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Cognitive decline in normal aging and early Alzheimer's disease: A continuous or discontinuous transition? A historical review and future research proposal

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Abstract: A longstanding debate in dementia research has been whether normal aging and Alzheimer's disease (AD) are extremes that lie along the same continuum (*continuity view*), or whether AD is categorically different from normal aging (*discontinuity view*). In other words, do only *quantitative* differences in neuropsychological test performance exist between normal aging and AD, or are there also *qualitative* differences? This question has been dominating dementia research for a century now and is characterized by inconsistent results and differences in methodological approach. In this review, I discuss studies that draw conclusions in terms of a continuous transition from normal aging to AD, followed by a discussion of studies that draw conclusions in terms of a discontinuous transition. In addition, several methodological issues are discussed that may explain the contrasting findings. This led to a proposal for investigating this topic in further research. I argue that only a latent variable (structural equation modeling) approach testing for measurement equivalence may or may not reveal structural (i.e. qualitative) differences in

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Her research (PhD 2003) focuses on the early assessment of dementia and how various memory components may improve prediction. In particular, she is interested in the nature of semantic processing deficits in (early stage) Alzheimer's disease and how this may contribute to more reliable differential assessment.

Furthermore, she is interested in explaining patterns of age-related cognitive deficits within the *normal* aging spectrum: from young-old (55+) to very old age (up to 96 years old). More specifically, she studies (by means of SEM) the interplay between episodic and semantic memory components, on the one hand, and processing speed and executive functioning, on the other hand.

PUBLIC INTEREST STATEMENT

Alzheimer's disease (AD) may already occur at age 50 (or before), but occurs more frequently when we get older. Especially at very old age, it is difficult to determine what is normal and what is not. Besides, we do not even know whether the transition from normal aging to AD is continuous or discontinuous. Normal aging and AD could be two extremes on the same continuum: people simply differ at a *quantitative* level. Or: Does AD represent a *qualitatively* different entity––a disease that could be acquired by some but not by others, even when they grow very old?

This review summarizes research results that seem to adhere the *continuity* or the *discontinuity hypothesis*. Various methodological factors are discussed that may explain the contrasting findings. To finally answer this longstanding debate, it seems crucial to choose a more advanced statistical approach that may specify whether differences are quantitative or also qualitative.

neuropsychological test performance between normal aging and AD. This outcome has important implications for the selection of optimal procedures of early AD assessment, particularly at very old age.

Subjects: Aging and Health; Dementia; Dementia & Alzheimer's Disease; Statistics for Social Sciences

Keywords: Alzheimer's disease; normal aging; cognitive decline; continuity view; discontinuity view; structural equation modeling; metric invariance

1. Introduction

A longstanding debate in dementia research (e.g. Berrios, 1994; Huppert & Kopelman, 1989) has been whether normal aging and Alzheimer's disease (AD) are extremes that lie along the same continuum (*continuity view*), or whether AD is categorically different from normal aging (*discontinuity view*). Thus, does everyone who lives long enough eventually develop dementia or AD in particular, or not? Berrios (1994) described this debate in historical context that exists for approximately a century now. Alois Alzheimer himself allegedly adhered the continuity view (1907), whereas Kraepelin, Barclay, and Robertson (1919) may rather have supported the discontinuity view (Berios).

The debate most likely originates from a large variability regarding course of the disease and age of onset (Fratiglioni et al., 2000; Harvey, Skelton-Robinson, & Rossor, 2003; Lobo et al., 2000). There are wide individual differences in the rate at which memory and other cognitive decline occurs in AD (Mayeux, Stern, & Spanton, 1985; Wilson, Gilley, Bennett, Beckett, & Evans, 2000). Concerning age of onset, Braak and Braak (1997) concluded that AD is an age-related, but not an age-dependent disease. On the one hand, AD may already occur in persons in their 50s, or, although highly uncommonly, even in their 30s, in persons without, for example, Down's syndrome. On the other hand, there are anecdotal reports of individuals, defined as "SuperAgers", who seem immune to both age-related memory impairment and age-related changes in cortical volume (Harrison, Weintraub, Mesulam, & Rogalski, 2012).

