It is also likely that the impact of illness is greater at older ages or in the context of increasing comorbidities, so that the interaction between health, age, and survival must be carefully considered in terms of conditional population inference.

Causal Inference

In understanding changes in cognition, health, and aging, questions related to causal inference and direction are inescapable. There is no doubt that physical health can influence cognition. Acute events such as stroke can have clear and catastrophic impact, but chronic diseases as well can lead to poorer brain function (e.g., Launer, Masaki, Petrovitch, Foley, & Havlik, 1995). On the other hand, there is evidence (e.g., Deary & Batty, 2007; Elias, Elias & Elias, 1990; Lubinski & Humphreys, 1997; Mehta, Yaffe, & Covinsky, 2002) that cognitive ability can also influence physical health across the life span: attaining a higher education level leads to elevated SES and better access to health care, positive health behaviors, and better understanding of health prescriptions. Moving forward, it will also be important to consider potential genetic sources and gene–environment interactions (e.g., Shanahan & Hofer, 2005, 2011) that may be common life-span pathways for both health and cognition, and to think carefully about sensitive periods and accumulation of effects.

Understanding within-person causal processes and causal heterogeneity in the population is challenging given

the observational nature of aging-related change data. Although widely spaced intervals are currently most typical in longitudinal research, intensive measurement designs and long-term studies with more frequent follow-up between major interval assessments are being implemented to better identify individual change and variation and to capture potential within-person causal processes and events. Very long-term longitudinal studies permit some basis for both understanding and adjusting for early life characteristics and contexts (e.g., SES) that affect lifelong developmental processes and late-life outcomes (e.g., Gow et al., in press; Hauser & Palloni, 2010; Kuh & Ben-Shlomo, 2004). During the later years, however, identifying temporal precedence of one factor over another is a challenging task that is easily misleading due to different sensitivities of measures, diagnostic thresholds, and confounding factors (e.g., Cole & Maxwell, 2003; Rogosa, 1980). Underlying pathology that does not meet clinical threshold may produce early changes in brain, cardiovascular, and other functions related to cognitive functioning and that will not be diagnosed until a later date (Hertzog, Schaie & Gribben, 1978). We encourage caution when extrapolating between-person individual differences to within-person cause on the basis of lead-lag approaches.

It is difficult to identify the causal processes at the individual level and in terms of causal heterogeneity in the population. With respect to understanding population aging, we can make a distinction between "common cause" and "common outcome," given the possibility that a common cause can lead to different manifestations of outcomes and that independent causes (e.g., risk factors) can lead to common outcomes (e.g., cognitive impairment). For example, different health-related processes may influence multiple systems within an individual. Age-related contextual influences (e.g., stress response related to loss of spouse or child) may be unique to each individual, although such influences may appear to have a common outcome in the population (e.g., Hofer, Berg, & Era, 2003; Sliwinski, Hofer, & Hall, 2003). Between-person causal heterogeneity is likely the main source of the difficulty in differentiating aging-related changes from changes associated with health processes within individuals. Additionally, differences in conclusions reached regarding associations between health and cognition may stem in part from differences in the questions addressed by the various methods employed in this area of research (see, e.g., Schaie, 1996, pp. 257–259).

Research on aging-related processes relies on a variety of designs and statistical models that can provide distinct and potentially complementary answers to different questions. The challenge is to consider the strengths and limitations of particular designs and statistical models for understanding the interdependency among individual change and variation (Hofer & Piccinin, 2010). It is worth reviewing the ways in which these methods and questions differ.

Questions Regarding Associations between Cognition and Health

Associations between Two Constructs, Measured Simultaneously

Is cognitive function related to individual differences in health?
Are individuals who are in worse health (presumably due to a change from prior functioning) more likely to also have worse cognitive performance?

