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Cognitive activity, education and socioeconomic status as preventive factors for mild cognitive impairment and Alzheimer's disease

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ABSTRACT

Growing epidemiological evidence suggests that premorbid participation in cognitive leisure activities (CLA) reduces the risk of dementia by increasing cognitive reserve. We investigated the differential effect of CLA, education, and socioeconomic status (SES) on the development of mild cognitive impairment (MCI) and Alzheimer's disease (AD). Participants in the prospective population-based ILSE study (*1930–1932; 12-year follow-up) were examined in three examination waves (t1:1993/94; t2:1997/98; t3:2005/07). In total, 381 subjects of the original cohort ($n = 500$) were re-examined at t3. Of these subjects 29% received the diagnosis of MCI and 7% of AD. Subjects participated in a thorough psychogeriatric examination and neuropsychological testing. Moreover, they took part in a detailed autobiographical interview and completed questionnaires including socio-demographic data and current frequency of participation in CLA. Subjects who were highly cognitively active at t1 had a significantly reduced risk of developing MCI/AD at t3 (scores adjusted for education, SES, gender, and depressive symptoms). Additionally, high education and high SES separately reduced the risk of MCI and AD. Our results confirm the hypothesis that a high level of CLA acts as a protective factor against the development of MCI and AD by increasing cognitive reserve. This effect is not accounted for by important potential confounders.

1. Introduction

Recent studies investigating protective factors against neurodegenerative disorders have frequently referred to the concept of cognitive reserve (Stern, 2002). This concept is based on the repeated observation that brain pathology and subsequent clinical dementia do not necessarily highly correlate if investigated on an individual level (Katzman et al., 1988; Stern, 2006). This finding suggests the existence of interindividual differences concerning the brain's ability to compensate for pathological changes.

A wealth of epidemiological studies has focused on identifying protective factors against Alzheimer's disease (AD) which represent potential constituents of cognitive reserve at the same time. One of the most frequently studied determinants in this context is education. Epidemiological studies consistently report that a high level of education is associated with a reduced risk of AD (Stern et al., 1994; Ganguli et al., 2000; Qiu et al., 2001; Anttila et al., 2002; Lindsay et al., 2002; Fratiglioni and Wang, 2007; Ngandu et al., 2007). The results indicate that early determined variables have the potential to moderate the occurrence of neurodegenerative processes decades later. Education might reflect the extent of early cognitive stimulation of the brain which might influence cognitive abilities and their cerebral correlates in turn (Le Carret et al., 2003). Accordingly, education is considered to be an essential aspect of cognitive reserve.

However, cognitive reserve is not only determined by education. According to epidemiological studies, numerous lifestyle habits practiced throughout people's lifespan have the potential to contribute to cognitive reserve. One aspect that recent studies have focused on is the relationship between late-life leisure activities and dementia risk. Studies consistently agree on a significant protective effect of cognitive leisure activities (CLA) (Scarmeas et al., 2001; Wang et al., 2002; Wilson et al., 2002a,b; Verghese et al., 2003; Karp et al., 2006; Wilson et al., 2010). As all of the cited studies controlled for education, the results suggest that early as well as late life variables have a high potential to significantly moderate the risk of AD by increasing cognitive reserve. Thus, cognitive reserve should not be seen as a fixed trait which is determined early in life but may be actively enhanced by individual lifestyle.

An important methodological issue in many studies has been the consideration of socioeconomic status (SES) due to its high association with education. Results concerning the association between SES and AD risk are rather inconsistent, with some studies suggesting a significant protective effect of high SES (Stern et al., 1994; Anttila et al., 2002) and others that do not report this relation (Wilson et al., 2005). One possible explanation for these inconsistent results might be the application of heterogeneous definitions of SES (childhood vs. late life SES). Some studies were only able to confirm a protective effect of SES if education was not hypothesized to function as a

Abbreviations: AD, Alzheimer's disease; CAS, cognitive activity score; CLA, cognitive leisure activities; MCI, mild cognitive impairment; SES, socioeconomic status.

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confounder (Evans et al., 1997; Karp et al., 2004), suggesting that education represents the actual relevant factor in this context.

