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Title

The role of brain integrity in the association between occupational complexity and cognitive performance in subjects with increased risk of dementia

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Abstract

Introduction: Mechanisms underlying the positive association between occupational mental demands and late-life cognition are poorly understood. The objective of this study was to assess whether the association between occupational complexity and cognition is related to and moderated by brain integrity in individuals at-risk for dementia. Brain integrity was appraised throughout

structural measures (Magnetic Resonance Imaging, MRI) and amyloid accumulation (Pittsburgh Compound B (PiB)-positron emission tomography, PiB-PET).
Methods: Participants from the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) neuroimaging sample -MRI (N=126), PiB-PET (N=41)- were included in a post-hoc cross-sectional analysis. Neuroimaging parameters comprised the Alzheimer´s Disease signature cortical thickness (ADS, Freesurfer 5.3), medial temporal atrophy (MTA), and amyloid accumulation (PiB-PET). Cognition was assessed using the Neuropsychological Test Battery. Occupational complexity with data, people, and substantive complexity were classified through the Dictionary of Occupational Titles. Linear regression models included cognition as dependent variable, occupational complexity, measures of brain integrity, and their interaction terms as predictors.
Results: Occupational complexity with data and substantive complexity were associated with better cognition (overall cognition, executive function) when adjusting for ADS and MTA (independent association). Significant interaction effects between occupational complexity and brain integrity were also found, indicating that, for some indicators of brain integrity and cognition (e.g., overall cognition, processing speed), the positive association between occupational complexity and cognition occurred only among persons with higher brain integrity (moderated association).
Conclusions: Among individuals at-risk for dementia, occupational complexity does not seem to contribute towards resilience against neuropathology. These exploratory findings require validation in larger populations.

Keywords: Aging, Alzheimer's disease, amyloid, cognition, lifestyle, mental stimulation, neuropathology, occupational complexity, prevention.

Introduction

Alzheimer's disease (AD) and dementia currently affect over 50 million people worldwide, being the most common cause of disability and mortality in older adults[1]. Prevention has been highlighted as pivotal to curb the expected exponential growth of cases globally. Up to 40% of dementia cases have been estimated as preventable by targeting modifiable risk factors[2].

Among modifiable exposures, mentally stimulating activities during adulthood, including occupational complexity, have been associated with better cognition in late life, lower risk of cognitive impairment, Alzheimer´s disease (AD), and dementia[3-6]. Occupational complexity relates to the mental demands that an occupation provides, which can be intellectual or social in nature, and are associated with specific cognitive processes[7, 8].

Occupational complexity has also been investigated in the context of multidomain interventions for risk-reduction of cognitive impairment and dementia. Using data from the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), we previously reported that, among older adults at-risk for dementia, those with prior exposure to higher occupational complexity with data, people, and substantive complexity had better cognitive performance[9].

The "resilience versus resistance" conceptual framework suggests that mentally stimulating activities might halt the development of AD-related pathology (i.e., resistance), or delay the clinical expression of underlying neuropathology (i.e., resilience)[10]. Within this framework, studies including measures of occupational complexity, cognition and brain pathology, can offer insights into the associations between work-related mental stimulation and the accumulation or clinical expression of brain pathology[10, 11]

Few studies have examined the association between occupational complexity and cognition while accounting for measures of brain integrity. In older individuals with mild cognitive impairment (MCI) progressing to dementia, and among patients with dementia due to AD, higher occupational levels have been associated with greater neuropathology burden, given comparable levels of cognition, suggesting that exposure to mentally demanding occupations may provide resilience to pathology[12, 13]. However, the same association was not significant in subjects with MCI not progressing to dementia and in cognitively healthy individuals[12]. Yet, another study in cognitively healthy individuals with increased risk of AD, found that higher levels of occupational complexity were associated with increased brain pathology, given the same level of cognition[7]. Heterogeneity of findings might reflect methodological differences, in terms of study population, assessment of occupational complexity, use of different measures of neuropathology and cognition.

More recently, two studies assessed the moderation effect of occupational complexity in the association between cognition and neuropathology, by testing interactions between occupational complexity and measures of brain integrity[14, 15]. Both studies reported no significant interactions when considering cognitively unimpaired individuals, whereas a significant negative moderation effect was reported for patients with MCI and AD dementia, indicating that the positive association between occupational complexity and cognition was stronger in individuals with reduced brain integrity (AD cortical thickness)[14].

Besides these cross-sectional studies, two longitudinal studies examined the relationship of work-related mental stimulation to changes in brain and cognition. A large multicohort prospective study reported a reduced risk of late-life dementia and AD in people with cognitively stimulating jobs, which was also associated with lower levels of plasma proteins linked to neurodegeneration[3]. Another study found that cognitively normal older adults with higher occupational complexity had slower decline of cerebrospinal fluid Aβ42 levels, whereas no such association was found in patients with MCI and AD dementia[16]. Findings from both studies suggest that higher work-related mental stimulation can reduce the accumulation of neuropathology in cognitively normal individuals[3, 16].

Although not conclusive, the available evidence shows a possible link between occupation-related mental stimulation and accumulation or clinical expression of brain pathology. Such relationship can vary across the cognitive spectrum, and it is yet unclear for people at risk of dementia, who are candidates for interventions aiming to delay the onset of cognitive impairment.

In this context, improved understanding of the link between occupation complexity, brain structure and late-life cognition can inform optimization of prevention strategies. To this aim, we performed a post-hoc exploratory study, based on the FINGER neuroimaging cohort, to assess whether the association between occupational complexity and cognition is related to and moderated by brain integrity in individuals at-risk for dementia. Brain integrity was assessed through structural Magnetic Resonance Imaging (MRI) measures -medial temporal atrophy (MTA) and AD signature cortical thickness (ADS)-, and brain amyloid burden, quantified with Pittsburgh Compound B (PiB)-positron emission tomography (PiB-PET). The relationship between PiB-PET and cognition in the FINGER trial has been previously reported[17] as well as the association between baseline MRI measures and cognition[18]. Provided that the association between occupational complexity and cognition may vary across the cognitive continuum and given previous reports of interaction effects between occupational complexity and measures of neuropathology, we expected that in persons at risk of dementia the association between occupational complexity and cognition might be affected by the level of brain integrity.