Nonetheless, Wilson et al. (2000) stated that as age is the most robust risk factor for developing AD, any attempt to account for the heterogeneity of AD should probably begin with age. In addition, it is important to be aware of the methodological characteristics of the research being conducted. Inconsistent findings regarding the rate of cognitive decline in relation to age may be influenced by, for example, sample sizes, the number or spacing of observations over time, follow-up participation, floor and ceiling effects on measures of cognitive function, and statistical methods to analyze longitudinal cognitive data (Wilson et al., 2000). Wilson (2008) concluded that controversy prevails in aging research whether or not neurological factors contributing to late life dementia are different from the factors contributing to subtle changes in memory and cognition seen in old people without dementia.

This debate is not only of scientific importance, but has also become more and more relevant for clinical practice considering increased average life expectancy and, consequently, increased prevalence of AD (e.g. Fratiglioni et al., 2000; Lobo et al., 2000). Evidence in favor of the discontinuity hypothesis emphasizes the importance of developing tests that are able to detect the precise nature of the cognitive problems characteristic of early AD, up to very old age (e.g. Spaan, Raaijmakers, & Jonker, 2005). In contrast, evidence in favor of the continuity hypothesis would recommend efforts of improving normative data or determining optimal cut-off scores of (existing) neuropsychological tests. Obviously, both types of efforts to improve clinical neuropsychological assessment of AD are dependent on thorough and systematic scientific research.

To further elucidate this long-lasting debate, first, it is crucial to clearly specify the research concepts that are related to the one and to the other hypothesis. (1) The continuity hypothesis states that normal aging and AD are extremes that lie along the same continuum. In other words,

everyone who lives long enough will eventually develop AD. In this case, cognitive changes at (very) old age are *not really* different from cognitive decline in (early) AD. Thus, these changes only differ in *degree*, at a *quantitative* level (e.g. Berg, 1985). (2) The discontinuity hypothesis, however, states that AD is categorically different from normal aging. Therefore, the cognitive changes at (very) old age do not only differ in degree but also in *kind*, at a *qualitative* level (e.g. Little, 1997). More specifically, the central research question is: Do only quantitative differences in neuropsychological test performance exist between normal aging and AD, or also qualitative differences? This question can be extended to quantitative or also qualitative differences in AD relevant neuroanatomical variables.

My approach to answer this research question is to critically review[1] studies that draw conclusions in terms of a continuous transition from normal aging to AD (Section 2), followed by a similarly critical review of studies that draw conclusions in terms of a discontinuous transition (Section 3). In Section 4, several methodological issues will be discussed that may explain the contrasting findings. This will lead to a proposal for investigating this topic in further research (Section 5).

2. A continuous transition from normal aging to Alzheimer's disease

Berg (1985) posed the question whether AD represents just an exaggeration of normal aging, which would be consistent with the continuity hypothesis. He encouraged researchers to investigate this question to provide a definite answer (which, in fact, still has not been found). To facilitate research, he formulated the following criteria in case AD is indeed just an exaggeration of normal aging: (1) normal aging and AD have the same causes and mechanisms; (2) there are only quantitative differences between the two; (3) given sufficient longevity, everyone will develop AD; (4) the study of one may lead to the solution of both; (5) when caretakers of an elderly, demented person seek our advice only after the illness is advanced and explain "We thought it was just old age," they are closer to the truth than we thought; (6) normal aging of the brain represents very mild or subclinical AD. Criteria 1, 2, and 6 have been investigated.

Regarding the first and sixth criterion (i.e. normal aging and AD have the same causes and mechanisms; normal aging of the brain represents very mild or subclinical AD), the following research findings are relevant. First of all, the neuropathology that is common for AD (plaques and tangles) is not specific for AD, but also occurs in normal aging, as was found by Price, Davis, Morris, and White (1991). In addition, they found that the location of the brain where particularly tangles were found differed along with the presence and severity of dementia (as was clinically determined by the Clinical Dementia Rating (CDR); Berg, 1988; Hughes, Berg, Danziger, Coben, & Martin, 1982), as well as with age. Tangles were present in all of the brains examined (also non-demented), and appear during aging in the anterior olfactory nucleus, the parahippocampal gyrus and the hippocampus, but are rare in the neocortex except in demented brains. Conversely plaques may develop first in the neocortex. Unlike tangles, plaques are not a consistent feature of aging, at least up to age 80. It should be noted that sample sizes of the various clinical groups were rather small.