Even though studies investigating the relationship between CLA and dementia controlled for potential confounders – such as age, education and sex – SES and its potential impact on the ability and motivation to participate in certain leisure activities have not been considered sufficiently. Moreover, mild cognitive impairment (MCI), which is associated with a higher risk of developing subsequent AD, has not been considered adequately in previous studies. Another issue that has not been considered by previous studies is that cohort effects might have influenced study outcomes, as earlier studies did not investigate birth cohorts. A birth cohort design provides the advantage of investigating subjects who grew up under very similar life conditions, which allows for a more solid interpretation of the findings — especially with respect to the impact of education and lifestyle factors.

In the present study, we thus investigated the potential impact of CLA on the development of both MCI and AD. In addition, we analyzed the relationships and interdependencies between CLA, education, and SES referring to the concept of cognitive reserve. The German Interdisciplinary Longitudinal Study on Adult Development and Aging (ILSE), which includes a representative birth cohort of subjects born between 1930 and 1932, served as the basis of our investigations.

2. Methods

2.1. Subjects

The ILSE is a prospective study on adult development and aging in Germany based on two birth cohorts born between 1930 and 1932 (C30) and between 1950 and 1952 (C50) respectively (Martin and Martin, 2000). Participants were randomly selected and recruited on the basis of community registers which comprise data on all inhabitants of German communities. This recruitment procedure resulted in a representative sample of 1002 participants for the respective communities (C30: $n=500$; C50: $n=502$). Subjects have been followed up since 1993/94, for an average time period of 12 years within three examination waves (t1:1993/94; t2:1997/98; t3:2005/07). The present study is based on the results of 381 participants from the 1930–32 birth cohort who completed the third examination wave at an average age of 74 years. In total, 119 subjects dropped out between t1 and t3: of these subjects 60 were deceased. Another 59 subjects did not participate due to relocation ($n=13$), health problems ($n=19$), lack of time and interest ($n=15$) or other reasons ($n=12$). Drop-outs were significantly less educated than those who finished t3. Related to this factor, drop-outs showed comparatively lower test results on most of the neuropsychological measures, which are highly associated with educational attainment. However, participants who left the study did not differ in any other demographic (e. g. sex, age, socioeconomic status) or measured variable (cognitive activity score at t1). The participants born between 1950 and 1952 were not considered in this study as prevalence of cognitive disorders was very low for this cohort as to be expected. Participants were carefully screened for physical and mental health by applying extensive interviews, physical examination and laboratory tests. Psychiatric disorders were assessed clinically and with the assistance of the German version of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R) DSM-III-R (Wittchen et al., 1991). The study was approved by the ethics committee of the University of Heidelberg. After complete description of the study to the subjects, written informed consent was obtained.

Severity of cognitive deficits was assessed by the Mini Mental State Examination (MMSE) (Folstein et al., 1975). In addition, the subtests logical memory I and II of the Wechsler Memory Scale (German version) (Wechsler, 2000) and the Trail Making Test (Reitan, 1992) were applied to address memory and learning, as well as attention and cognitive flexibility. Additional neuropsychological tests were derived from the “Nürnberger-Alters-Inventar” (Oswald and Fleischmann, 1986) and the “Leistungsprüfsystem” (Horn, 1983), which are commonly used test batteries in Germany. The following subtests were applied for the present study (Schönknecht et al., 2005): *memory* — immediate word list recall, delayed word list recognition; *visuospatial functioning* — spatial orientation, block design; *verbal comprehension* — information subtest; *abstract thinking* — similarities subtest; *speed* — number-connection test; *attention/concentration* — D2.[1]

2.2. Cognitive activity score (CAS)

The examination at t1 included a questionnaire that referred to the frequency of participation in leisure activities. In total, five items measuring activities that predominantly pertain to cognitive aspects (reading books, reading newspapers/magazines, solving crossword puzzles, participating in courses, participating in professional training) were derived from the questionnaire and allowed for the calculation of CAS. Participants were asked to indicate their current level of participation in the above-mentioned activities. Frequency of participation for each activity was coded as 0 (never), 1 (sometimes) or 2 (often). The CAS was calculated as the sum score of the five items (range: 0–10 points). Participants were classified as poorly (≤3 points), moderately (4–7 points) or highly (≥8 points) cognitively active at t1.