A vast majority of research on cognition, with or without attention to health, and with or without the availability of longitudinal data, has been based on cross-sectional information. Cross-sectional information can address the ways in which individuals differ, but not from a directly developmental or within-person point of view, as it does not contain information regarding how individuals change (except as inferred by proxy of age differences). In other words, cross-sectional information tells us how people are currently functioning, but not how they have changed.

To the extent that higher chronological age increases the probability of a variety of conditions, including ill health and cognitive decline, cross-sectional associations in age heterogeneous samples can be driven by spurious associations as a result of mean trends (e.g., Hofer & Sliwinski, 2001; Hofer, Flaherty, & Hoffman, 2006; Kraemer, Yesavage, Taylor, & Kupfer, 2000). Such associations might be due to lifelong or cohort influences such as fewer educational and nutritional/medical opportunities for the generations we currently study as "elderly" relative to more recent generations (though nutrition in particular may be declining in the most recent generations; Mirowski, in press), or to outliers. In addition, the health of individuals who agree to participate in a study is generally better than those who do not (Mendes de Leon, 2007; Morrell, Brandt, & Ferrucci, 2009). At the very least, we can be sure that the older members of a sample survived until their late age, whereas this will not be true of some of the initially younger participants. Ideally, these sources of variance would be conditioned on prior to the interpretation of associations among variables.

One way to isolate particular cohort influences is to recruit an age homogeneous sample, in which such cohort differences are held constant. To the extent that influences within a cohort affect both predictor and outcome (e.g., health and cognition, in your preferred order), a spurious association may still be possible, but, overall, we should expect a smaller impact of cohort influences. If cross-sectional data are the only option, age homogeneous (narrow age cohort) or a set of age homogeneous slices (sequential narrow age cohort) are recommended (Hofer, Flaherty, & Hoffman, 2006; Hofer et al., 2003). Although health status and mortality selection no doubt still play a role (deceased individuals are no longer available in the population, and unhealthy individuals are less likely to respond to recruitment requests),

the potentially confounding effect of cross-sectional age differences is removed from the analysis.

Associations between Constructs across Time: Cross-Lag Analyses

> Do individual differences in health at one occasion predict individual differences in cognitive function at another?

When data are available at more than one point in time, it becomes possible to look at within-person changes, to be discussed later, but it is also possible to consider lagged associations of between-person differences within a particular variable across time as well as cross-lagged associations between variables across time. Although not common in cognitive aging per se, one busy avenue of such research has been to understand the time course of health and cognition-related changes. Health, or cognition, at an earlier point in time, has been used to predict cognition, or health, at a later point (e.g., Singh-Manoux & Marmot, 2005). Such lagged analyses, however, consider the association between individual (between-person) differences at one point in time and individual (between-person) differences at another point in time. Although change in at least some individuals is inferred by the reordering of scores on a particular variable from one occasion to another, the change that can be reported from such an analysis is represented in terms of stability or degree of association between occasions; in terms of changes in rank ordering rather than in terms of amount of change. A cross-lagged analysis is, similarly, a reflection of the relative status of individuals on two (or more) variables at two (or more) occasions. It does not reflect within-person change. Given that a variable with good reliability can be highly correlated with itself over time, it is not a surprise when conclusions based on a lagged association are the same as those at baseline. This has been found for baseline blood pressure with both baseline and follow-up Mini-Mental State Examination score (Guo, Fratiglioni, Winblad, & Viitanen, 1997), and for body mass index and hypertension with subsequent and concurrent cognition (Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003).

Cross-lagged models often treat later occasion variables as outcomes and earlier occasion data as "predictor" and "control" variables. However tempting and logical it might seem to "control" for earlier performance when predicting either later or change in performance, such control is appropriate only in the context of random assignment to groups. Extensive discussions of this issue are available in the context of analysis of covariance and group differences generally (e.g., Fitzmaurice, Laird, & Ware, 2004; Maris, 1998) as well as in the analysis of change in cognitive function (e.g., Glymour, Weuve, Berkman, Kawachi, & Robins, 2005). Fitzmaurice and colleagues (2004) explain clearly that the meaning of a high or low value at baseline may be different for nonrandomly assigned groups. They point out the difficulty with statistically equating weight in developing boys and girls: the same objective weight may be "light" for a boy and "heavy" for a girl.