Sample sizes were much larger in the study by Schneider, Arvanitakis, Leurgans, and Bennett (2009). Similar to Price et al., Schneider et al. concluded that clinically diagnosed probable AD and mild cognitive impairment (MCI; e.g. Petersen et al., 1999), even amnestic MCI, are pathologically heterogeneous disorders, with many persons exhibiting mixed pathologies. Richards and Brayne (2010) summarized that although plaques and tangles are rarely absent in patients with a clinical diagnosis of AD, these brain features are not pathognomonic, and some people with postmortem evidence of these were cognitively spared at death. Thus, neuropathology seems heterogeneous or diffuse, considering that too many qualitative differences are found among AD patients, whereas the classical pathological features may also occur in non-demented individuals. Therefore, Richards and Brayne concluded, in line with the previous studies, that AD is unlikely to refer to a discrete neuropathological entity and may represent a syndrome rather than a disease.

The second criterion formulated by Berg (1985) was that there are only quantitative differences between normal aging and AD. As Buckner (2004) reviewed, within a unitary factor framework, mild

memory decline common in aging exists along a single continuum with memory impairment associated with dementia. Dementia is considered as an acceleration of the same processes that affect cognition in all individuals. Many epidemiological, longitudinal, aging studies seem to adhere to this principle, consistent with the continuity view. These studies (e.g. Brayne & Calloway, 1988; Huppert & Brayne, 1994) assume a gradual, continuous transition from normal aging to AD, without sudden accelerations (or "dents") in the course of decline. According to Bäckman, Jones, Berger, Laukka, and Small (2005), labels such as "normal aging," "preclinical AD," "MCI," and "early AD" are best viewed as instances on a dimension of brain and cognitive functioning rather than discrete categories.

However, the previously discussed neuropathological patterns found in AD as well as normal aging cannot automatically be translated to a similar distribution of cognitive functioning in AD and normal aging. As Salthouse (2011) discussed, inferences that age-related brain changes *cause* age-related cognitive changes, may not be true, when these are based on correlational information. For this reason, more advanced statistical models may provide useful information: *structural equation modeling* (SEM; e.g. LISREL 8.80; Jöreskog & Sörbom, 2007). SEM is a statistical technique for building and testing statistical models, which are often causal models. It is a hybrid technique that encompasses aspects of confirmatory factor analysis (CFA), path analysis, and regression. SEM encourages confirmatory, rather than exploratory, modeling; thus, it is suited to theory testing, rather than theory development. It usually starts with a hypothesis, represents it as a model, operationalizes the constructs of interest with a measurement instrument and tests the model. Among its strengths is the ability to model constructs as *latent variables*––variables which are not measured directly (e.g. cognitive functions), but are estimated in the model from measured variables (e.g. neuropsychological tests) which are assumed to "tap into" the latent variables. This allows the modeler to explicitly capture unreliability of measurement in the model, in theory allowing the structural relations between latent variables to be accurately estimated. SEM is an extension of the general linear model that simultaneously estimates relationships between multiple independent, dependent, and latent variables.

Salthouse and Becker (1998) argued that although performance of AD patients is significantly impaired relative to that of healthy elderly controls on various cognitive measures, the extent to which the effects of AD on different variables are independent of one another is not yet known. By means of single common factor analysis, they found that the majority of effects of AD was shared among different cognitive variables. Their results indicated that if an adjustment was made for the general effects of AD, then there were no remaining effects of AD on nearly 75% of the variables and consistent independent effects only on variables assessing episodic memory.

Similar results, using CFA, were found by Johnson, Storandt, Morris, Langford, and Galvin (2008). After controlling for AD-specific changes in episodic memory, the same hybrid model was found applicable to both AD and normal aging. This model contained one general factor that maximized detection of dementia, and three specific factors (verbal memory, visuospatial ability, and working memory) that revealed the heterogeneity of dementia's associated cognitive deficits. Johnson et al. (2008) stated that this hybrid CFA model allows for direct (quantitative) comparisons of cognitive abilities between different disorders or normal aging.

Chapman et al. (2010) also found, using principal components analysis, that qualitatively the same model of cognitive performance fitted to both AD and normal aging. Chapman et al. concluded that the close similarities across clinical groups (AD, MCI, normal aging) in their underlying neuropsychological dimensions support the use of a common metric system for measuring neuropsychological factors in all these elderly individuals. They argue that a common metric system is a useful and powerful measurement tool for gauging neuropsychological performance in AD, MCI, and normal elderly. The factor scores derived from this metric may then be used to diagnose patients with AD or predict progression to AD in MCI patients, under the assumption that neuropsychological performance only differs at a quantitative level.