Methods

Study design & study population

This is a cross-sectional study, including participants from the FINGER trial (ClinicalTrials.gov identifier: NCT01041989) with available MRI or PiB-PET scans and cognitive tests, conducted in connection with baseline FINGER visit. This subsample constitutes the FINGER neuroimaging cohort. The FINGER study protocol, baseline sample characteristics, and primary findings have been described in detail[19-21]. FINGER is a 2-year, multicenter, multidomain randomized clinical trial, in which 1260 community dwellers were recruited at six different sites across Finland. FINGER study participants were enrolled from previous population-based observational studies and did not have dementia or substantial cognitive impairment. The eligibility criteria included: age 60-77 years and Cardiovascular Risk Factors, Aging and Dementia (CAIDE)[22] Risk Score ≥6 points, indicating the presence of modifiable vascular and lifestyle-related risk factors for dementia. Furthermore, participants had to meet one of the following criteria: Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list memory task ≤19 words (maximum score 30), CERAD word list recall ≤75% (maximum 100%), or a Mini–Mental State Examination score of 20-26 (maximum score 30). These criteria identified individuals whose cognitive abilities were at the mean level or slightly lower than expected for age, according to Finnish normative values (0.5 SD below the average of the Finnish general population)[23]. The exclusion criteria were previously diagnosed dementia; suspected dementia at screening visit; conditions affecting the safe participation in the intervention (e.g., malignant tumour; major depression; symptomatic cardiovascular disease; revascularization within 1 year); severe impairment in hearing, vision or communication ability, or other conditions preventing cooperation as judged by the study physician; and participation in another trial.

The FINGER neuroimaging subsample included participants from three different study sites (Turku, Kuopio and Oulu) for MRI scans (N=132) and one study site (Turku) for PiB-PET scans (N=48). In connection to the MRI, PiB-PET assessment was conducted for the same group of 48 participants at one site (Turku). At the time when MRI and PET resources became accessible at each site, the most recently recruited individuals were selected for imaging if there were no contraindications[24]. The present cross-sectional, exploratory study included 126 participants from the MRI sample and 41 participants from the PiB-PET sample, assessed during the baseline of the FINGER study. Selection of participants was based on availability of neuroimaging data, and information on occupational complexity, as well as on *APOE* status for the PiB-PET sample (Supplementary figure). The mean baseline MMSE score was 27.0 (SD 1.98) for the MRI sample, and 27.0 (SD 1.66) for the PET sample (**Table 1-2**). Neuroimaging measures used in this study were MTA, ADS cortical thickness, and PiB-PET status (positive or negative). These measures have been associated with cognitive performance and changes, as well as with risk of AD and dementia[17, 25, 26], and MTA and PiB-PET are used in clinical practice for diagnostic purposes. We chose three measures of occupational complexity (complexity with data, complexity with people, and substantive complexity), which have previously

been associated with late-life cognition, dementia risk, and brain integrity[5, 7-9]. The cognitive measures used in the study included the pre-specified primary and secondary outcomes of the FINGER trial from the baseline assessment[20, 21].
The FINGER study was approved by the Helsinki and Uusimaa Hospital District Coordinating Ethical Committee (94/13/03/00/09). All participants gave written informed consent, and a separate consent was acquired for MRI and amyloid-PET scans.

MRI assessment
A subsample of 155 participants from four of the six study sites underwent structural MRI at the beginning of the FINGER study, following a standard protocol. Quality control was performed by an experienced neuroradiologist, and images were excluded if there were brain lesions potentially affecting volumetry and/or scanning issues such as no full-brain coverage, artifacts, intensity inhomogeneity, and not adequate grey/white matter contrast. Of the scans from three centers (Turku, Kuopio and Oulu), 132 passed the quality control (all scans from Seinäjoki center were excluded due to acquisition issues). Different MR systems were used, 1.5T Avanto Siemens (3D-MPRAGE sequence, voxel size 1.2×1.2×1.2mm, repetition time (TR) 2400ms, echo time (TE) 3.5ms, inversion time (TI) 1000ms) at the Kuopio and Oulu sites, and 3T Ingenuity Philips (3D-turbo field echo [TFE] sequence, voxel size 1.0×1.0×1.0mm, TR 8.1ms, TE 3.7ms) at the Turku site. At each MRI site, regular phantom scans were performed, and quantitative measures of signal-to-noise ratio, uniformity, and geometric distortion were carried out. Freesurfer (version 5.3, http://surfer.nmr.mgh.harvard.edu/) was used to measure volumes and regional cortical thickness. The ADS was calculated by averaging the cortical thickness bilaterally from the following regions: entorhinal, fusiform, middle temporal and inferior temporal region[26].
The MTA was assessed by a single rater who was blinded to the clinical data, applying on T1-weighted images a visual rating scale (Scheltens scale) commonly used in clinical practice[27]. MTA was rated from single coronal slice at the level where cerebral peduncles, pons and hippocampus were all visible. The grading for MTA was done from 0 (no atrophy) to 4 (end-stage atrophy) bilaterally.

PET assessment
PiB-PET was performed in one center (Turku University Hospital) for 48 participants at the baseline FINGER visit. [11 C]PiB (N-methyl-[11C]2-(4methylaminophenyl)-6-hydroxybenzothiazole) was produced as previously described[28]. On average 406.3 (standard deviation (SD) 107.7) MBq of PiB was injected intravenously and a scan from 60–90min (3×10min frames) after injection was performed with a Philips Ingenuity TF PET/MR scanner. The scans were visually interpreted by two experienced readers and judged visually as positive or negative after consensus. Participants graded as PiB positive showed cortical retention of 11C-PiB-PET in at least 1 cortical region typically affected by amyloid in AD, whereas participants graded as PiB negative had only nonspecific 11C-PiB-PET retention in white matter[17].