The same difficulty arises in the context of regression. For example, individuals at different levels of "health" at baseline will have low cognitive functioning for different reasons than for those in prime physical condition, and it is not logically possible to equate the meaning of their scores. Results obtained from such an analysis cannot be meaningfully interpreted. Although information on prior characteristics is desirable, controlling for a somewhat younger version of the variable of interest (e.g., cognitive performance) is not generally recommended (Fitzmaurice et al., 2004; pp. 122–126). Instead, statistical analysis should include variables such as age, and interactions with other predictors (e.g., health) given that age and other individual differences (e.g., education) may also operate as moderators of associations between predictors and outcomes.

A further assumption of cross-lagged models is that although the cognition and health variables may correlate at any particular point in time, all "causal" influence is lagged (Rogosa, 1980; see Cole & Maxwell, 2003 for further assumptions and their relation to longitudinal mediation models). Although a cause must occur before an effect, when both are measured at intervals of a year or more, as in most longitudinal research, it may not be logically possible to determine which variable is the cause for all or most individuals. Both could have changed, for example, in the days before a particular occasion of measurement, and the true "cause" may not show as large a change as the "effect." This is a critical point because it is very tempting to use cross-lagged correlation (CLC) magnitude, or significance of CLC differences, as an index of causal or chronological precedence. The relative magnitude of the associations has been, but should not be, used as an indicator of causal priority, as it is influenced by the relative stability of the two variables, and will favor the variable with increasing variance over time (Rogosa, 1980).

Analysis of Change across Two Points in Time

> Does a change in health precede (weak inference) or cause (strong inference) change in cognition?

When considering change as the difference between a person's scores at two points in time, it is possible to describe the association between change in one variable and level of another variable at a later date (e.g., Comijs et al., 2004), or level at an earlier date in one with subsequent change in the other (e.g., Kang, Logroscino, De Vivo, Hunder, & Grodstein, 2005). These strategies are often used when one of the variables has not been measured on multiple occasions. For example, some information has been collected

only at the baseline wave, or collection of a new variable has only been initiated at a later wave. If both variables are available at multiple waves, then it is possible to work with change scores in both variables. Change scores have been much maligned (e.g., Cronbach & Furby, 1970; Harris, 1963; Lord, 1956), but more recent conclusions are that these difficulties exist primarily in situations where either change is minimal or too similar across individuals to provide reliable differentiation (Rogosa, Brandt, & Zimowski, 1982). In addition to relying on factor-level variables, which reduce the measurement error problematic in change scores, a number of additional solutions have been proposed for dealing with situations in which reliability is a concern and factor models not an option (e.g., Frerichs & Tuokko, 2005; Tombaugh, 2005).

Change has typically been defined according to actual amount of change (e.g., Newson & Kemps, 2005), as a dichotomy (changed/not changed) or diagnosis (i.e., change implied; e.g., Rubin et al., 1998), and as change of more than some group-referenced amount such as a standard deviation (e.g., Eslinger, Swan, & Carmelli, 2003) or other group-referenced quantity, such as tertiles, quartiles, or quintiles (e.g., Carmelli, Swan, LaRue, & Eslinger, 1997; Karlamangla, Singer, Greendale, & Seeman, 2005). Difference scores between two points in time have been treated as predictors (e.g., Habib, Nyberg, & Nilsson, 2007) and as outcomes (e.g., Chodosh, Kado, Seeman & Karlamangla, 2007; Weaver et al., 2002) in regression, with (e.g., Alves de Moraes, Szklo, Knopman, & Sato, 2002; Chodosh et al., 2007; Kang et al., 2005) and without (e.g., Knopman et al., 2001) "correction" or "control" of initial level of health or cognition.