3. A discontinuous transition from normal aging to Alzheimer's disease

The above-mentioned criteria by Berg (1985) were proposed to examine whether AD represents just an exaggeration of normal aging, which would be consistent with the continuity hypothesis. In this section, research findings will be discussed that reported contrasting findings in AD, compared to normal aging, which would be consistent with the discontinuity hypothesis. These findings may be interpreted in accordance with nosological thinking that has dominated the previous century (Berrios, 1994): AD represents a separate diagnostic category, apart from the normal aging process, with also a separate neuropathology (e.g. medial temporal lobe atrophy, etc. Braak & Braak, 1991).

The first criterion (Berg, 1985) was: normal aging and AD have the same causes and mechanisms. The study of Ritchie and Kildea (1995) argues oppositely. In their meta-analysis of nine epidemiological studies, also including sufficient numbers of very old people (over age 80), they fitted the prevalence of dementia curve. This curve was best described as a flattened S curve that fitted a modified logistic function rather than an exponential pattern. They concluded that senile dementia seems better conceptualized as an "age-related" (i.e. occurring within a specific age range) rather than as an "aging-related" disorder (i.e. caused by the aging process itself). Very elderly survivors may be at a diminished risk of dementia.

In addition, contrasting findings are described in the following studies, regarding both the first criterion of Berg and his sixth criterion, i.e. normal aging of the brain represents very mild or subclinical AD. In these studies (rather), selective neuropathology is found in AD. West, Coleman, Flood, and Troncoso (1994) found that the most distinctive AD-related neuron loss was seen in the CA1 region of the hippocampus. In the normal aging group, there was almost no neuron loss in this region. West et al. concluded that the neurodegenerative processes associated with normal aging and with AD are qualitatively different and that AD is not accelerated by aging, but is a distinct pathological process.

Furthermore, Krasuski et al. (1998) found that by means of MRI, measured volumes of the anterior–posterior parahippocampal gyrus, which contains the entorhinal cortex, were reduced, but the amygdala and hippocampal volumes show greater reduction, relative to healthy controls. Nonetheless, despite significant differences in group means, particularly the hippocampal volumes of their control subjects overlapped with those of AD patients. Golomb et al. (1993) found that a third of their cognitively normal elderly sample had MRI evidence of hippocampal atrophy, which was associated with subclinical memory deficits. Whether these supposedly control subjects with reductions in hippocampal size are in fact at risk for future cognitive decline explained by dementia is unclear.

This overlap may indeed be explained by not all controls really being controls, considering Raz and Rodrigue's (2006) review that the entorhinal cortex is affected almost exclusively in those who showed significant ante-mortem cognitive decline. In contrast, the effects of normal aging on the volume of the entorhinal cortex are negligible. In addition, reduced hippocampal volume is a good predictor of a concurrent AD and of AD-type pathology in (supposedly) non-demented individuals.

This selective neuropathology in AD, in contrast to normal aging, may also be associated with selective behavioral problems, as Serra et al. (2010) examined. They found associations in regions implicated by AD neuropathology and behavioral problems, such as mood disorders, anxiety, agitation, psychotic symptoms, disinhibition, and delusions, rather than these problems representing a psychological reaction to cognitive disabilities. This suggested that these behavioral problems are likely to represent clinical features of AD and should be regarded for their diagnostic and prognostic value.

To conclude, Buckner (2004) reviewed that frontal-striatal change may underlie mild memory difficulties in aging that are most apparent on tasks demanding high levels of attention and controlled processing. In contrast, through separate mechanisms, AD preferentially affects the medial

temporal lobe and cortical networks, including posterior cingulate and retrosplenial cortex early in its progression, often before clinical symptoms are recognized. Disruption of the medial temporal lobe memory system leads directly to memory impairment. This seems inconsistent with the criteria of Berg (1985) that normal aging and AD have the same causes and mechanisms, and that normal aging of the brain represents very mild or subclinical AD. This also suggests the existence of not only quantitative but also qualitative differences in cognitive performance. This would be in contrast with the second criterion formulated by Berg (1985), which will be further discussed below.

There are many studies, conducting *cross-sectional* research, that report specifically disturbed cognitive processes in AD patients on tests of episodic memory, verbal and spatial span, and semantic encoding, including qualitative differences in performance characteristics, relative to even *very old* non-demented controls (e.g. Carlesimo et al., 1998; Perri, Serra, Carlesimo, & Caltagirone, 2007; Spaan, Raaijmakers, & Jonker, 2003; Spaan et al., 2005). However, these cross-sectional studies do not provide insight into the nature of decline over time in the same individuals.