Cognitive assessment
The cognitive measures used in the FINGER study were defined using an extended version of the Neuropsychological Test Battery (NTB)[29], administered by psychologists. The NTB total score consisted of combined scores from the 14 different tests listed below. Domain-specific scores of executive functioning, processing speed, and memory were also defined.
The processing speed domain included Letter Digit Substitution, Concept Shifting (condition A), and Stroop (condition 2) test. The executive functioning domain included Digit Span, Concept Shifting test (Condition C), Trail Making test (shifting score: time in part B - time in part A), Category Fluency test and a 40-item version of the Stroop test (interference score: time in part 3 - time in part 2). The memory domain included Visual Paired Associates test (immediate and delayed recall), Logical Memory test (immediate and delayed recall), and Word List Memory test (learning and delayed recall).

The internal consistency for these tests was as follow: NTB Total, Cronbach α = 0.84; processing speed domain, Cronbach α = 0.75; executive function domain, Cronbach α = 0.69; memory domain, Cronbach α = 0.75.

Occupational complexity and education assessment

The information on current or last-held occupation was collected from the participants at baseline, through a questionnaire including a question asking if the person was retired or still working, and an open-ended question asking the participant to specify the current or (if retired) last-held job.

The occupational complexity scores were derived using occupational codes from the U.S. Dictionary of Occupational Titles (DOT) that includes the estimation of occupational complexity for over 12,000 occupations. These codes have been previously matched with the 1980 census for Nordic countries (Nordic Occupational Classification)[5].

Three measures of complexity were used in this study. Complexity of work with data (score range 0-6, with higher scores indicating higher complexity), which measures the level at which a person is dealing with information in his or her daily work. Complexity with people (score range 0-8, with higher scores indicating higher complexity), which refers to work demands related to interacting and working with other people. Substantive complexity (score range 0-10, with higher scores indicating higher complexity), which reflects general complexity. This measure has been previously derived through a principal component analysis and includes eight factors: general educational development, specific vocational preparation, complexity of work with data, intelligence aptitude, verbal aptitude, numerical aptitude, abstract interest in the job, and temperament for repetitive and continuous processes[30].

For each occupation, complexity scores were assigned by two raters (AR and ADM) through a consensus discussion. A third opinion was sought from a senior researcher (IK) when the first two raters were not certain that they had made the optimal coding. Occupational complexity scores could not be assigned to 6 participants, for whom information on occupation was missing or was too general to be coded into complexity (e.g., planner, housewife). Educational attainment was assessed at baseline as self-reported years of formal education.

APOE assessment

Genomic DNA was extracted from venous blood samples with Chemagic-MSM1 (PerkinElmer) using magnetic beads. *APOE* genotyping was determined by polymerase chain reaction using TaqMan genotyping assays (Applied Biosystems (ABI), Foster City, CA, USA) for two single-nucleotide polymorphisms (rs429358 and rs7412) and an allelic discrimination method on the ABI-7500 platform[31].

Statistical analysis

For NTB components that were skewed, zero-skewness log-transformation was used. The components were transformed to z-scores, standardized to the mean and standard deviation, with higher scores indicating better performance. The NTB total and domain-specific scores were calculated by averaging z-scores for each of the individual tests. For a participant to receive an NTB total score, a minimum of 8 out of 14 tests were required in order to calculate the score. For processing speed, 2 of 3 sub-domain tests were required, for memory 3 of 6 tests, and for executive functioning 3 of 5 tests.

All occupational complexity scores were transformed using zero-skewness-log-transformation and standardized into z-scores to be used in the regression models.

Standardized z-scores were calculated for the ADS. The MTA visual ratings were calculated bilaterally, and for the analysis we used the mean of left and right ratings to create three main categories (ratings 0-0.5, 1, and 1.5-3.0), as it was done in a previous study on the same cohort[24]. The PiB-PET measures were used as dichotomized (negative or positive)[17]. For baseline comparisons between individuals with and without neuroimaging, t-test, median test, and chi-square test were used as appropriate.

Linear regression models were used to estimate the cross-sectional associations between occupational complexity and cognition including MRI or PET measures as covariates. Each dimension of occupational complexity was tested in separate models. In all models, an interaction term between the imaging measure and occupational complexity was initially included. If the interaction coefficient was significant ($p<.05$) it was retained in the final model, and related average marginal associations between occupational complexity and cognition for different values of MRI and PiB-PET markers were estimated and presented graphically (Figures 1-3). The main effects in the models with ADS show the estimated association between occupational complexity and cognitive outcomes for individuals with average ADS (centred at the mean that is zero). For MTA the main effect is for individuals with MTA in category 1 (MTA = 0-0.5) and for PiB-PET the main effect is for individuals in the PiB-PET negative group. The interaction effect for ADS reflects the change in the association between occupational complexity and cognition for 1SD increase of the ADS variable. For MTA (used as indicator variable, with group 1 set as the reference category) it is the difference in the association between occupational complexity and cognition between the MTA category (2 or 3) and the reference category 1, and for PiB-PET it is the difference in the association between occupational complexity and cognition between the PiB-PET negative and positive groups. All analyses were adjusted for age, sex, and education. MRI regression models also included study site to account for the use of different scanners[24]. Since a previous study in the FINGER PiB-PET cohort reported an association between *APOEε4* and amyloid positivity[17], PiB-PET models also included *APOE* status as covariate (carriers of at least 1 ε4 allele vs noncarriers). In sensitivity analysis, *APOE* was added as covariate also in the MRI models (*APOE* missing for 13 participants within the MRI sample).
Stata 17 software package (StataCorp, College Station, Texas, USA) was used for all analyses.

