An assessment of neurocognitive speed in relation to frailty

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Abstract

Objectives: to evaluate the relationship between neurocognitive speed (NCS) and frailty; to consider how this relationship is affected by how frailty is operationalised.

Design: secondary analysis of the baseline cohort of the Oxford Project To Investigate Memory and Aging (OPTIMA), a longitudinal observational cohort.

Subjects: of 388 participants who underwent a comprehensive intake assessment followed by an annual follow-up for at least 3 years, data on all measures were available on 164 people.

Measurements: NCS was defined as a combined score of <18 on the pattern comparison test (<11 is abnormal) and letter comparison test (<7 is abnormal). Frailty was defined from a modified Phenotype model, the Edmonton Frailty Scales (EFS) and a frailty index (FI); the latter two were adapted here to exclude cognitive measures.

Results: in multivariate logistic (NCS as < or ≥18) and linear regression (NCS as continuous variable), only the FI (OR = 0.87) was significant (P < 0.05). When all frailty measures were included in the multivariate analysis only, FI (OR = 0.88) was significant (P < 0.05). Mini-mental Status Examination remained significantly related to NCS throughout all analysis.

Conclusion: NCS slows with increasing frailty as shown with the FI.

Keywords: frailty, aged, measurement, neurocognitive speed, cognitive impairment, older people

Introduction

Frailty, as a state of increased risk of adverse health outcomes, is common in older adults. Even so, the operationalisation of frailty is disputed [1–4]. Although various definitions typically each show a strong, graded association between frailty measures and outcomes such as falls, hospitalisations, disability and death, which items should be seen to make up an operational definition of frailty is unsettled. In particular, whether cognitive impairment is an important attribute, or should be separate, remains debated [5, 6].

Several frailty measures include some cognitive testing [7–10]. In contrast, the most widely cited operational definition of frailty employs a phenotype of five attributes (weight loss, slow gait, impaired grip strength, exhaustion and reduced activities), but excludes cognition [11]. Motor slowing, especially manifest as slow gait speed, is seen has having key importance [12–13]. Likewise, slow gait speed is increasingly accepted as a harbinger of cognitive disorders: several cohort studies have demonstrated that motor slowing independently predicts the time to onset of persistent cognitive impairment [14–16]. This reflects that gait speed, a complex phenomenon, is related to information processing and thus formally, neurocognitive speed (NCS).

Neurocognitive or perceptual processing speed as assessed here refers to the speed at which relevant information...
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can be activated in the performance of a task, and not the rate at which information decays or is displaced [22]. Although much of the variance in processing speed is accounted for by age, the balance of that variance is likely to reflect true cognitive deficits as shown by de Jager et al. [23].

How frailty relates to NCS remains untested. It is also unclear whether that relationship is influenced by the frailty instrument selected. Our primary objective was to see whether frailty was related to NCS and whether that varied by the instrument used to measure frailty.

Methods

Setting

This is a secondary analysis of data from an English cohort study. The Oxford Project To Investigate Memory and Aging (OPTIMA) is a longitudinal observational cohort established in 1988 to investigate dementia, health-related variables associated with dementia and the impact of these variables on outcomes [17]. Although frailty has not been formally monitored, the variables that comprise the various definitions of frailty are largely available in this cohort. Three operational definitions [frailty phenotype, the frailty index (FI) and the Edmonton Frail Scale] can be compared.

Starting in 1988, OPTIMA participants underwent a comprehensive intake assessment followed by annual medical and neuroimaging assessments for at least 3 years, and 6-monthly neuropsychological assessments including the CAMDEX (Cambridge Examination for Mental Disorders in the Elderly) [18] and the National Adult Reading Test (NART) [19]. Participants were required to have sufficient reading ability and vision (corrected with spectacles if necessary) to complete the paper-and-pencil cognitive tests. From November 1997 to June 1998, a healthy control cohort (n = 160) was included in the OPTIMA intake. Domain-specific neurocognitive testing, including NCS was only then introduced to this subset. A high proportion (n = 150) had sufficient NCS and frailty data to be included in the study. NCS testing was added to subsequent new participants in the main OPTIMA cohort starting from November, 1999. From this time through to March 2007, an additional 228 consecutive new OPTIMA participants (including those with and without cognitive impairment) were enrolled, of whom 86 had the required data for analysis. Of the combined participants in these two groups (n = 388), there were 236 participants aged 65 or older in whom the study measures, including NCS and frailty data were recorded. Of the 152 excluded, 17 were missing frailty data and 143 were missing NCS speed data. To eliminate the potential confounding effect of dementia, we excluded an additional 72 subjects (30.5% of the cohort) with a diagnosis of dementia. This included all subjects with vascular dementia using NINCDS AIREN criteria [20] or possible or probably Alzheimer’s disease using NINCDS ADRDA criteria [21]. In short, of the 388 participants eligible, complete data were available for 236, and 164 of these have no diagnosis of dementia.