For all of these, in an age heterogeneous sample, it remains important to include baseline age in the model. Adjusting for between-person age and sex differences is essential in order for associations among change to be defined relative to like-aged peers and to minimize the potential for inflated associations due to mean trend differences related to age-graded and sex differences in changes in health and mortality selection (e.g., older individuals are more likely to be ill and suffer cognitive loss than younger adults in general; sex differences in morbidity and survival age).

The recently developed latent change score version of cross-lagged analysis, the Bivariate or Dual Latent Change Score Model (McArdle & Hamagami, 2001) evaluates, among many other parameters, the conditional association between each construct at Time t and change in the other between Time t and $t + 1$. Models of this type are growing in popularity (e.g., Finkel, Reynolds, McArdle, Hamagami, & Pedersen, 2009; Gerstorf, Hoppmann, Anstey, & Luszcz, 2009; Ghisletta & Lindenberger, 2005), but specific examples addressing links between health and cognition were not found. Given the parallels with cross-lagged models, it may be important to approach conclusions regarding the precedence of one domain over the other with caution.

Prediction of Cognitive or Health State

Does decline in cognition predict mortality or disease incidence?
Does worse health increase the risk of "cognitive decline" (defined as a state change)?

When change is defined as change in state, based on a clinical or arbitrary cutoff, the outcome (e.g., cognitive decline) may be treated as binary event as in survival analysis (event history, Cox regression) or logistic regression (e.g., predicting whether someone is in a diagnostic group, or has experienced a change in health or cognitive function). When implemented with cognitive change as an outcome, survival analysis requires expressing change as an event (e.g., Cricco, Simonsick, & Foley, 2001; Elkins, O'Meara, Longstreth, Carlson, Manolio, & Johnston, 2004). This generally requires the defining of some arbitrary amount (e.g., a standard deviation or a set number of points on a test) as clinically or functionally meaningful, or the setting of some clinical or other threshold level of performance. This captures the crossing of a particular threshold, but not the distance traveled to reach it. The advantage of the survival model is its handling of right censoring. The disadvantage is the assumption that everyone would ultimately experience the event if they were followed for long enough. Singer & Willett (2003) articulate three major features appropriate for such event-based models: "(a) a well-defined "event" . . .; "(b) a clearly identified "beginning of time"; and (c) a substantively meaningful metric for clocking time." Unfortunately, in observational studies of aging, "time" is often "time since birth," resulting in a great deal of left censoring in the study of older adults. Similar to survival models, multistate models estimate the probability of transitions through a series of discrete states, such as healthy, diseased, diseased plus comorbidity or complication, or dead.

Despite their extensive use in health research, survival analysis use in the cognitive change literature has tended to be limited to dementia or other pathological states. However, joint growth-survival models (Ghisletta, 2008; Ghisletta, McArdle, & Lindenberger, 2006; Guo & Carlin, 2004; Henderson, Diggle, & Dobson, 2000) provide an innovative solution to the prediction of future events, such as diagnosis or death, based on individual differences in level and rate of change.

Analysis of Rate of Change in Cognition

Growth curve models facilitate the study of between-person differences in within-person change by, conceptually, estimating within-individual regressions of performance on time as well as on expected predictors of these individual regression parameters (e.g., intercept, or level, and slope, or rate of change). Since the mid-1990s, such models, variously known as mixed effect, random effect, multilevel, or (latent) growth curve, have become increasingly popular.

Before this time, information on change within individuals was generally limited to difference scores across sets of two occasions. These models, and the software to estimate them, which had been developing over the previous 40 years (e.g., Rao, 1958; Tucker, 1958; Laird & Ware, 1982), have allowed a shift of emphasis from group to individual-level change that encompasses three or more occasions, taking into account the lack of independence of observations within individuals. Unlike the methods employed before this time such as repeated measures analysis of variance, individual differences in change can be treated as a characteristic of interest, rather than as error variance. Also, by estimating a systematic rate of change over multiple occasions, it is possible to make use of unbalanced data and to eliminate at least some of the measurement error that is part of individual data points.

