

AGING, HEALTH, AND HEALING

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Discontinuity of Dementia and Age-Related Cognitive Decline

F.M. Reischies and U. Lindenberger

In old age, a multitude of physical constraints, weaknesses, or diseases appear in various parts of the body, also afflicting the brain. One important question is, if within the third part of the life span of an individual, there is a general degenerative decline in more or less all physical and mental domains, or are we confronted with a simply additive phenomenon of the various diseases—each with different etiological and pathogenetic factors?

The more general question is, accordingly, is there continuity or discontinuity, can the development be predicted from the lifetime data, or is there a break in the development of an individual, because a certain pathogenetic factor starts to be effective? The theoretical issues are summarized in Table 18.1.

We will examine this question for dementia. Besides the relevance for gerontological interest in continuity versus discontinuity, the question has additional impact for the diagnostic process. The cut-off values used for diagnosis are difficult to validate in the case of senile dementia. The question is, are we looking for those individuals who are within the lower tail of a normal distribution—using a statistical, eccentricity cut-off (± 2 standard deviations)—or are there reasons to identify individuals, g., by discontinuity in the distribution of the dementia scores? (see *slow*, Brayne et al., 1988). Furthermore, the problem has relevance with respect to health cost considerations. If dementia is a continuous phenomenon and an inevitable fate in very old age, one might argue that it should not be handled as a purely medical issue with respect to payment for diagnosis and treatment.

Physicians are used to seeing dementia as a discontinuous phenomenon. Underlying is the disease model (Cohen, 1988), which implies an invasion of a pathogenetic agent or a consequence of a toxic influence or stressor. After a delay or a latent period, the disease becomes apparent.

Table 18.1 Continuity versus Discontinuity with Special Emphasis on Cognitive Decline**1. Continuity**

The pathogenetic factors are effective on every subject over the lifetime

- predictability from lifetime data and age
- lower tail of normal distribution (eccentricity cut-off)
- more mild cases as moderate and especially severe cases
- multifactorial contribution to variability; addition of residuals from adverse events (toxic, metabolic, degenerative, cerebrovascular, etc.)

2. Discontinuity

A new pathogenetic factor is effective in the lifetime of an individual

- break in the development, lack of predictability out of lifetime data
- after a latent period the disease becomes apparent
- whereas the time of onset may be unpredictable from lifetime data or especially age, the course of the progression, once started, may be continuous (e.g., exponentially accelerating) in a regular manner

Group differences: "Normal" versus "Pathological"

- quantitative difference in certain parameters (concerning the pathogenetic factor)
- difference between the two groups regarding the relation to variables of a different domain (which are related to the pathological factor)
- pattern difference between groups
- group differences in the relation between variables of the same domain

Score distribution:

- bimodal
- or mixture distribution: bimodal

Also a gene might be effective only in later life (as for the middle ages in Huntington's disease). But at least for the dementia of Alzheimer's type, no such pathogenetic factor could be identified so far.

Instead, several arguments are in favor of a continuity model of the senile dementia of Alzheimer's type (SDAT). At first, a continuous decline of the performance in cognitive tests over the life-span could be observed, especially in speed, as well as in reasoning and some memory parameters (Salthouse, 1982). At the age of 70 years, when dementia starts to become more prevalent (Jorm et al., 1987; Wernicke et al., 1994), there remains only about 40% of the maximal speed performance, which could be observed within the third decade. Because there is a high variability in cognitive abilities in the population as well as in the rate of decline it could be argued that subjects with a more pronounced drop of speed performance (or premorbid low speed), might have passed a critical value, a dementia threshold, and so a decompensation of cognitive functioning develops.

The second argument in favor of continuity is that specific neuropathological features of the SDAT could not be demonstrated. The ultimate diagnosis of SDAT relies on a quantitative pattern of neuropatho-

logical, morphological abnormalities. Even in critical areas, as in the parahippocampal gyrus, these features are also common in healthy old age (Matsujama, 1984).

MIXTURE DISTRIBUTION ANALYSIS

Brayne (Brayne et al., 1988) put forward the argument that there is a continuous distribution of several dementia scores, which means no bimodality, in 70–80-year-old subjects of an epidemiological study.