Measures

We included demographic data (age at study entry, sex and total years of education), and the level of home support (% independent). We also identified the self-reported problems with mobility, and performance on the Mini-mental Status Examination (MMSE).

We defined abnormal NCS as a low score (<18) on the sum of the pattern comparison test (PCT, abnormal <11) and the letter comparison test (LCT, abnormal <7). Briefly, the PCT was conducted by having the subject compare pairs of line patterns and quickly stating whether the two patterns are the same or different. The number of correct responses within 20 s in series of these pairs made available to the subject comprised the score. The same procedure was followed for the LCT in which columns of letter pairs were presented [22]. The PCT and LCT have each been individually validated and used elsewhere where the tests differentiate older adults from younger [22] and dementia subjects from controls [23] with high sensitivity and specificity, suggesting that processing speed deficits do occur with dementia in addition to the decline in speed associated with ageing. By excluding subjects with dementia, we minimised but did not eliminate the possible confounding influence of visuospatial abnormalities.

In operationalising frailty, we employed the phenotypic definition, the Edmonton Frail Scale and the FI. All five original items in the phenotypic definition of Frailty [11] were approximated with comparable variables (Supplementary data are available in Age and Ageing online, Appendix A). Likewise, modifications were made to the items in the Edmonton Frail Scale (Supplementary data are available in Age and Ageing online, Appendix B) to capture available data. Of the 11 items (17 points) in the Edmonton Frailty Scales (EFS) [8], 5 of the items used in our analysis (number of medications, depression, weight loss, urinary incontinence and the clock drawing test) are a precise or very close approximation of the original item. Reasonable substitutions within the same domain were used for five more items. The General Health Question was not available, leaving 10 items (15 points) in the EFS. To avoid confounding, some recalculation was required for one measure, the CDT, given that it measures cognition, an obvious confounder with NCS. Consequently, we removed it also and analysed the remaining nine items in the modified EFS (13 points). Of the 62 variables available in the OPTIMA database (Supplementary data are available in Age and Ageing online, Appendix C) which met inclusion criteria [24] as potential health deficits in an FI (i.e. increasing with age; prevalence of at least 1%; <5% missing data; related to an adverse outcome and cover several organ systems), seven are cognitive measures (memory changes, general mental functioning changes, clouding/delirium, history of cognitive
impairment, short-term or long-term memory impairment, onset of cognitive symptoms).

Analysis

Initially, multivariate logistic regression was used to find the effect of the frailty assessments on NCS (dichotomised at a cut-point of 18 as explained above) while adjusting for age, sex, education and MMSE. Secondly, multivariate linear regressions were performed to find the effect of the various frailty measures on the ‘raw’ NCS (as a continuous variable) while again adjusting for age, sex, education and MMSE. Matlab (Statistica toolbox) and SPSS (PASW-18) were used to conduct statistical analyses.

Results

After excluding 72 subjects with dementia, there were 164 subjects with complete NCS data, and each had enough data to complete all three frailty measures. Their mean age at study entry was 74.0 [standard deviation (SD) 7.0], with 53.0% female. The majority (98.2%) lived independently in the community. The remainder lived in a dependent state in private or sheltered accommodation. The mean total years of education were 13.0 (SD: 3.5). Mobility problems were reported in 5.5%. The mean MMSE for the sample was 26.7 (SD: 4.32). The mean scores for the frailty scales were as follows: the phenotype 0.95 (SD = 1.00), EFS 1.7 (SD = 1.6), FI 0.137 (SD = 0.099). The mean scores for the PCT was 11.8 (SD = 3.4), for the LCT was 7.5 (SD = 2.5) and for total NCS was 19.3 (SD = 5.4). Subgroups with and without abnormal NCS (cut-point, NCS = 18) were compared according to all of the other study measures (Table 1).