Results

Sample characteristics

One hundred and twenty-six FINGER study participants with MRI scans were included in the data analysis (age, mean and SD: 70.0(4.5) years, 46% women), as well as 41 participants with a PiB-PET scan (age: 70.6(5.0) years, 44% women). **Tables 1-2** shows the main characteristics of participants with and without neuroimaging data at the study sites where scans were available. For the MRI sample, there were no significant differences between the individuals with and without an MRI scan at the same study site regarding age, sex, education, cognition, scores of occupational complexity with data and people, while scores of substantive complexity were higher for subjects with an MRI scan compared to those without a scan (median [interquartile range, IQR]: 4.7[3.9], vs 4.3[3.8], $p=0.04$). For the PiB-PET sample, there were no significant differences between individuals with and without scans.

Table 3 shows the associations between occupational complexity and cognition, adjusting for MRI or PiB-PET measures, including interaction effects between occupational complexity and the imaging measures.

Associations between occupational complexity and cognition: effect of ADS

The results of regression models including ADS showed that higher occupational complexity with data and substantive complexity were associated with higher NTB total score and executive-function performance (**Table 3**). Significant interactions between occupational complexity and ADS were found for the association with NTB total score (complexity with people and substantive complexity), executive function (complexity with people) and memory (complexity with data and substantive complexity). The beta coefficients were positive for all these interactions (**Table 3**), and the effect on the association between occupational complexity and cognition is presented in **Figure 1**. This figure shows the average marginal association between occupational complexity and cognition for increasing levels of ADS, and illustrates that the association between specific dimension of occupational complexity and cognition was significant only for higher values of ADS, reflecting higher brain integrity. No association was found between occupational complexity and processing speed. In sensitivity analyses including also *APOE* as covariate in the models (information missing for N=13

subjects), we found similar results compared to analysis without *APOE,* although some of the associations were no longer significant (results not shown).

Association between occupational complexity and cognition: effect of MTA
The analyses including MTA showed that higher occupational complexity with data and substantive complexity were associated with better cognition, for NTB total score, executive function, and processing speed. There was also a positive association between occupational complexity with people and performance in processing speed (**Table 3**). Significant interactions between occupational complexity and MTA were found for the association with NTB total score (substantive complexity) and processing speed (complexity with data and people, substantive complexity). The beta coefficients for all these interactions were negative (**Table 3**). **Figure 2** shows that the association between specific dimension of occupational complexity and cognition was significant only for the MTA category 1 (ratings 0-0.5), indicating less regional atrophy. No association was found between occupational complexity and memory. Also in these models, the inclusion of *APOE* as covariate did not substantially change the results, compared to analyses not including *APOE* (results not shown).

Association between occupational complexity and cognition: effect of PiB-PET
The results of the regression models including amyloid status on PiB-PET showed that higher values of occupational complexity with data and with people were associated with higher cognitive scores in the processing speed domain, and higher complexity with people was also associated with better performance in executive function (**Table 3**). Significant interactions between occupational complexity and amyloid status were found for the association with NTB total score (complexity with data), executive function (complexity with people) and processing speed (complexity with data and people). The beta coefficients for these interactions were negative (**Table 3**). **Figure 3** shows that the association between specific dimensions of occupational complexity and cognition was significant only for subjects classified as amyloid-negative. No association was found between occupational complexity and memory.

Discussion
In this cross-sectional study in people at risk of dementia, occupational complexity with data and substantive complexity were associated with better cognition (overall cognition, executive function) across all levels of ADS and MTA measures (independent association). Significant interaction effects between occupational complexity and brain integrity were also found, indicating that, for some indicators of brain integrity and cognition (e.g., overall cognition, processing speed), the positive association between occupational complexity and cognition occurred only among individuals with higher brain integrity (moderated association). Finally, for some indicators of occupational complexity and cognition, there was neither independent nor moderated association.
In a previous analysis of the whole FINGER cohort, where neuroimaging measures were not included, we found that higher levels of all dimensions of occupational complexity were associated with higher performance in the cognitive domains included in the FINGER trial as primary or secondary outcomes[9].
Exploratory findings from the present study can be interpreted within the resistance and resilience theory[10]. In accordance with the definitions of “cognitive resilience” and the “cognitive benefit criterion”, a negative moderation effect, indicating that the association between a measure of mental stimulation and cognition is stronger for higher levels of neuropathology, is considered the ideal indicator of a resilience effect[11, 15]. At the same time, an independent effect, showing that higher mental stimulation is associated with better cognitive performance after partialing out the effect of brain integrity, can also reflect resilience, although it is weaker evidence compared to the moderation effect[11, 15].
Part of our findings showed that, in individuals at risk of dementia, the association of higher occupational complexity with better cognition was independent of brain integrity levels. This was observed for occupational complexity with data and substantive complexity, when considering

overall cognition and executive function in relation to ADS and MTA, and might reflect a resilience mechanism[11, 15]. Occupational complexity with data and substantive complexity have been linked to reduced dementia risk, and occupational complexity with data has been shown to influence the magnitude of the beneficial effects of the FINGER trial[5, 9, 32].

Part of our results, mainly within the domain of overall cognition and processing speed, showed interactive effects between occupational complexity and brain integrity. Such interactions were not consistent with the resilience theory, as all models indicated significant associations between higher occupational complexity and better cognition only in individuals with higher brain integrity.

A seminal study in patients with AD dementia showed that previous exposure to jobs with higher substantive complexity, more interpersonal skills, and higher physical demands, was inversely related with brain parietal perfusion, given the same level of cognition[13]. More recently, another study reported similar results in patients with AD dementia or amnestic MCI (aMCI) progressing to dementia, in whom higher occupational level was inversely related to glucose metabolism in posterior temporo-parietal areas. No association between occupation and neuropathology was found in persons with a MCI not progressing to dementia, and healthy controls[12]. A third study in middle-aged, cognitively healthy adults with risk factors for AD, including family history and *APOE*ε4 carrier status, found that, when matching individuals for cognitive level, greater occupational complexity -measured as total complexity and complexity with people- was associated with lower brain integrity, quantified as hippocampal volume and whole brain atrophy[7]. Overall, the studies support the notion that occupational complexity might confer resilience to neuropathology, although findings in individuals at-risk of dementia (stable MCI, or carriers of non-modifiable risk factors for AD) are contradictory, and not directly comparable with the present investigation, due to differences in the assessment and operationalization of occupational complexity, and/or use of different measures of neuropathology.