In contrast with the *longitudinal* studies discussed in the previous section (e.g. Bäckman et al., 2005; Brayne & Calloway, 1988; Huppert & Brayne, 1994), the longitudinal study by Grober et al. (2008) did *not* find a gradual, continuous transition from normal aging to AD. Grober et al. found from seven years before the assessment of AD, several accelerations in the course of decline: first in episodic memory functioning, and several years later in executive functioning. Johnson, Storandt, Morris, and Galvin (2009) found similar results in their longitudinal study with better statistical methodology. The best-fitting model for each of four cognitive factors in a group of 310 elderly individuals that stayed non-demented was linear. In contrast, Johnson et al. (2009) found a sharp "inflection point" followed by accelerating decline in multiple domains of cognition (including memory and visuospatial ability) in the course of decline in a group of 134 elderly individuals who were assessed with AD during follow-up. These results were also obtained when data were limited to a subset ($N = 44$) with autopsy-confirmed AD.

The findings discussed above seem consistent with the multiple factor framework, as was reviewed by Buckner (2004). In this model, separate factors are hypothesized to affect cognition in aging, each with distinct causes, risk factors, anatomic targets, and cognitive sequelae. This is also supported by the study of Siedlecki, Honig, and Stern (2008), adopting a more advanced SEM approach. They performed exploratory factor analysis and a series of confirmatory factor analyses to, ultimately, find a five-factor model of cognitive functioning that fitted well across three clinical groups: cognitively healthy older adults, patients diagnosed with questionable dementia, and patients diagnosed with probable AD. This model, thus, obtained *configural invariance* across the three groups, similar to the approach and findings of studies that were discussed in Section 2 (Chapman et al., 2010; Johnson et al., 2008; Salthouse & Becker, 1998). For a model to demonstrate configural invariance, the relations among the latent constructs (i.e. cognitive factors) and their measured variables (i.e. cognitive tests) should be the same across different groups (Horn, McArdle, & Mason, 1983). That is, the *structure* of the model should be invariant.

Although a structurally same cognitive model may be applicable to both (early) AD and normal aging, there may *still be consistent qualitative differences* across separate diagnostic groups. Thus, configural invariance of a model across different groups does not necessarily imply that this model and each cognitive construct within it are measuring the same constellation of cognitive abilities in the various clinical groups that are investigated. There may still be differences in relations among variables and, thus, differences in what the variables may be measuring. In other words, the cognitive profile derived from a model may represent a different set of cognitive processes in (early) AD than in normal aging. If there are qualitative differences (such that the model is not invariant), then differences across groups are difficult to interpret because the meaning of the construct may be changing (e.g. Horn & Mcardle, 1992; Little, 1997).

To further investigate the existence of qualitative differences, Siedlecki et al. subsequently performed an analysis of *metric invariance*. Metric invariance is established when the *magnitude of the unstandardized coefficients*––i.e. the factor loadings of each measured variable (i.e. cognitive test) on its respective latent construct (i.e. cognitive factor)––is not significantly different across groups (Horn & Mcardle, 1992). This is tested by constraining the factor loadings to be the same across the groups and comparing the fit of the constrained (metric invariance) model to the baseline (configural) model. If the metric model does not fit significantly worse, then it can be argued that the model demonstrates metric invariance. Note that this does not imply that the group means are identical across groups.

However, the analysis performed by Siedlecki et al. did *not* show metric invariance. Specifically, their memory construct may have represented something different in the questionable dementia and AD groups as compared to the healthy older adult group. They interpret this specific finding as consistent with the underlying pathology in early AD.

Similar results, using a similar statistical approach, were found by Mitchell, Shaughnessny, Shirk, Yang, and Atri (2012). They conducted CFA to test a four-factor model of cognitive functioning in a group of amnestic MCI and AD patients vs. a group of cognitively healthy older adults. This model obtained adequate configural invariance across groups, but their metric invariance model showed significantly reduced fit, relative to their baseline (configural) model. Therefore, as was found by Siedlecki et al., the model of Mitchell et al. was *not* metric invariant either.

These results (Mitchell et al., 2012; Siedlecki et al., 2008) suggest that not only quantitative but also qualitative differences in cognitive performance exist between (early) AD and normal aging. This provides support for the discontinuity hypothesis.