The regression coefficients from the multivariate, linear regression analyses indicate that both the frailty phenotype and FI were significantly associated with reduced NCS (Table 2); however, unlike the FI, the frailty phenotype was only significant when the MMSE was taken out of the analysis. In all models, the MMSE was independently associated with NCS. Neither age nor sex nor education had an independent influence on NCS. When all previously significant frailty measures were entered into the multivariate linear regression, only the FI and the MMSE remained in the model (Table 2, final rows for linear and logistic regressions).

In parallel multivariate analysis done now using NCS as a binary cut-point at <18 and logistic regression, the same factors were significant with the same analysis. Without other frailty assessments, the frailty phenotype OR was 0.67 (95% CI = 0.46–0.99), whereas the FI OR was 0.87 (95% CI = 0.81–0.95). When both frailty measures were put into the analysis along with other covariates, only the FI (and MMSE) remained significant with an OR = 0.88 (95% CI = 0.80–0.96).

Discussion

In a non-demented and independent population, we demonstrated a significant relationship between NCS (also known as visuomotor or information processing speed), a measure of cognitive function and frailty. This supports a close relationship between cognitive function and frailty. While this relationship was demonstrated with both of the two most widely used frailty assessments (the FI and a modified version of phenotypic frailty), a relationship independent of the MMSE score was only demonstrated in the FI. The relationship of NCS with frailty was not evident using a modified version of the Edmonton Frail Scale.

Our conclusions do not make any determination on causality; we show only that there exists a strong correlation between frailty and NCS. Another limitation to our analysis is the operationalisation of the phenotype definition. The original frailty phenotype definition included five variables, three of which are performance measures. Our current definition includes clinical assessments instead of performance measures (for the weakness/slow gait/low physical activity). Even so, a number of publications have been obliged to modify the original phenotype operationalisation [25, 26]. This typically reflects that not all of the original variables have been included in routine cohort studies. With these caveats in mind, we did not show that our modified frailty phenotype was correlated with slower NCS. Similarly, a modified version of the EFS, with the cognitive component removed was not associated with slower NCS. Prospective studies, perhaps in a community sample with a more representative incidence of dementia, would be required to determine whether the original frailty phenotype and original EFS correlate with NCS.

Although in the development and prospective validation of the frailty phenotype definition, cognitive impairment was associated with frailty, it was excluded from their covariate-adjusted Cox proportional hazard model on theoretical grounds. It is clear that it would be redundant to equate frailty with an end state of declining cognition; namely dementia. This alone, however, is not adequate rationale for excluding cognition from frailty as the same could be said about the end stage of any of the phenotype characteristics. Even so, subsequent work with the phenotypic definition of frailty has found it to be a risk factor for mild cognitive impairment [27] and for Alzheimer’s disease [28, 29]. Likewise, cognitive

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Table 1. Subject characteristics as a function of performance in neurocognitive speed (NCS) (n = 164)

<table>
<thead>
<tr>
<th>Neurocognitive speed</th>
<th>NCS ≥18</th>
<th>NCS &lt;18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (95% SD)</td>
<td>74.3 (±6.7)</td>
<td>73.3 (±7.7)</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>49.1</td>
<td>61.5</td>
</tr>
<tr>
<td>Education in years (95% SD)</td>
<td>13.3 (±3.5)</td>
<td>12.3 (±3.4)</td>
</tr>
<tr>
<td>Living arrangements (% dependent)</td>
<td>0.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Mobility problem (%)</td>
<td>2.7</td>
<td>11.5</td>
</tr>
<tr>
<td>MMSE Score (95% SD)</td>
<td>28.0 (±2.3)</td>
<td>23.8 (±6.0)</td>
</tr>
<tr>
<td>Mean number of frailty phenotype items present (95% SD)</td>
<td>0.79 (±0.92)</td>
<td>1.29 (±1.09)</td>
</tr>
<tr>
<td>Mean EFS Score (95% SD)</td>
<td>1.36 (±1.48)</td>
<td>2.33 ±2.30</td>
</tr>
<tr>
<td>FI Score (95% SD)</td>
<td>0.110 (±0.078)</td>
<td>0.195 (±0.114)</td>
</tr>
</tbody>
</table>
impairment is a risk for phenotypic frailty [30]. A recent report has demonstrated that a FI made up only of deficits not known to be risks for dementia predicted dementia risk, even in a multivariate model that controlled for age [31]. This suggests that cognitive impairment and frailty are closely linked, even before a formal dementia diagnosis has been made.