The mixture distribution analysis is a statistical method to determine if one or more populations underly a given distribution of parameter scores. The optimal fit of the empirical data is the criterion. Under the assumption of one or two (or more) distributions, the statistically significantly best fit can be determined. Furthermore, the relative contribution of the populations can be given in percentage, if more than one population is appropriate. The location parameters of the populations can be estimated as well as the estimation of an optimal cut-off point (for further details see Böhning et al., 1992; Reischies et al., submitted).

The analysis was done for the dementia score of the multidisciplinary intake assessment ($n = 928$ subjects) of the BASE study (Smith et al., this volume). There were equal numbers of participants in the three age groups and in the two gender groups. The dementia score of the multidisciplinary intake assessment was used—the short Mini Mental State score, which was developed by the Folstein group (Klein et al., 1985). This score uses 20 items of the Mini Mental State Examination (postdistractional short-term recall, orientation items, calculation, and spelling). The cut-off score is zero.

For all age groups, there was a significantly better fit assuming two populations compared with one population. This turned out to be the case not only for the short Mini Mental State, but also for published data from other dementia scales (Reischies et al., submitted); thus, inhomogeneity of the severity of the items of the short Mini Mental State test may not explain the results. For the older age group (see Figure 18.1, ages 90 to 104), one can demonstrate that there are two separate populations: one within the normal range of scores, and one within the pathological range. The percentage of the total distribution consisting of the dementia component increases from 5% (70 to 79 years) to about 20%, but it is not very much higher in the oldest age group. The location parameters of the normal component shift in the direction of the cut-off score (Reischies et al., in preparation). As a consequence, the distribution of the scores of the normal population spreads over the cut-off point of zero (see Figure 18.1). Therefore it seems reasonable to correct the cut-off point. It should be age-adjusted in order not to have many false-positive decisions.

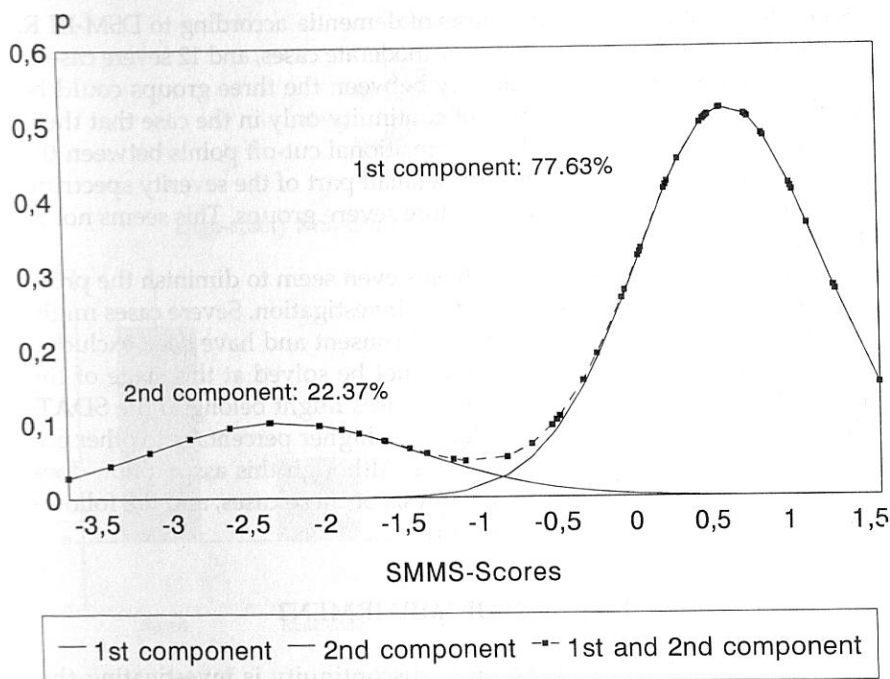


FIGURE 18.1 Mixture distribution analysis of the short Mini Mental State Score of the multidisciplinary intake assessment (Reischies et al., submitted). The data for the oldest age group (>90) are given. The approximation of the empirical distribution (broken line) is explained by two distributions, one within the normal range (1st component), which contains 77.63% of subjects, and a second component within the pathological range, which contains 22.37% of subjects. The first distribution spreads over the conventional cut-off (zero). Therefore a large proportion of cases would be wrongly assigned to the dementia group.