2.3. Assessment of covariates

Education and SES were assessed in the course of an interview at t1 and cross-checked with the respective statements in a socio-demographic questionnaire. Education of participants – which was defined as years of formal education – was categorized as low (<10 years), medium (10–15 years) or high (>15 years). The assessment of participants' SES was based on their monthly household income at t1. Three categories were defined indicating a low (≤2000 Deutsche Mark (DM)), medium (2000–4000 DM) or high (≥4000 DM) SES. Depressive symptoms at t1 were determined with the aid of Zung's Self-Rating Depression Scale (SDS) (Zung, 1965). Subjects were classified as having no depressive symptoms if they scored below 50 points.

2.4. Diagnostic categories

MCI was diagnosed according to the aging-associated cognitive decline (AACD) criteria as described elsewhere (Schröder et al., 1998). We decided to apply the AACD criteria in our study context as it is a stable and broad MCI concept. Moreover, previous studies showed that the AACD concept has a high predictive validity with respect to dementia onset (Ritchie et al., 2001; Schönknecht et al., 2005). The assessment of mild cognitive disorder (MCD) was based on the ICD-10 criteria (Schönknecht et al., 2005). For the diagnosis of AD and vascular dementia (VaD), the National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and the NINCDS-ADRDA and the National Institute of Neurological Disorders and Stroke - Association Internationale pour la Recherché et l´Enseignement en Neurosciences (NINDS-AIREN) criteria were applied (McKhann et al., 1984; Roman et al., 1993). All diagnoses were undertaken by a consensus conference consisting of two specialists in psychiatry under supervision of a specialist in Old Age Psychiatry.

2.5. Statistics

SAS software (version 9.2; SAS Institute, Cary, NC, USA) was used for all statistical analyses; *P*-values less than 0.05 were considered significant. Group differences were calculated by univariate analyses of variance (ANOVAs) in case of continuous variables and chi-square tests in case of categorical variables. Group differences concerning neuropsychological test performance from t1 to t3 were calculated by repeated univariate ANOVA.

In order to assess the effect of CLA participation on MCI and AD risk, odds ratios (OR) were calculated. Logistic regression analyses were performed in order to determine statistical significance at 95%-confidence intervals. In order to adjust for potential confounders, education, SES, gender and SDS scores were included into the logistic regression model.

3. Results

In total, 381 persons – i.e. 76.2% of the 500 subjects initially recruited from 1993/94 – were reassessed at the third examination wave. Subjects who met the criteria for other mental disorders such as major depression ($n=6$), anxiety disorders ($n=16$), substance abuse ($n=3$), VaD ($n=4$) or MCD ($n=29$) at t3 were excluded from the analyses, leading to a reduced sample size of 323 subjects. Complete data sets were available for 321 persons: Of these subjects, 26 fulfilled criteria for AD, 108 for MCI, and for 187 control subjects no mental disorders were diagnosed. All of these subjects were cognitively unimpaired at baseline.

Demographic and clinical characteristics of the diagnostic groups are provided in Table 1. There were no significant gender-specific differences in the remaining sample. AD and MCI patients were slightly older than controls; this difference gained significance due to the large sample size and low standard deviations. MMSE scores differed significantly among all three groups, with AD patients scoring lowest, followed by the MCI and the control groups respectively. The mean SDS score of our sample was 33.5 points (standard deviation (S.D.) = 6.8) with scores ranging between 20 and 57 points. MCI patients scored significantly higher on the SDS scale than AD patients and controls — however, their scores were still within the non-pathological range ($M=35.2$, S.D. = 6.5).

Participants of the control group differed significantly from MCI and AD patients in terms of educational background. Our results clearly show that controls enjoyed more years of education. For

[1] D2 consists of 14 lines with the letters “d” and “p”. Each letter is accompanied by one to four strokes. The task is to detect all ds with two strokes within a time limit of 20 s per line.