Interestingly, when all of the frailty measures were included in the analysis, the phenotype fell out of significance, whereas the FI and MMSE stayed significant. This is supported by previous analysis showing that while the phenotype and EFS are easier to operationalise, the FI has greater power in defining a population.

The EFS is a lesser known frailty assessment but has been validated in a number of population health studies [8, 32–34]. It specifies fewer items, but more than the frailty phenotype. Here, the EFS had fewer variables still, due to unavailability in the data set and due to potential confounding effects from cognitive values. It is likely that as the number of items in the EFS decreased, so too did the sensitivity of this assessment. This is in keeping with a study that looked at randomly sampling variables to make up a frailty measure; there, adding more items decreased the confidence intervals associated with a range of associations with adverse outcomes [35].

These results must be interpreted with caution. The potential influence of missing data must be acknowledged. Of the 388 Optima subjects, 143 were missing NCS data. We compared this group to the 245 who had NCS data. Even though we found no differences in age, sex or years of education, people in whom NCS data were complete less often had mobility problems (5 vs. 10% with missing data), and had a higher MMSE score (25.6 vs. 24.8). A second caution is that the frailty measures, especially the frailty phenotype and EFS are reconstructed approximations of their original form. The latter of these has had its cognitive component removed. The FI, by design, has the flexibility to include slightly different components without requiring any such disclaimer. Thirdly, we acknowledge that some collinearity of the three frailty measures may influence their statistical significance in the multivariate model. However, the demonstrated association between NCS and frailty may also explain why the FI, which is derived from a definition of frailty that includes cognition, retains its capacity to define a frail population.

Many studies have evaluated frailty, including the narrowly defined frailty syndrome, and aspects of physical function in relation to low mood and cognitive impairment, and found them to be related. [14, 15, 29, 31, 36, 37] With respect to motor speed, it is an item in the frailty phenotype, [11] very common at all grades of frailty [38] and seen by some commentators as at the heart of all frailty [13]. Even though impaired NCS is associated with motor slowing, [15] that aspect of the relationship has not been explored with regard to frailty. It needs to be because motor slowing also has been related to cognitive impairment [15]. In consequence, the current data allows for some understanding of frailty as a broad construct that relates to an impairment of reserve that includes brain function in its cognitive and motoric manifestations. From this, we conclude that there is no scientific need to exclude the brain from consideration in frailty; indeed motor and cognitive function, and affect, cannot conceptually be disentangled from so-called ‘physical frailty’; all the more so because the idea of frailty seeks coherence in, and proves useful as, an integrative concept [39].

![Table 2. Linear regression coefficients of covariates to ‘raw’ NCS (continuous NCS variable)](image)