Growth models are sometimes estimated with generalized estimating equations (Liang & Zeger, 1986; e.g., Comijs et al., 2009; Cui et al., 2007; Dufouil, Alperovitch, Ducros, & Tzourio, 2003; Kuo et al., 2005), which, while accounting for the lack of independence of repeated measures, treat the dependence as a nuisance and focus on the marginal, or population averaged, effects. Although this can address public health (population average) questions, individual development or change and unit-specific effects conditional on particular covariates are not part of the model (Skrondal & Rabe-Hesketh, 2004; Twisk, 2004). It also has a stronger assumption regarding the missing values (missing completely at random) compared with random coefficient models that assume missing data are missing at random (MAR). Growth models open up a variety of analytic opportunities, each with strengths and challenges for modeling associations between health and cognition. Two overarching issues to address are the choice of time metric and the separation of between-person and within-person information.

Time metric.—As estimation methods and software developed, data requirements have become more flexible. Earlier analyses (ca. 1990s) were limited to situations with balanced data (all individuals measured at the same set of occasions). However, advances in the implementation of full information maximum likelihood and other estimation methods in various software packages (e.g., MX: Neale, 1994; HLM: Bryk, Raudenbush, & Congdon, 1994; MLwiN: Prosser, Rasbash, & Goldstein, 1996; BUGS: Spiegelhalter, Thomas, Best, & Gilks, 1996), as well as some creative approaches to coax other software to approximate this flexibility (e.g., multigroup analysis in SEM: McArdle & Anderson, 1990) soon allowed the analysis of more and more unbalanced designs. Rather than tracking time according to occasion number, it became possible to use actual time elapsed since baseline, and, eventually, age, as the index of time. Alternate time metrics were explored, describing change relative to distance from dementia diagnosis, attrition, and death (e.g., Hoffman, in press; Sliwinski, Hofer, Hall, Buschke, & Lipton, 2003), as these may better account for systematic changes in cognition. The possibility of modeling concurrently unfolding processes has also been considered, including the simultaneous estimation of both parallel (Thorvaldsson, Hofer, & Johansson, 2006) and serial (e.g., change point: Hall, Ying, Kuo, & Lipton, 2003; Wilson, Beckett, Bienias, Evans, & Bennett 2003) time processes.

Convergence.—As discussed previously, longitudinal studies of age heterogeneous samples include both cross-sectional age differences and longitudinal age changes. Ware (1985) underscored the importance of separating these two sources of time (or age) information in growth models by explicitly regressing the growth parameters (i.e., intercept and slope) on the cross-sectional age data (i.e., on initial between-person age differences). To the extent that they differ (and one might expect that they do, or one would just collect cross-sectional data), any estimate of their combined effect cannot be clearly interpreted. It is not logically possible to report estimates of within-person change without separating the between- and within-person information in this way (or studying an age homogeneous sample). Growth models of age heterogeneous samples using a "time in study" (i.e., time since baseline) metric have generally included such an initial between-person age variable (e.g., age at baseline). However, most "age-based" time metric analyses, in which age, rather than time since baseline, is the chronological index, have not accounted for baseline age differences. Age-based models must similarly regress growth parameters on baseline age in order to separate longitudinal changes from between-person differences. These baseline age parameters represent the expected difference in the growth parameters attributable to having entered the study at a different age (see Sliwinski, Hoffman, & Hofer, 2010 for further details). In addition to allowing for differences due to possible cohort effects, particularly in the study of aging in later life, it is essential that differences due to healthy participant (e.g., Mendes de Leon, 2007) or mortality selection effects (Kurland et al., 2009) be modeled.

An appropriate health variable, however defined, could be used in a growth model of cognitive change in ways that address a variety of questions.

Does Initial Health Status Predict Subsequent Rate of Change in Cognitive Functioning?