To the best of our knowledge, only two studies have tested the moderated association of occupational complexity with cognition[14, 15]. Boyle et al.[15] used two different cohorts of cognitively healthy older adults. In one of the two cohorts a positive association between higher total occupational complexity and better global cognition was found, when accounting for hippocampal volume or grey-matter volume. In the other cohort, however, higher total occupational complexity was linked to better verbal fluency when adjusting for grey-matter volume. As findings were different across cohorts, the authors considered them as not significant[15]. Similar to our study, positive moderation effects were detected in one of the two cohorts when testing interactions between occupational complexity and measures of brain integrity[15]. Also in this case, results differed between the two cohorts, and were considered not significant. Of note, this study used the same complexity rating method (DOT) as applied in our study, but calculated an index for total occupational complexity, which also included complexity with things. The latter has been shown to have weaker or non-significant associations with cognition and dementia risk[5, 33], so its inclusion in the model by Boyle et al. could have led to an underestimation of the association between occupational complexity and cognition.

Another recent study, in middle-aged and older adults with and without cognitive impairment, examined the moderating effect of three different measures of brain integrity on the association between occupational complexity, classified in four levels (International Standard Classification of Occupations, ISCO-08), and cognition[14]. Similar to our results, independent positive effects of occupational complexity were found in cognitively unimpaired individuals, but no moderation by neuropathology was detected. In patients with MCI or AD dementia, a significant negative interaction between occupational complexity and ADS cortical thickness was found, indicating that, in line with the resilience theory, the positive association between occupational complexity and cognition was stronger in individuals with reduced brain integrity[14].

Overall, both studies indicate lack of or weak evidence for resilience mechanisms in subjects with no cognitive impairment. These findings are consistent with our study, where we found only independent effects, but not moderated effects, supportive of resilience.

Knowledge on the role of neuropathology in the association between occupational complexity and cognition is limited. The studies available suggest that there are variations across the cognitive continuum, with some evidence of resilience effects in subjects with dementia or rapidly progressing toward such diagnosis. For subjects at risk of dementia the picture is less clear. Methodological differences across studies, including variations in methods used to identify "at-risk" individuals, as well as in measures of neuropathology and occupational complexity, make findings not directly comparable.

Our findings suggest that some dimensions of occupational complexity, namely substantive complexity and complexity with data, might have a positive association with cognition, independent of brain integrity, which is weak evidence of resilience mechanisms.

However, we also found that, for some indicators of neuropathology and cognition, the positive link between occupational complexity and cognition is present only for higher levels of brain integrity. This is in not in line with the resilience theory. Rather, it seems to indicate that, in individuals at-risk but without substantial cognitive symptoms, the positive effect of occupational complexity on cognition might be greatest in individuals with minimal neuropathology, as they could better capitalize on greater brain integrity. Consistent with this hypothesis, similar results were found in a study testing the moderation effects of education, in the association between cognition (memory) and brain integrity (hippocampal volume)[34].

The differences in interaction effects, observed in our study only for distinct measures of cognition, occupational complexity, and indicators of brain integrity, reflect the inconsistent evidence from the literature on moderation effects for occupational complexity[14, 15]. Differences within our study might be due to multiple factors, including population characteristics in terms of cognition, occupational complexity levels, measures of brain integrity considered, and sample size. However, we cannot exclude that, in people at increased risk of dementia, specific dimension of occupational complexity might interact differently with neuropathology, in relation to specific cognitive functions. For instance, in this study interactions were detected more frequently within the processing speed domain, compared to memory and executive function. This could be partly explained by the stronger association we previously reported in the FINGER cohort between processing speed and all dimensions of occupational complexity[9]. Also, changes in processing speed often occur in the early stages of neurodegeneration[35]. The present study is exploratory, thus results must be verified in other cohorts, to improve risk assessment for late life dementia and optimize preventive interventions. It is in fact possible that resilience mechanisms might differ in at-risk, asymptomatic, or early symptomatic stages of cognitive impairment, compared to more advanced stages of cognitive deterioration, and it is possible that occupational complexity does not contribute to resilience in at-risk individuals.

It is important to note that interaction effects can be difficult to detect, as shown by conflicting results in studies on occupational complexity, but also for other activities, such as education and early life cognitive abilities[14, 15, 34, 36-38]. Although the spectrum of brain pathology was well represented here, in terms of PiB-PET (36% of the study participants were amyloid positive) and MTA (51% of subjects had MTA=1 and 38% had MTA >1), the effect of AD pathology on cognition might be small in preclinical stages. Participants in the present study had no substantial cognitive problems, with low variance in cognitive scores and in complexity with people (for which associations were detected less frequently).

Strengths and limitations

The main strengths of this study comprise the high-quality of the data collected, including the thorough cognitive assessments. The assessment of occupational complexity was based on a validated method, which allows to examine several dimensions of work-related intellectual demands. Also, we used multiple measures of brain integrity, including clinically relevant measures of AD-related neuropathology: the Scheltens MTA scale is routinely used in clinical settings for diagnosis of AD and monitoring of disease progression; the PiB-PET is considered the benchmark for PET-amyloid imaging, and is also used to aid AD diagnosis[39]. Among other MRI measures, the ADS cortical

thickness is associated with AD risk and progression, and has been shown to be a reliable marker of neurodegeneration and memory impairment[26]. Another strength is that education was included as a control variable in the data analysis, as schooling represents the main mentally stimulating activity in early adulthood.

The main limitation of the present study is the cross-sectional, exploratory design, which does not allow to infer effects of occupational complexity on cognitive changes across levels of brain integrity. Also, the relatively small sample size of the FINGER neuroimaging cohort, especially for the PiB-PET sample (N=41), limited statistical power and thus the possibility to identify independent and interactive effects for indicators of occupational complexity while considering measures of brain integrity. Validation of our findings in larger cohorts is thus warranted.