SEVERITY OF DEMENTIA

Further evidence in favor of discontinuity can be derived from the assumption that dementia cases belong to the lower tail of the normal distribution. Then there should be a prediction of more mild dementia cases compared with moderate and especially severe cases. The question can be investigated especially well if a threefold distinction of the severity is made. This is the case because, e.g., otherwise a high sensitivity and low specificity cut-off for mild cases might suggest more cases in the mild category.

One hundred-fifty-six subjects of the intensive protocol were examined. Psychiatrists, applying the GMS-A and HAS interviews (Copeland

et al., 1991), gave a clinical diagnosis of dementia according to DSM-III R. In our study, we found 9 mild cases, 7 moderate cases, and 12 severe cases.

An even distribution of frequency between the three groups could be explained under the assumption of continuity only in the case that there is a special partition of the relative transitional cut-off points between the severity groups, which assigns only a small part of the severity spectrum to the mild group and more to the more severe groups. This seems not to be plausible.

Selection factors like ethical problems even seem to diminish the probability of severe cases taking part in the investigation. Severe cases might not be able to understand the informed consent and have been excluded from the study. A further problem cannot be solved at this stage of the Berlin Aging Study. Whereas the mild cases might belong to the SDAT, the severe cases could possibly belong in a higher percentage to other etiological groups like vascular dementia. Although this assumption does not seem to be probable, the final analysis of these cases, and the follow-up investigation, should be waited for.

PATTERN OF IMPAIRMENT

The last approach to the question of discontinuity is investigating the pattern of test performance. The continuity position will predict the same pattern of impairment in mild age-related cognitive decline and dementia. The difference would be a matter of the degree of impairment. The discontinuity position will predict, however, a different pattern of test results of age-related cognitive decline and dementia. We analyzed two categorical decisions: a dementia diagnosis and a cluster-analytic dichotomy between impaired older and nonimpaired younger subjects.

Two contrasts are calculated. At first, within the group of nondemented subjects, we compare cognitively impaired and nonimpaired subjects, i.e., mostly an age effect (80.97 sd 7.97 vs. 89.25 sd 8.09 years). Secondly, within the cognitively impaired subjects, we compare the demented and nondemented subjects. For this group the question is, what makes the difference that some of the impaired subjects are diagnosed with dementia?

Subjects are the 156 participants of the intensive protocol. The diagnosis was made independently from the test results. A battery of computerized tests was applied, the BASECOG battery (Lindenberger et al., 1993), which supplies 5 factors of cognition. The effect size statistics with confidence intervals was calculated (Hedges et al., 1985).

The first comparison (see Figure 18.2) included only nondemented subjects. Cognitively impaired subjects were compared with nonimpaired subjects. The overwhelming differentiating effect is mental slowing. This

		Dementia	
		no	yes
Ability	high	●	
	low	●	

High-ability Non-demented versus Low-ability Non-demented

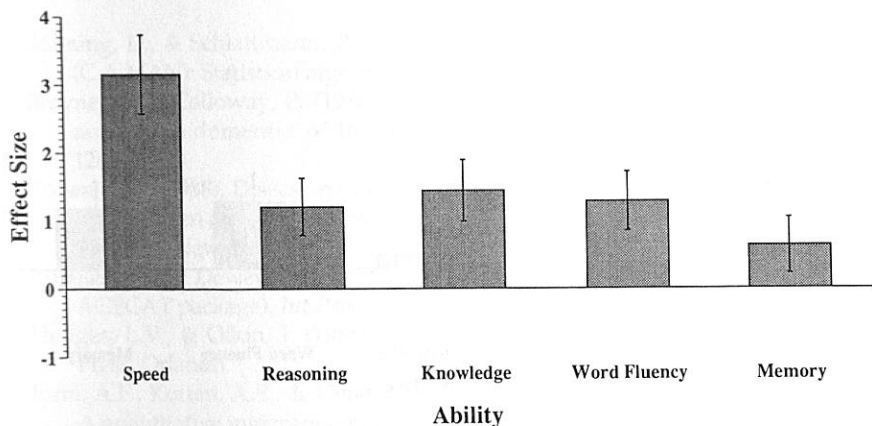


FIGURE 18.2 Comparison of nondemented subjects with high and low intellectual abilities according to a cluster analysis of the test data. The major differentiating factor is speed.

result is entirely consistent with a large body of literature about aging effects (Salthouse, 1982).