Health as baseline covariate.—Indices of health (or any domain) have mainly been included as time invariant predictors in growth models (e.g., Clark et al., 2007 [though this and other age-based models cited here did not control for baseline age differences]; Ganguli, Vander Bilt, Saxton, Shen, & Dodge, 2005; Hebert et al., 2004; Van Dijk, Van Gerven, Van Boxtel, Van der Elst, & Jolles, 2008; Waldstein, Giggey, Thayer, & Zonderman, 2005). In other words, health

has been represented as the value obtained for each participant at baseline. This can provide information about the rate of change in cognitive performance for people who enter the study at a particular age and a particular level of "health" or who have a particular diagnosis or event (which may be available prospectively in a longitudinal study). Although it is valuable to include health in the model, this approach does not directly address the association between a change in health and a change in cognition (except through inference that someone already in poor health must have experienced a change from a healthier status). Because some participants will experience health changes after the baseline visit, use of only baseline information can provide only a limited answer with respect to the association between changes in health and changes in cognition. For example, Elias, Robbins, Elias, and Streeten (1998) report finding a stronger association between cognitive change and blood pressure (BP) when BP was averaged over all examinations than for initial BP alone. It is possible, however, to model the influence of changes in health in several ways that make more time-sensitive use of the health information: as a time-varying covariate, as a simultaneously estimated growth process, or as a reference point in chronological time.

Does Longitudinal Variation in Health Status Account for Within-Person Change and Variation in Cognitive Functioning?

Health as a time varying covariate.—Health can be included in a growth model as a monotonically (e.g., Knopman, Mosley, Catellier, & Coker, 2009) or intermittently (e.g., Béland, Zunzunegui, Alvarado, Otero, & del Ser, 2005) time-varying covariate. As a monotonic variable (e.g., occurrence of a stroke between third and fourth occasions of measurement: 0 0 0 1 1), it can operate as a switch that allows a different level or rate of change in cognitive function after an event (for details, see Singer & Willett, 2003). In the case where some individuals never experience the health transition, a separate variable should perhaps be included to capture any "preclinical" differences that exist between non transitioning and transitioning individuals, though this may risk introducing Peto's (1981) horse-racing bias. In situations where it is believed that, for example, transient health changes such as colds, fatigue, etc., may influence cognitive performance for some individuals at some occasions, it is sensible to partial this variance from the observed scores at each occasion. This can be accomplished by representing health at each occasion as a (within-person) deviation from each person's health at the intercept, which is also included in the model (capturing the between-person deviations; as explained in Grimm, 2007). Although this does not provide a direct estimate of the influence of health fluctuations on the rate of change in cognition, it does result in cognitive change estimates that have been "corrected" for health fluctuations. When the health variable of interest has a time trend, it may be more appropriate to model this trend as a growth trajectory that may be correlated with a cognitive function trajectory.

Are Individual Differences in Patterns and/or Rates of Change in Health Associated with Rates of Change and Time-specific Variation in Cognition?

Health as a simultaneously unfolding process (multivariate growth model). —If an individual's health is viewed as changing, then the association between changes in health and changes in cognitive performance can be represented in a growth curve context by simultaneously estimating trajectories for the two variables and focusing on the correlation between the two trajectories. Small, Dixon, and McArdle (2010) present a piecewise parallel growth model of several measures of cognition and a composite self-reported health score that included self-rated health, frequency of recent illness episodes, and chronic illness. They found mainly cross-sectional associations between this health measure and cognition, with changes in self-reported health associated only with changes in semantic decision time in individuals younger than age 75. The wide initial age range and the discontinuity in rate of change allowed by the piecewise specification may contribute to the weighting toward cross-sectional associations. It would be interesting as well to explore whether a health index based more on duration and progression of chronic illness, rather than episodes, or distinguishing among types of illnesses may be more correlated with cognitive change. With such creative and thoughtful implementations, this method has good potential to support research on within-person changes in health and cognition.