Another limitation is that measures of occupational complexity were based on the last-held job, which might not reflect overall level of complexity during a person´s working life. However, previous studies comparing scores of occupational complexity derived from the last-held job or multiple jobs found negligible differences[40].

Finally, the FINGER study involves older Finnish individuals with multiple risk factors for dementia, and with average cognitive performance <0.5SD below the mean level for the cognitively normal Finnish population[19]. Therefore, the results of this study cannot be generalized to either individuals who already have substantial cognitive impairment, or to those with high cognitive performance, as both profiles were not included in FINGER. However, the FINGER population is representative of a significant proportion of the general Finnish population of older adults, who can be candidate to interventions to reduce the risk for dementia.

This study contributes to the understanding of the potential role of occupation related mental stimulation in the clinical expression of brain pathology in individuals who are at risk of dementia. The FINGER trial model is being adapted and tested globally within the WW-FINGERS network of multidomain trials for dementia risk reduction[41]. As evidence on the cognitive benefits of lifestyle-based multidomain interventions emerges, it is also becoming clear that better-defined risk groups need to be recognized, to optimize benefits of such interventions, as there is no “one-size fits all” solution[41]. For most individuals, occupation related mental stimulation spans over decades. Thus, proper understanding of its effect on the clinical expression of brain pathology over the whole cognitive continuum can help define risk profiles which are related to better response to preventative interventions, and can also help to better assess results of trials aiming to delay or prevent dementia onset in older adults, ultimately supporting precision prevention.

Conclusion

This study adds insights on the role brain integrity might play in the association between occupational complexity and cognitive performance. We showed that, among older individuals at-risk for dementia identified through a validated dementia risk score, occupational complexity does not seem to provide resilience against neuropathology.

Statement of Ethics
This study protocol was reviewed and approved by the Helsinki and Uusimaa Hospital District Coordinating Ethical Committee, approval number (94/13/03/00/09). All participants gave written informed consent, and a separate consent was acquired for MRI and amyloid-PET scans.

Data availability statement
The datasets presented in this article are not readily available because Public deposition of the de-identified data set is not possible due to legal and ethical reasons, and complete de-identification is not possible as this investigation is part of an ongoing study. The study participants gave informed consent which includes data use only under confidentiality agreement. Further, the data contains large amount of sensitive information and public data deposition may pose privacy concerns. Those fulfilling the requirements for viewing confidential data as required by the Finnish law and the Finnish Institute for Health and Welfare are able to access the data after completion of material transfer agreement. Requests to access the datasets should be directed to kirjaamo@thl.fi

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Conflict of Interest

All authors declare that they have no conflicts of interest.

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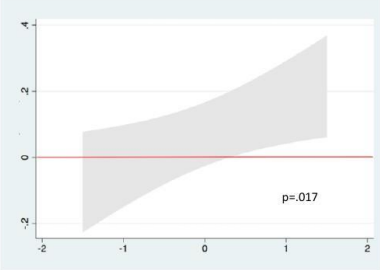
Figure legend

Figure 1a-e. In each figure the Y-axis shows the beta coefficient for the association between occupational complexity and cognition, for different values of Alzheimer´s Disease signature cortical thickness (ADS) on the X-axis. The shaded grey area represents the 95% confidence interval (CI) for the regression coefficient. Significant associations between occupational complexity and cognition are found when the grey area does not overlap zero (red horizontal line). Average marginal effects were estimated from regression analyses including occupational complexity, ADS, and interaction occupational complexity x ADS, age, sex, education and study site. Marginal associations were estimated only for parameters in which the interaction had a level of significance $p<0.05$.
P-values are shown for the interaction occupational complexity x ADS.

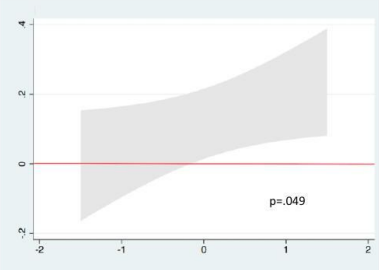
Figure 2a-d. In each figure the Y-axis shows the beta coefficient for the association between occupational complexity and cognition, for different values of medial temporal atrophy (MTA) on the X-axis**.** The bars represent the 95% confidence interval (CI) for the regression coefficient (represented by blue dots). Significant associations between occupational complexity and cognition are found when the bars do not overlap zero (red horizontal line). Average marginal effects were estimated from regression analyses including occupational complexity, MTA, and interaction occupational complexity x MTA, age, sex, education and study site. Marginal associations were estimated only for parameters in which the interaction had a level of significance $p<0.05$.
P-values are shown for the interaction occupational complexity x MTA group 3 compared to group 1.
MTA ratings were grouped into three levels: MTA 1: ratings 0-0.5 (n=18 individuals); MTA 2: rating 1 (n=65 individuals); MTA 3: ratings 1.5-3.0 (n=24 individuals).

Figure 3a-d. In each figure the Y-axis shows the beta coefficient for the association between occupational complexity and cognition, for different values of PiB-PET neuroimaging marker (positive and negative) on the X-axis. The bars represent the 95% confidence interval (CI) for the regression coefficient (represented by blue dots). Significant associations between occupational complexity and cognition are found when bars do not overlap zero (red horizontal line). Average marginal effects were estimated from regression analyses including occupational complexity, PiB-PET, and interaction occupational complexity x PiB-PET, age, sex, education and *APOE* status. Marginal associations were estimated only for parameters in which the interaction had a level of significance $p<0.05$.
P-values are shown for the interaction occupational complexity x PiB-PET.