4. Methodological explanations for the contrasting findings

As Wilson et al. (2000) discussed, inconsistent research findings regarding the nature of decline in relation to age and in AD may be influenced by, for example, (small) sample sizes (e.g. Carlesimo et al., 1998; Krasuski et al., 1998; Price et al., 1991; West et al., 1994), the number (or spacing) of observations over time (if any: e.g. Carlesimo et al., 1998; Perri et al., 2007; Spaan et al., 2005), dropout at follow-up participation (e.g. Spaan et al., 2005), floor and ceiling effects on measures of cognitive function, and statistical methods to analyze data (the latter two are discussed below). Therefore, the discrepancy of research findings and conclusions, as described in Sections 2 and 3, may be explained by these and several other methodological issues that will be further discussed in the current section.

First of all, the characteristics of the contrasted clinical groups may differ a lot. For example, various studies that were discussed in Section 2 or *3[2] investigated differences in performance between very healthy and clearly demented participants, and thus did *not include a preclinical AD or MCI group* (of whom the majority may be in a preclinical stage of AD; Albert et al., 2011): e.g. *Carlesimo et al. (1998), Johnson et al. (2008), Price et al. (1991), Salthouse & Becker (1998), and *Siedlecki et al. (2008). Fortunately, in the past 10 years, the inclusion of a preclinical AD group or at least a MCI group has become rather common practice: e.g. Bäckman et al. (2005); Chapman et al. (2010), *Grober et al. (2008), *Johnson et al. (2009), *Krasuski et al., (1998), *Mitchell et al. (2012); *Perri et al. (2007), Schneider et al. (2009); *Serra et al. (2010), *Spaan et al. (2005).

In addition, the age range of the participants that are involved in several studies is often rather narrow and does *not (or hardly) include (particularly) cognitive healthy elderly individuals that are of very old age* (i.e. over age 80): e.g. Brayne & Calloway (1988), *Krasuski et al. (1998), *Perri et al. (2007), Salthouse & Becker (1998), *Serra et al. (2010). However, a growing number of studies do include participants of very old age: e.g. Bäckman et al. (2005), *Carlesimo et al. (1998), Chapman et al. (20100, *Harrison et al. (2012), Johnson et al. (2008), *(2009); Price et al. (1991), *Ritchie & Kildea (1995), Schneider et al. (2009), *Siedlecki et al. (2008), *West et al. (1994).

When the characteristics of the contrasted clinical groups differ a lot and/or "the very old" are not included, this *may cause a bias in favor of the* ***discontinuity*** *view*. Nonetheless, group differences may still be merely quantitative, rather than qualitative. It is therefore important to examine all aspects of normal vs. pathological aging that may or may not precede the development of AD. As Bäckman, Small, Wahlin, and Larsson (2000) discussed, prevalence and incidence of various diseases related to cognitive functioning (e.g. dementia, circulatory disease, and diabetes) greatly increase with advancing age. What should define "normal aging" in very late life? The influence of various concomitant conditions (e.g. sensory deficits, depression, and vitamin deficiency) on cognitive performance may be magnified, reduced, or unchanged at very old age. Bäckman et al. (2000) stated that delineating conditions that follow these patterns is another way of addressing the issue of continuity vs. discontinuity of cognitive functioning across the adult life span.

In addition, Raz and Rodrigue (2006) reviewed that––independent of dementia––the human brain shrinks with age and brain shrinkage is selective and differential, not uniform, or randomly distributed. They found that the subcortical white matter and the hippocampus show substantial shrinkage in the older old and the rate of shrinkage may be accelerated by hypertension. They stated that the evidence suggesting that a large share of age-related changes is accounted by vascular pathology continues to accumulate. The hippocampus appears especially vulnerable to multiple negative modifiers of aging. Other putative negative modifiers are stress and hormonal depletion.

Secondly, *reduced construct validity of the administered neuropsychological tests* (i.e. one test often represents the influence of more than one cognitive process) complicates the detection of specific patterns of cognitive performance or deficits (e.g. Spaan et al., 2003). This may also enhance the probability that a certain cognitive construct measures a different constellation of cognitive abilities in different clinical groups that are investigated. For example, Siedlecki et al. found that their cognitive model was not metric invariant across (early) AD and normal aging, most likely because their memory construct may have represented something different in the one vs. the other group.