What is the Expected Rate of Change in Cognition prior to (or following) a Particular Health Event (e.g., dementia diagnosis, stroke, myocardial infarction)?

Health event as a reference point.—Growth curves of cognitive performance can be modeled with a time metric aligned according to an event or diagnosis (e.g., Sliwinski et al., 2003). Rather than using time elapsed since the first occasion, or chronological age (centered at some sensible value), the intercept in the analysis, and hence the aligning of individuals relative to one another in time, could be specified relative to the event of interest. Unfortunately these timelines cannot be defined for individuals who do not experience the event (or who experience a different event), so it is difficult to compare those who experience the event (or diagnosis) with those who do not. Laukka, MacDonald, & Bäckman (2006, 2008) dealt with this creatively by modeling the most salient event for each individual and setting an arbitrary "event" date for individuals not experiencing an event, allowing inclusion of all individuals in the analysis.

Although this introduced some interpretational complexity, it allowed them to conclude that individuals nearing death did not reliably differ from surviving controls, and that individuals with preclinical dementia declined at almost twice the rate of the other two groups. A further challenge will be to consider situations in which individuals experience more than one event. If only one can provide the chronological reference point, which one should be chosen, and how should the additional events be incorporated—perhaps as a time-varying covariate?

Another alternative is the random change point model for joint modeling of cognitive decline and time to dementia proposed by Jacqmin-Gadda, Commenges, and Dartigues (2006). In this model, an inflection point is identified for each person using a piecewise polynomial trajectory specification to describe the cognitive decline in the prediagnosis stage of dementia, estimate the time between the acceleration of the cognitive decline and the diagnosis of dementia, and evaluate whether the shape of the change depends on covariates of interest. Their examination of change in Benton Visual Retention scores from participants in the Paquid study showed little difference in rate of change by educational level before the change point, but after the change point the shape of change differed significantly between individuals with low and high education. They concluded that the time between the change point and the diagnosis of dementia was longer for individuals with low education, for whom the cognitive decline was smooth with a change point that was difficult to detect.

Although multioccasion data and growth models increase the sophistication with which health-cognition associations can be modeled, these models require careful consideration of initial and continuing (i.e., mortality) sample selection effects and potential confounders. Despite spiraling complexity, Ware's (1985) caution regarding the necessity of separating initial between person differences from subsequent within person changes must not be forgotten.

Discussion

The question of how to separate the effects of ill health from aging is not a new one. Busse (1969) framed it in terms of primary and secondary aging, and it is clearly a complex issue. Given that late-life deterioration likely results from interactions among aging and disease, their effects may not be fully distinguishable (Blumenthal, 2003; Newman & Ferrucci, 2009). With age comes increasing likelihood of disease, cognitive loss, and death. As such, a variable representing initial between-person differences in age should be included in any analysis of an age heterogeneous sample, regardless of whether the data are cross-sectional or longitudinal, in order to at least partially separate potential influences of generational differences, healthy participant, or mortality selection. If age is not adjusted for or evaluated as a moderator in the analytic model, associations between health and cognition may be spurious and due to the average trend of age differences. Likewise, if health and SES variability are not controlled, associations between age and cognition may be spurious and due to health and SES differences and interactions.

Is it necessary to establish causality? Perhaps given the broad variety of ways in which individuals may find themselves in poor health, suggestions of causality would be useful as a means to focus public health efforts (though this would also be possible based on prevalence data). It would also provide the evidence required for people to attribute cognitive declines to health, per se, rather than to aging, where the former may more often be viewed as modifiable.

Establishing causality requires demonstration that better health results in less cognitive decline. Logic and ethics limit test of treatments causing illness, but interventions designed to keep people healthier are certainly possible. Individual features such as exercise, diet, and medical intervention have been studied, in the interest of isolating key factors, but given the likely importance, and likely interaction, of multiple factors, a "super life and care" scenario could be devised, encompassing health promotion and illness prevention at all levels: behavioral, environmental, medical, psychological. Two foreseeable difficulties are identifying the timing and duration of the intervention—presumably the longer the better in terms of impact—and health behavior compliance, which may be inconsistent.