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>MMSE</th>
<th>Phenotype</th>
<th>EFS13</th>
<th>FI</th>
<th>Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivariate linear regressions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B (SE)</td>
<td>N/A</td>
<td>$-0.88 (0.43)$</td>
<td>N/A</td>
<td>N/A</td>
<td>14.9 (4.5)</td>
</tr>
<tr>
<td> </td>
<td> </td>
<td>$P = 0.04$</td>
<td> </td>
<td> </td>
<td>$P &lt; 0.01$</td>
</tr>
<tr>
<td>B (SE)</td>
<td>$0.44 (0.10)$</td>
<td>$-0.60 (0.41)$</td>
<td>N/A</td>
<td>N/A</td>
<td>6.0 (4.7)</td>
</tr>
<tr>
<td>$P &lt; 0.01$</td>
<td>$P = 0.15$</td>
<td> </td>
<td> </td>
<td> </td>
<td>$P = 0.21$</td>
</tr>
<tr>
<td>B (SE)</td>
<td>$0.43 (0.11)$</td>
<td>N/A</td>
<td>$-0.21 (0.29)$</td>
<td>N/A</td>
<td>6.69 (4.9)</td>
</tr>
<tr>
<td>$P &lt; 0.01$</td>
<td> </td>
<td> </td>
<td>$P = 0.46$</td>
<td> </td>
<td>$P = 0.18$</td>
</tr>
<tr>
<td>B (SE)</td>
<td>$0.34 (0.105)$</td>
<td>N/A</td>
<td>N/A</td>
<td>$-0.23 (0.08)$</td>
<td>7.90 (4.7)</td>
</tr>
<tr>
<td>$P &lt; 0.01$</td>
<td> </td>
<td> </td>
<td> </td>
<td>$P &lt; 0.01$</td>
<td>$P = 0.10$</td>
</tr>
<tr>
<td>B (SE)</td>
<td>$0.29 (0.11)$</td>
<td>$0.07 (0.46)$</td>
<td>N/A</td>
<td>$-0.24 (0.08)$</td>
<td>6.34 (4.86)</td>
</tr>
<tr>
<td>$P &lt; 0.01$</td>
<td> </td>
<td>$P = 0.88$</td>
<td> </td>
<td>$P &lt; 0.01$</td>
<td>$P = 0.20$</td>
</tr>
<tr>
<td>Multivariate logistic regressions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>N/A</td>
<td>$0.61 (0.42–0.87)$</td>
<td>N/A</td>
<td>N/A</td>
<td>0.17</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>$1.31 (1.14–1.50)$</td>
<td>$0.67 (0.46–0.99)$</td>
<td>N/A</td>
<td>N/A</td>
<td>0.007</td>
</tr>
<tr>
<td>$P &lt; 0.001$</td>
<td>$P = 0.045$</td>
<td> </td>
<td> </td>
<td> </td>
<td>$P = 0.360$</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>$1.31 (1.13–1.51)$</td>
<td>N/A</td>
<td>$0.93 (0.72–1.20)$</td>
<td>N/A</td>
<td>0.001</td>
</tr>
<tr>
<td>$P &lt; 0.001$</td>
<td> </td>
<td>$P = 0.563$</td>
<td> </td>
<td> </td>
<td>$0.006$</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>$1.19 (1.04–1.36)$</td>
<td>N/A</td>
<td>N/A</td>
<td>$0.87 (0.81–0.95)$</td>
<td>0.007</td>
</tr>
<tr>
<td>$P = 0.012$</td>
<td> </td>
<td> </td>
<td> </td>
<td>$P = 0.001$</td>
<td>$P = 0.74$</td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>$1.19 (1.04–1.36)$</td>
<td>$0.94 (0.59–1.49)$</td>
<td>N/A</td>
<td>$0.88 (0.80–0.96)$</td>
<td>0.006</td>
</tr>
<tr>
<td>$P = 0.012$</td>
<td> </td>
<td>$P = 0.779$</td>
<td> </td>
<td>$P = 0.004$</td>
<td>$P = 0.071$</td>
</tr>
</tbody>
</table>

Significant coefficients are in bold ($P < 0.05$). Sex, age and education remain non-significant throughout each analysis.

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Our results show that there is a significant and strong relationship between frailty and cognition. These results add to the growing literature of the close relationship between a broad construct of frailty to go beyond only physical impairments and to include cognition.

**Key points**

- We have demonstrated a significant relationship between NCS, a measure of cognitive function and frailty.
- This supports a close relationship between cognitive function and physical components of frailty. Cognitive function appears to be an inherent characteristic of frailty.
- This association was evident in relation to the two most commonly used measures of frailty, the FI and a modified version of phenotypic frailty, though the latter was not independent of the MMSE score. NCS was not associated with a modified version of the Edmonton Frail Scale.

**Conflicts of interest**

No commercial products are discussed in this paper. Further, each of the authors declares no proprietary interest in any of the results.

**Supplementary data**

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

**References**

Sarcopenia and cognitive impairment in elderly women: results from the EPIDOS cohort

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Abstract

Background: common pathophysiological pathways are shared between age-related body composition changes and cognitive impairment.

Objective: evaluate whether current operative sarcopenia definitions are associated with cognition in community-dwelling older women.

Design: cross-sectional analyses.

Subjects: a total of 3,025 women aged 75 years and older.

Measurements: body composition (assessed by dual energy X-ray absorptiometry) and cognition (measured by short portable mental status questionnaire) were obtained in all participants. Multivariate logistic regression models assessed the association of six operative definitions of sarcopenia with cognitive impairment. Gait speed (GS, measured over a 6-meter track at usual pace) and handgrip strength (HG, measured by a hand-held dynamometer) were considered additional factors of interest.

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