The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study

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Summary

Background Few data are available about how social networks reduce the risk of cognitive impairment in old age. We aimed to measure this effect using data from a large, longitudinal, epidemiological clinicopathological study.

Methods 89 elderly people without known dementia participating in the Rush Memory and Aging Project underwent annual clinical evaluation. Brain autopsy was done at the time of death. Social network data were obtained by structured interview. Cognitive function tests were *Z* scored and averaged to yield a global and specific measure of cognitive function. Alzheimer's disease pathology was quantified as a global measure based on modified Bielschowsky silver stain. Amyloid load and the density of paired helical filament tau tangles were also quantified with antibody-specific immunostains. We used linear regression to examine the relation of disease pathology scores and social networks to level of cognitive function.

Findings Cognitive function was inversely related to all measures of disease pathology, indicating lower function at more severe levels of pathology. Social network size modified the association between pathology and cognitive function (parameter estimate 0·097, SE 0·039, p=0·016, R^2=0·295). Even at more severe levels of global disease pathology, cognitive function remained higher for participants with larger network sizes. A similar modifying association was observed with tangles (parameter estimate 0·011, SE 0·003, p=0·001, R^2=0·454). These modifying effects were most pronounced for semantic memory and working memory. Amyloid load did not modify the relation between pathology and network size. The results were unchanged after controlling for cognitive, physical, and social activities, depressive symptoms, or number of chronic diseases.

Interpretation These findings suggest that social networks modify the relation of some measures of Alzheimer's disease pathology to level of cognitive function.

Introduction

Several clinicopathological studies over the past two decades have shown that many elderly people with extensive pathology of Alzheimer's disease do not clinically manifest cognitive impairment.[1–4] This ability to tolerate the pathology of this disease without obvious clinical consequences is increasingly referred to as cognitive or neural reserve.[1,5] Identification of factors associated with neural reserve has important implications for disease prevention. For example, one such factor is education. Clinicopathological studies suggest that the relation between quantitative measures of Alzheimer's disease pathology and level of cognition differ by duration of formal education.[6] Another potential factor that could modify this relation is social networks. Social networks have been related to a reduced risk of death and a reduction in a wide variety of adverse health outcomes in old people.[7] Several studies have also examined the relation between the extent of social ties and cognitive function and dementia. Most,[8–10] but not all,[11] showed that people with more extensive social networks were at reduced risk of cognitive impairment. Little is known about the cellular, molecular, and neuropathology of social networks and potential neurobiological mechanisms underlying this association. Although social networks could be directly related to the accumulation of Alzheimer's disease pathology, it seems more likely that social network size is related to reserve capacity capable of reducing the likelihood that the disease pathology will be clinically expressed as cognitive impairment. We aimed to test this hypothesis using data from the Rush Memory and Aging Project—a large, longitudinal, epidemiological, clinicopathological study of ageing and Alzheimer's disease.

Methods

Participants and procedures

Participants were elderly people without known dementia in the Rush Memory and Aging Project[12] (see acknowledgments). Each participant gave written informed consent and an anatomical gift act for brain donation. The study was approved by the Institutional Review Board of Rush University Medical Center. More than 1100 people have agreed to participate and have completed their baseline clinical assessment. The overall annual follow-up rate of survivors exceeds 90%, and the autopsy rate exceeds 75%. Post-mortem data were available for analysis from the first 89 people.

All participants underwent a uniform structured clinical assessment that included a medical history, neurological examination, and neuropsychological performance

testing. Neuropsychological test results were reviewed by a board-certified neuropsychologist who gave an opinion about the presence and severity of cognitive impairment. Each participant was assessed in person by a physician. On the basis of this evaluation, and review of the cognitive testing and the neuropsychologist's opinion, participants were classified with respect to Alzheimer's disease and other common conditions with the potential to affect cognitive function, according to the recommendations of the joint working group of the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA)[13] as previously described.[12] Annual follow-up evaluations were identical in all essential details and were done by examiners unaware of previously obtained data. At the time of death, all available clinical data were reviewed and a summary diagnostic opinion was given as to the most likely clinical diagnosis at death. Summary diagnoses were made by reviewers unaware of all post-mortem data.