Another dilemma to address is whether average population declines in health and cognitive function arise due to small declines in most of the population or large drops in smaller subsets of individuals (i.e., the limited impact hypothesis; Luszcz, 1998; Salthouse, 1991). Declines are likely to involve a mix of both of these processes—with small relatively global changes in cognition due, for example, to peripheral sensory declines and reduced engagement, and larger declines in subsets of individuals, associated with various pathological processes. If such a mix existed, some of the inconsistencies in the literature may have arisen from low power to detect small changes, and from a tendency to define "change" or "decliners" relative to the available sample and measures, both approaches that would emphasize the more sizable declines.

Part of the value of longitudinal studies is their long follow-up: having information about the timing of mortality and whether an individual eventually receives a diagnosis of dementia may be critical to understanding the changes we are able to measure during the period of active study data collection. This returns us to the issue that, unlike mortality, not everyone will experience particular health (or disease) states. Different sets of physical conditions (and life experiences) will have different (and in some cases similar) impact on cognition in different individuals. This multiplicity of population cause and effect remains a challenge to any work done in the area.

At a descriptive level, physical health and cognitive function seem generally to be correlated, though the association is stronger for some aspects than others. It is certainly worthwhile to further explore which aspects of health are most related to late life changes in cognition, but it will be difficult to establish cause in the context of observational data. To advance our understanding of the interplay between health and cognition in the context of aging will require longitudinal designs and careful analysis of within-person change and variation in a highly multivariate context. Design confounds include initial sample selection and follow-up of continuing participants (population mortality selection), changes related to morbidity and terminal decline, and the need to condition change on both age and time to death (e.g., Kurland et al., 2009; Piccinin et al., in press).

The study of cross-sectional associations between health and cognition is presumably intended as a proxy for the study of changes in health and changes in cognition. In fact the word "change," rather than "difference" is often used. If cross-sectional data only are available, then statistical control of age differences should be implemented. If we intend to measure change, however, we must measure repeatedly: often enough to better locate cognitive and health changes in time, as well as to be able to differentiate between gradual, relatively linear change, and more abrupt, nonlinear change.

To specifically address questions relating to associations between changes in health and changes in cognition, methods such as the variety possible through growth curve modeling that make use of all the longitudinal data seem promising. Careful attention to separating the between-person age difference information available in age heterogeneous samples from the within-person age change and time-specific variation information contained in the repeated measurements will be required. For new studies, closer collaborations between psychology and medicine, where both can simultaneously bring their best measures and knowledge to the table, would provide the greatest support for the next steps of progress in this area. Creative and less intrusive data collection designs, making use of the convenience of the Internet, may lead to some innovative ways to achieve some of these goals.

A significant public health goal is to maximize health span, the period of life in which individuals remain relatively free of physical and cognitive impairment. Understanding the processes leading to change in health, physical function, and cognition is a major goal internationally. We have discussed many of the methodological issues related to understanding the impact of aging and health-related processes on cognitive impairment and change. Analysis of existing longitudinal studies has a major role in producing new results, with replication of research findings across independent longitudinal studies being essential for a cumulative and innovative science. However, replication and extension of results from longitudinal studies is currently limited by the paucity of published information on particular research questions, differences in the design, sample composition, measurements, and statistical analysis, and practical limits on full reporting of results. One approach to achieve this is through a collaborative coordinated analysis approach for building a broad foundation for cumulating scientific knowledge by facilitating efficient analysis of multiple studies in ways that maximize comparability of results and permit evaluation of study differences (Hofer & Piccinin, 2009; 2010). The variety of samples (e.g., different birth cohorts), measurements (e.g., early childhood data), contexts (e.g., country, culture), and research designs, particularly in the area of longitudinal aging research, is a major advantage for understanding the interdependency among cognition, health, and aging.

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