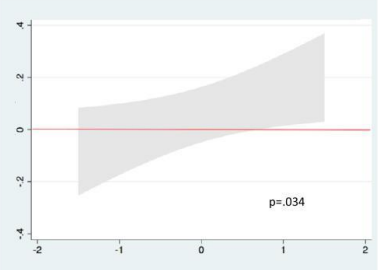
a) NTB Total: interaction complexity with people and ADS



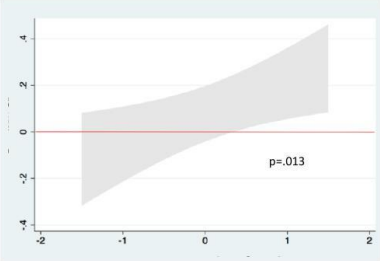
b) NTB Total: interaction substantive complexity and ADS



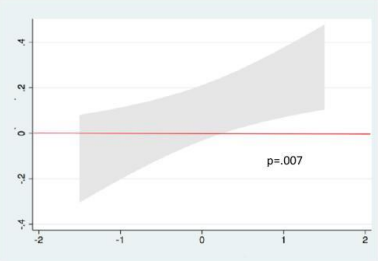
c) Executive function: interaction complexity with people and ADS



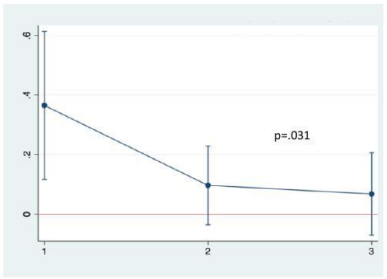
d) Memory: interaction complexity with data and ADS



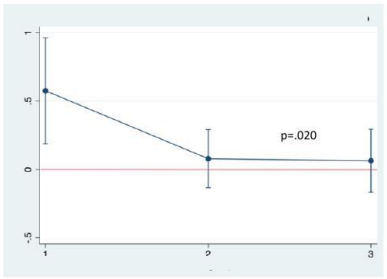
e) Memory: interaction substantive complexity and ADS



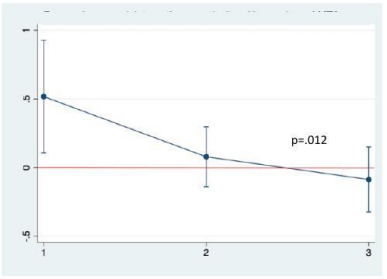
a) NTB Total: interaction substantive complexity and MTA



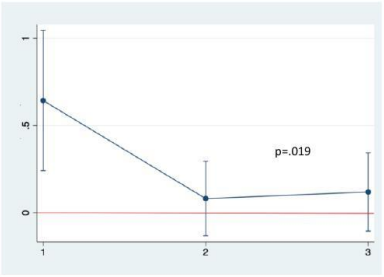
b) Processing speed: interaction complexity with data and MTA



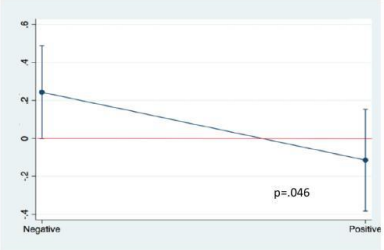
c) Processing speed: interaction complexity with people and MTA



d) Processing speed: interaction substantive complexity and MTA

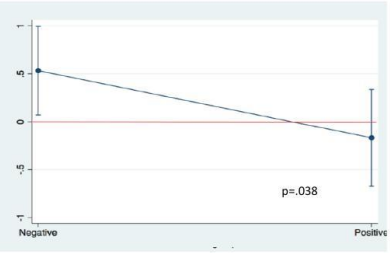


a) NTB Total: interaction complexity with data and PiB-PET



b) Executive function: interaction complexity with people and PiB-PET

c) Processing speed: interaction complexity with data and PiB-PET



d) Processing speed: interaction complexity with people and PiB-PET

Table 1 Comparison between FINGER participants with and without MRI brain scans (and information on occupation) at the neuroimaging study sites.

MRI sample*	Subjects with brain scan (N=126)	Subjects without brain scan (N=537)	P-value
Age at baseline, years	70.0 (4.5)	69.3 (4.7)	.13
Number of women, N (%)	58 (46%)	253 (47%)	.83
Education, years	9.0 [2.0]	8.0 [3.0]	.78
MMSE	27.0 (1.98)	26.9 (2.0)	.63
Occupational complexity			
Complexity with Data	3.15 [3.5]	3.0 [3.2]	.30
Complexity with People	1.1 [1.7]	1.2 [1.6]	.43
Substantive complexity	4.7 [3.9]	4.3 [3.8]	.04
Cognition and MRI measures			
NTB Total score	-.07 (.52)	-.12 (.56)	.31
NTB Executive function	-.04 (.58)	-.14 (.66)	.11
NTB Memory function	-.11 (.60)	-.11 (.65)	.99
NTB Processing Speed	-.04 (.78)	-.13 (.82)	.30
AD Signature thickness, mm, mean (range)	2.76 (2.4 – 3.11)	-	-
Visually rated MTA, median (range)**	1.0 (0.0-3.0)	-	-

Main characteristics of the MRI sub-sample with occupational complexity, and participants at the same study sites without brain scan. Unless otherwise specified, data are reported as number (N); mean and standard deviation (SD); median and interquartile [IQR] range. Scores on the NTB total, executive functioning, processing speed, and memory are mean values of z-scores of the cognitive tests included in each cognitive outcome, with higher scores suggesting better performance. The original values of AD signature thickness and occupational complexity are presented. Z-transformed variables have been used in the regressions. P-values are based on t-test, median test, or chi-square test. Abbreviations: AD: Alzheimer´s disease; MMSE: Mini Mental State Examination; MTA: medial temporal atrophy; NTB: neuropsychological test battery. *MRI was conducted at four out of the six FINGER study sites (Seinäjoki, Turku, Oulu and Kuopio). We included MRI scans that passed quality control (all scans from the Seinäjoki site were excluded due to acquisition issues). **Visually rated MTA: by Scheltens scale of severity, which ranges from 0 (normal, no atrophy), to 4 (advanced atrophy). MTA ratings were grouped into three levels: MTA 1: ratings 0-0.5 (n=18 individuals); MTA 2: rating 1 (n=65 individuals); MTA 3: ratings 1.5-3.0 (n=24 individuals).