Thirdly, in many studies, only a few tests (i.e. measuring one or a few cognitive functions) or even only cognitive screening tests––such as the *Mini-Mental State Examination* (MMSE; Folstein, Folstein, & McHugh, 1975), the *Cambridge Examination of Mental Disorders of the Elderly* (CAMDEX; e.g. Roth, Huppert, Mountjoy, & Tym, 1998), or CDR––were administered (e.g. Brayne & Calloway, 1988; Huppert & Brayne, 1994; Price et al., 1991). This limits the possibility to derive a sufficiently broad cognitive profile from the results. Obviously, conclusions drawn in each study, in terms of which cognitive functions show greatest decline with age and in AD, are always dependent on the battery of specific cognitive tests or tasks that were administered. In addition, and more importantly, particularly the cognitive screening test method reduces the reliability of the clinical diagnosis that has been determined. This is also acknowledged by Price et al. (1991): it is possible that some subjects in their study that were assessed as non-demented were, in fact, in an early stage of dementia. It is therefore difficult to determine whether the density and distribution of tangles and plaques in non-demented cases are related to incipient AD, or to the normal aging process (Price et al., 1991).

Also, Krasuski et al. (1998) and Golomb et al. (1993) acknowledged the possibility that *not all controls were actually controls*. As Buckner (2004) reviewed, it is difficult to obtain a sample of older adults free from AD. He summarized that in many studies, participants are assumed to be spared from AD if they achieve a certain level of performance on a global cognitive screening test (e.g. MMSE). Such methods eliminate severely impaired individuals but lead to the inclusion of older adults in the early stages of the disease who, because of high baseline functioning and other mitigating factors, retain average global cognition during the initial progression of the disease. The relevance of this issue is that several studies of non-demented aging have found correlations between atrophy of the medial temporal lobe, or substructures within the medial temporal lobe, and memory performance (e.g. Krasuski et al., 1998).

Both the second and the third issue, concerning the cognitive tests that were used, *may lead to conclusions in favor of the* ***continuity*** *view*.

Finally, studies often differ in the adopted statistical approach. Commonly, the investigation is at the level of individual *tests* but conclusions are drawn at the latent level of cognitive *functions* (e.g. Bäckman et al., 2005; Brayne & Calloway, 1988; Carlesimo et al., 1998; Grober et al., 2008; Huppert & Brayne, 1994; Perri et al., 2007; Spaan et al., 2003, 2005). This also disregards the examination of the *interrelations* between the cognitive (measured *and* latent) variables (e.g. Spaan, 2015). This more complete examination, also taking into account the impact of measurement errors of the individual tests (i.e. particularly relevant when construct validity is reduced), is possible with SEM (e.g. LISREL 8.80; Jöreskog & Sörbom, 2007; Chapman et al., 2010; Johnson et al., 2008, 2009; Mitchell et al., 2012; Salthouse, 2011; Salthouse & Becker, 1998; Siedlecki et al., 2008).

In fact, all these data together represent the *qualitative* performance profile of the tested subjects of each clinical group. Moreover, these types of analyses correspond nicely with the interpretation of the cognitive profile that is done in adequate neuropsychological assessment of each individual patient. We should never base our assessment of cognitive functioning of a patient on the results of only one or a few neuropsychological tests. Instead, we attempt to link performance on tests that aim to measure the same cognitive function, as well as to make cross-connections between different cognitive functions.

In this respect, it should be noted that two studies that draw conclusions in terms of the continuity hypothesis (Johnson et al., 2008; Salthouse & Becker, 1998), beforehand, made a *qualitative* adjustment to the model they claimed was invariant across normal aging and AD. Salthouse and Becker (1998), first, adjusted for the general effects of AD; *then* they found that there were no remaining effects of AD on nearly 75% of the variables and consistent independent effects only on variables assessing episodic memory. In addition, Johnson et al. (2008) reported that *after* controlling for AD-specific changes in episodic memory, their hybrid CFA model allowed for direct (*quantitative*) comparisons of cognitive abilities between different disorders or normal aging. These adjustments probably *created a bias toward the* ***continuity*** *view*.

Configural and metric invariance are two different levels of measurement invariance. As was argued by the end of Section 3, the investigation whether a cognitive model has configural invariance across normal aging and AD is not enough to answer the question of continuity vs. discontinuity. Despite configural invariance, there may still be differences in relations among variables and, thus, differences in what the variables may be measuring: i.e. *qualitative* differences (e.g. Little, 1997). Therefore, also metric invariance should be tested across groups (e.g. Horn & Mcardle, 1992). If this analysis is neglected, this may *bias toward the* ***continuity*** *view* as well.