21 cognitive performance tests were administered each year. Details of the cognitive function tests have been previously reported.[12,14] Briefly, one test, the mini-mental state examination (MMSE), was used to describe the cohort but was not used in analyses. A second test, complex ideational material, was used for diagnostic classification but was not used in the composite measure of cognition. The remaining 19 tests were used to assess five domains of cognitive function. There were seven tests of episodic memory including immediate and delayed recall of story A from logical memory and of the east Boston story, and word list memory, recall, and recognition. Three measures assessed semantic memory including a 15-item version of the Boston naming test, verbal fluency, and a 15-item reading test. There were three tests of working memory including digit span forward and backward and digit ordering. There were four tests of perceptual speed, including symbol digit modalities test, number comparison, and two indices from a modified version of the Stroop neuropsychological screening test. Finally, there were two tests of visuospatial ability, including a 15-item version of judgment of line orientation, and a 16-item version of the Raven's standard progressive matrices.

The primary outcome measure in the study was a global measure of cognitive function. We focused on the continuous measure of cognition, rather than a dichotomous variable of dementia or Alzheimer's disease, because doing so allowed us to fully examine the spectrum of both pathology and cognition, and their association with social networks, in the most direct way and with the greatest statistical power. Furthermore, because factors affecting neural reserve are likely to affect some cognitive systems more than others, we did a series of secondary analyses to explore five different cognitive abilities. This approach is identical to that we have taken in similar analyses with data from another study.[6,15] The raw scores from the 19 tests were converted to *Z* scores and averaged to yield a global cognitive summary, and measures of five different cognitive abilities as previously described.[12,14]

We quantified social network size with three sets of standard questions about the number of children, family, and friends of each participant and how often they interacted with them.[10] Because we wanted to measure the influence of premorbid social networks on the relation between pathology and cognition, we restricted the analyses to social network data from the baseline assessment. Participants were asked about the number of children they have and see monthly. They were asked about the number of relatives (besides spouse and children) and other close friends to whom they feel close and with whom they felt at ease and could talk to about private matters and could call upon for help, and how many of these people they see monthly. Social network size was the number of these individuals seen at least once per month.[10]

We also assessed five potential mediators and covariates that could account for or confound the association of social networks with cognition, as previously reported. We only used data from the baseline evaluation to be concurrent with the assessment of social networks. We assessed current participation in nine cognitively stimulating activities,[14] five physical activities,[12] and six social activities.[10] Depressive symptoms were assessed with a ten-item version of the Center for Epidemiologic Studies depression scale.[12] We measured seven chronic diseases—diabetes, hypertension, heart disease, cancer, thyroid disease, head injury, and stroke.[12]

Brains of deceased participants were removed, weighed, cut into 1-cm-thick coronal slabs, and immersion fixed in 4% paraformaldehyde for 72 h. Tissue blocks from the mid-frontal gyrus, the superior temporal gyrus, the inferior parietal gyrus, the entorhinal cortex proper, and the hippocampus (CA1/subiculum) were embedded in paraffin, sectioned at 6 μm and stained with a modified Bielschowsky silver stain. Neuritic plaques, diffuse plaques, and neurofibrillary tangles were counted in the region that appeared to have the maximum density of each pathological index as previously described, resulting in 15 measures.[16] A composite measure of global Alzheimer's disease pathology was created as previously described by dividing each raw count by the standard deviation of the mean for the same neuropathological index in that region and averaging the scaled scores to yield the composite measures.[16]

Multiple tissue blocks from entorhinal cortex proper, hippocampus (CA1/subiculum), superior frontal cortex, dorsolateral prefrontal cortex, inferior temporal cortex, angular gyrus cortex, anterior cingulate cortex, and calcarine cortex were embedded in paraffin and cut into 20-μm sections. Up to 24 sections were available for each case for each post-mortem index. Amyloid-β was labelled with an N-terminus directed monoclonal antibody (10D5, courtesy Elan Pharmaceuticals; 1:1000). Immunohistochemistry was done as previously described[17]