Table 2 Comparison between FINGER participants with and without PiB-PET brain scans (and information on occupation) at the neuroimaging study sites.

PET sample*	Subjects with brain scan (N=41)	Subjects without brain scan (N=185)	P-value
Age at baseline, years	70.6 (5.0)	70.1 (4.5)	.54
Number of women, N(%)	18 (44%)	90 (49%)	.58
Education, years	9.0 [2.0]	9.0 [2.0]	.69
***APOE* ε4 carriers, N(%)**	11 (27%)	73 (42%)	.07
MMSE	27.0 (1.66)	27.2 (2.1)	.52
Occupational complexity			
Complexity with Data	3.2 [2.8]	3.0 [2.5]	.44
Complexity with People	1.0 [1.7]	1.5 [1.5]	.17
Substantive complexity	4.8 [4.0]	4.4 [3.1]	.07
Cognition and PiB-PET			
NTB Total score	-.01 (.53)	-.05 (.52)	.68
NTB Executive function	.02 (.57)	-.11 (.63)	.23
NTB Memory function	-.06 (.60)	.03 (.60)	.39
NTB Processing Speed	.04 (.90)	-.10 (.75)	.28
Amyloid positive (%)	15 (36.6%)	-	-

Main characteristics of the PiB-PET sub-sample with occupational complexity, and participants at the same study sites without brain scan. Unless otherwise specified, data are reported as number (N); mean and standard deviation (SD); median and interquartile [IQR] range. Scores on the NTB total, executive functioning, processing speed, and memory are mean values of z-scores of the cognitive tests included in each cognitive outcome, with higher scores suggesting better performance. The original values of occupational complexity are presented. Z-transformed variables have been used in the regressions. P-values are based on t-test, median test, or chi-square test. Abbreviations: AD: Alzheimer´s disease; *APOE*: Apolipoprotein E; MMSE: Mini Mental State Examination; NTB: neuropsychological test battery. *PiB-PET were conducted in one of the six study sites, Turku, in the same participants who also underwent MRI.

Table 3 Associations between occupational complexity and cognition, while including measures of brain integrity.

	NTB Total			Executive function			Memory			Processing speed		
	ß	SE	P	ß	SE	P	ß	SE	P	ß	SE	P
AD signature thickness (ADS) (N=126)												
Data	.11	.05	**.031**	.13	.05	**.020**	.08	.06	.198	.12	.08	.129
Data x ADS	-	-	-	-	-	-	.13	.05	**.013**	-	-	-
People	.07	.05	.150	.06	.05	.287	.07	.06	.234	.08	.08	.300
People x ADS	.10	.04	**.017**	.09	.04	**.034**	-	-	-	-	-	-
Substantive	.11	.05	**.026**	.13	.06	**.028**	.09	.06	.147	.16	.08	.062
Substantive x ADS	.08	.04	**.049**	-	-	-	.13	.05	**.007**	-	-	-
MTA* (N=126)												
Data	.11	.05	**.032**	.12	.05	**.026**	.09	.06	.156	.57	.20	**.004**
Data x MTA2	-	-	-	-	-	-	-	-	-	-.50	.21	**.020**
Data x MTA3	-	-	-	-	-	-	-	-	-	-.51	.22	**.020**
People	.06	.05	.252	.04	.05	.448	.06	.06	.318	.52	.21	**.014**
People x MTA2	-	-	-	-	-	-	-	-	-	-.44	.23	.062
People x MTA3	-	-	-	-	-	-	-	-	-	.-60	.24	**.012**
Substantive	.37	.13	**.004**	.11	.06	.043	.09	.06	.168	.64	.20	**.002**
Substantive x MTA2	-.27	.13	**.044**	-	-	-	-	-	-	-.56	.21	**.010**
Substantive x MTA3	-.30	.14	**.031**	-	-	-	-	-	-	-.52	.22	**.019**
PiB-PET (N=41)												
Data	.24	.12	.052	.06	.10	.565	.03	.10	.748	.53	.23	**.025**
Data x PiB-PET	-.36	.17	**.046**	-	-	-	-	-	-	-.70	-.32	**.038**
People	.07	.08	.396	.29	.13	**.027**	.04	.09	.670	.55	.23	**.025**
People x PiB-PET	-	-	-	-.33	.16	**.049**	-	-	-	-.74	.30	**.018**
Substantive	.08	.09	.351	.07	.09	.431	.04	.10	.708	.20	.17	.231
Substantive x PiB-PET	-	-	-	-	-	-	-	-	-	-	-	-

Linear regression models were used to estimate the association between occupational complexity and cognitive scores, while adjusting for measures of brain integrity (MRI or PET). Each dimension of occupational complexity was tested in separate models. The interaction term between occupational complexity and brain integrity was kept in the model if significant ($p<.05$). The table shows the ß coefficients, SE and P values for the association between occupational complexity scores and cognitive scores, and the interaction between occupational complexity and measures of brain integrity. MTA was used as indicator variable, with group 1 set as the reference category. The PiB-PET measures were used as dichotomized (negative or positive). All models were adjusted for age, sex, and education. MRI regression models also included study site as covariate, and PiB-PET models also included *APOE* status.

*Visually rated MTA: by Scheltens scale of severity, which ranges from 0 (normal, no atrophy), to 4 (advanced atrophy). MTA ratings were grouped into three levels: MTA 1: ratings 0-0.5 (n=18 individuals); MTA 2: rating 1 (n=65 individuals); MTA 3: ratings 1.5-3.0 (n=24 individuals).

Abbreviations: AD: Alzheimer´s disease; ADS: Alzheimer´s disease signature thickness; ß: standardized beta coefficient; MTA: medial temporal atrophy; NTB: neuropsychological test battery; SE: standard error.