Subsequently, if configural as well as metric invariance are always investigated in a study, it may be of reduced importance to the question of continuity vs. discontinuity, which specific cognitive functions are examined. In advanced research, it would be more interesting when studies vary in their test approach, instead of always administering the same battery of tests.

5. Conclusions and suggestions for further research

In this review, an attempt was made to shed some light on a longstanding debate in dementia research: Are normal aging and AD extremes that lie along the same continuum (*continuity view*), or is AD categorically different from normal aging (*discontinuity view*)? In other words, do only *quantitative* differences in neuropsychological test performance exist between normal aging and AD, or are there also *qualitative* differences?

As was summarized in the previous section, this debate is characterized by inconsistent results and differences in methodological approach. Several methodological explanations for the contrasting findings were discussed in Section 4. This discussion leads to the following proposal for

investigating this topic in further research. I argue that only a latent variable approach testing for measurement equivalence is appropriate to investigate whether *also* qualitative––rather than *only* quantitative––differences in neuropsychological test performance exist between normal aging and AD (e.g. Horn & Mcardle, 1992; Little, 1997). The few studies that used this approach seem to provide support for the discontinuity hypothesis. Moreover, alternative (methodological) explanations were extensively described for the outcome of studies that draw conclusions in favor of the continuity hypothesis (see Section 4).

The study by Spaan and Dolan (2010) is another example that used the same statistical approach. We attempted to avoid the methodological disadvantages that were discussed in the previous section. We investigated the hypotheses of continuity vs. discontinuity by means of a multi-group SEM approach, testing for configural as well as metric invariance. We used data collected in a sample of 80 early or preclinical AD patients and 80 age-, education-, and gender-matched controls, of a broad age range (55–87 years), on a newly developed computerized neuropsychological test battery with refined construct validity (for a more extensive description of this test battery, see Spaan, 2015; for a more extensive description of the study sample, see Spaan, 2016). The results of our study showed adequate configural invariance across the two groups (RMSEA = .063), but no metric invariance (RMSEA = .085; reduced fit: $\Delta\chi^2 = 75.02$, $\Delta df = 12$, $\rho < .001$). Our results were, therefore, in favor of the discontinuity hypothesis.

Nonetheless, far more studies using this measurement invariance approach should be conducted to try to replicate the previously found results that seem consistent with the discontinuity hypothesis. Moreover, it may relevant to clinical practice to investigate the boundaries of this hypothesis. A suggestion would be to not only involve AD patients but also other type of dementia patients. In addition, the investigation of the influence of various diseases related to cognitive functioning and (advanced) aging (circulatory or cardiovascular system disease, hypertension, diabetes, etc.; e.g. Bäckman et al., 2000; Raz & Rodrigue, 2006) would be interesting.

In sum, this long-lasting continuity vs. discontinuity debate is not only of scientific relevance, but also has large consequences for our actions in clinical practice. The preliminary evidence, described in this review, which seems in favor of the discontinuity hypothesis, emphasizes the importance of developing tests that are able to detect the precise nature of the cognitive problems characteristic of early AD (e.g. Spaan, 2016; Spaan et al., 2005). Nonetheless, efforts of improving normative data or determining optimal cut-off scores of (existing) neuropsychological tests are still very important, especially at very old age, in order to reliably answer the question what is normal and what is not when we grow older.

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Notes
1. Journal articles were obtained from computerized database searches of PsycINFO, PubMed and Google Scholar (no year limit). The key words were: "Alzheimer's disease"; "continuity" or "continuous"; "discontinuity" or "discontinuous"; "quantitative"; "qualitative"; "measurement invariance"; "metric invariance". Some articles

were also located by citation. Criteria for inclusion were rather broad. Studies were included if a group of AD patients was directly compared with an appropriate control group, *and* if the results were explicitly *or* implicitly relevant to the continuity or the discontinuity hypothesis. I.e. not all studies made explicit interpretations in terms of these hypotheses, but were included anyway, if their results seemed relevant to the debate. Studies were excluded if they concerned a completely different research topic. Relevant results are described in this review.

2. Studies that draw conclusions in terms of a discontinuous transition from normal aging to AD (discussed in Section 3) are noted by means of a *-symbol in this section of the text. Studies that draw conclusions in terms of a continuous transition (discussed in Section 2) are noted without a *-symbol.

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