The second comparison (Figure 18.3) applies to the subsample of impaired participants. The question was: What pattern of impairment characterizes subjects which are independently diagnosed as demented? Results showed that the slowing effect does not at all distinguish the demented and nondemented impaired and older subjects. Under the continuity assumption we would expect a large speed effect. Instead fluency and memory impairment is more prominent in dementia subjects within the impaired sample.

CONCLUSION

There are three arguments in favor of discontinuity: First, a significantly better fit of the dementia score data is given by a bimodal mixture distribution. Second, there seems to be a pattern of memory and fluency deficits characteristic for dementia subjects—but not impaired speed,

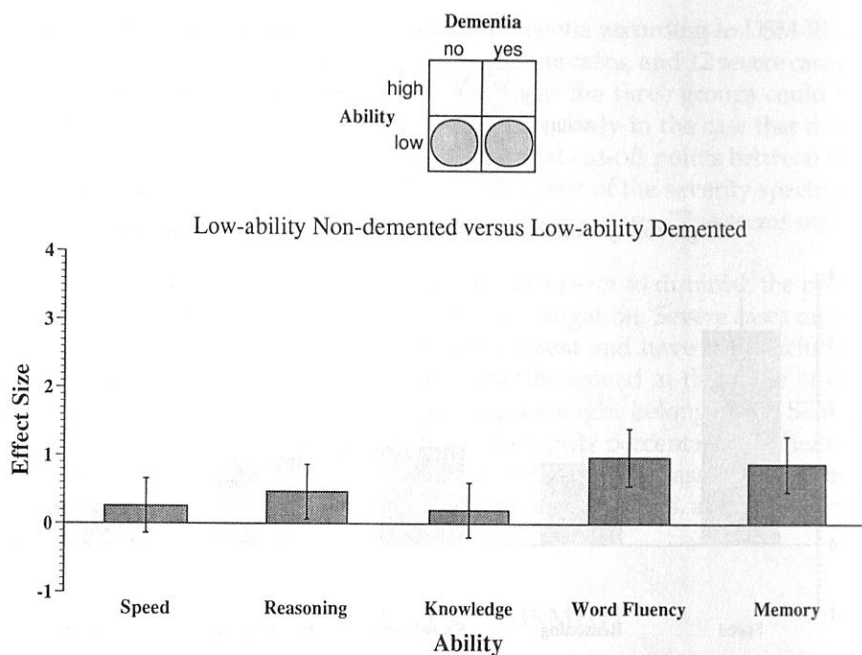


FIGURE 18.3 Comparison of demented and non-demented subjects within the group with low cognitive abilities. It is not speed which differentiates these groups, but word fluency and memory.

which characterizes age effects. Third, there is no evidence of a higher prevalence of mild dementia compared with moderate and severe cases.

There are, however, also arguments in favor of continuous age-related effects: First, the mental slowing differentiating nonimpaired and impaired older subjects and second, the shift of the dementia score for the major subpopulation in the direction of the cut-off score for dementia.

Two implications of the results should be mentioned at the end:

1. The arising question is whether an eccentricity cut-off (-2 standard deviations) is valid for dementia scores of a population like the 90+ age group—or if a mixture distribution derived cut-off may be more appropriate. The estimation of the prevalence of dementia in the very old may be too high, if—as usual, and necessary, e.g., for the NINCDR criteria—a deficit in a dementia score is included in the criteria. Then a fixed cut-off value may produce a large proportion of false-positive diagnoses (Figure 18.1). A mixture distribution-derived cut-off may be more appropriate.

2. A two-step test-diagnosis (Reischies, 1987) may be an economic and valid procedure. In the very old the diagnostic investigation for dementia should look first for slowing, which indicates an age-associated impairment, and at step 2 the impairment of memory and fluency may indicate dementia.

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