

Research Article

Timed Up and Go in people with subjective cognitive decline is associated with faster cognitive deterioration and cortical thickness

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Abstract:**Introduction:**

Early markers of neurodegeneration provide an opportunity to detect, monitor, and initiate interventions in individuals who have an increased risk of developing dementia. Here, we investigated whether the "Timed Up and Go test (TUG) is associated with early brain neurodegeneration and whether the TUG test could be a marker of cognitive decline, in people with Subjective Cognitive Decline (SCD).

Methods:

This is a longitudinal analysis of the Dementia disease initiation (DDI) study, a prospective, community-based, cohort study from Norway, designed to investigate early markers of cognitive impairment and dementia. Participants were classified as SCD and healthy controls (HC). The main studied variables were the TUG test and cognition as measured with the Mini-mental state examination and CERAD memory composite score (CERAD-MC). Additionally, we investigated the cross-sectional association of brain morphology with the TUG using 1.5T-MRI.

Results:

The sample included 45 participants (SCD=21, HC=24) followed during a mean time of 1.50 ± 0.70 years. At baseline, the cognitive performance did not differ between the groups, but TUG was longer in SCD. Slower baseline TUG was associated with a faster cognitive decline in both groups and it was also associated with reduced cortical thickness especially in motor, executive, associative, and somatosensory cortical regions in people with SCD.

Discussion/Conclusion:

TUG predicted cognitive change in individuals with SCD, and there was a negative association between TUG and cortical thickness. TUG is a promising cheap and non-invasive marker of early cognitive decline and may help initiate interventions in individuals who have an increased risk of dementia.

Introduction

Dementia and cognitive impairment are growing issues in public health causing a high rate of disability and social costs.[1] With increasing life expectancy, the challenge will grow in the future.[2] The slow early development of neurodegenerative diseases provides a unique opportunity to detect, monitor, and intervene in individuals at predementia stages.

Subjective cognitive decline (SCD) is a frequent condition occurring in 10-15% of people aged 65 or older. SCD is defined as a self-experienced persistent decline in cognitive capacity, compared with a previously normal cognitive status, which is unrelated to an acute event, and represents one of the earliest symptoms of dementia [3, 4]

The assessment of physical mobility is an essential component of the geriatric assessment of older adults.[5] Muscle mass, strength, performance, and balance in older adults have been associated with the development of unfavorable outcomes, including falls, future disability, and mortality.[6-8] Some indicators of reduced muscular function, such as gait speed and the Timed Up and Go (TUG) have also been shown to be associated with faster cognitive decline and progression to dementia in people with mild cognitive impairment[9-13]. Indeed, alterations in gait speed have been shown to precede cognitive decline by several years before the clinical onset of dementia [14, 15]. TUG involves tasks that require central nervous system coordination[16, 17] and involves physical measures that indicate muscle wellbeing, sarcopenia, and frailty.[18] To perform the TUG, the person in evaluation is asked to rise from a standard armchair, walk to a line on the floor 3 meters away, turn, return, and sit down again. Therefore, this test is quick, requires no special equipment or training, and can be easily included as part of a routine medical examination.[19]

However, longitudinal research regarding the role of the TUG in individuals with SCD is limited, and early markers indicating risk factors of cognitive decline progression in people with SCD are needed. In this study, firstly, we studied whether the TUG test could be a marker of cognitive decline in people with SCD. Secondly, we investigated whether TUG is associated with early brain changes.

Materials and Methods:

Design, participants, and setting

This is a longitudinal analysis of the Dementia disease initiation (DDI) study, a prospective, population-based, longitudinal multicenter cohort study from Norway. The DDI was designed to investigate early cognitive and biological markers to detect and track cognitive deterioration.

DDI uses a standardized protocol for participant selection, assessment, and disease-stage classification (SCD, mild cognitive impairment (MCI), and dementia) according to published and validated criteria.[20-22]. Data collected include the nature of cognitive decline (cognitive domain, onset), concerns and worries, including feeling worse compared to age-matched peers, and informant confirmation of decline (when available). Participants were classified as SCD according to the SCD-I framework, which requires normal objective cognitive performance on formal neuropsychological testing, in combination with a subjectively experienced decline in any cognitive domain.[22]

Participants were recruited from referrals to local memory clinics or self-referrals responding to advertisements in media, newspapers, or news bulletins. Healthy controls (HC) without subjective cognitive complaints were recruited from spouses of participants with either MCI or SCD and volunteers responding to media advertisements or news bulletins. Criteria for inclusion were age between 40 and 80 years and a native language of Norwegian, Swedish, or Danish. Exclusion criteria were dementia, brain trauma, stroke, severe psychiatric disorder, or any severe somatic disease that might influence cognitive functions, intellectual disability, or other developmental disorders. The cohort described here was recruited from 2013 to 2021. For further description of the DDI cohort and methods, refer to the study by Fladby et al. (2017).[23] Participants were assessed at baseline and again evaluated at follow-up (average 1.5, min 1.4 max 2.4 years). Data from 45 participants recruited and studied in one of the centers, Stavanger University Hospital, were analyzed to avoid scanner variability.[24] One participant did not continue in the

study and was considered as a dropout during baseline and year 2. See the Flowchart of the study sample in Supplemental Material.

Measurements

TUG was defined as the time measured in seconds that the participant used for walking a distance of 3 meters, turn, walk back to the chair, and sit down again. The protocol to measure TUG was the following: The participant wore regular footwear and used customary walking aid (none, cane, or walker). No physical assistance was given. The participant started with the back against the chair, the arms resting on the chair's arms, and his/her walking aid at hand. The participant was instructed that on the word "go", he/she may get up and walk at a comfortable and safe pace to a line on the floor 3 meters away, turn, return to the chair, and sit down again. The test was performed 3 times, the first execution is to make the participant familiar with the exercise. The average time from the 2nd and 3rd execution is calculated and used for evaluation. The participant was allowed to rest for a few minutes between each trial of the test.

For the cognitive outcome of this study, we used the Mini-Mental State Examination in its validated version in Norwegian (MMSE)[25], and the CERAD memory composite score (CERAD-MC) constructed comprising subtests from The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). The composite included CERAD subtests total learning, recall, and recognition and was constructed following an established method for cognitive composites. [26, 27] and have previously been shown to be accurate in detecting prodromal AD.[28] Raw scores for the CERAD subtest total learning (30 items), recall (10 items), and recognition (20 items) were standardized to a score between 0 – 100. Then, these scores were summed and averaged to compute a 0 – 100 standardized composite score. [29]

Imaging analysis:

The data were collected on a 1.5T Philips Ingenia (Best, the Netherlands) at the Department of Radiology at Stavanger University Hospital with the same ds Head 16-channel coil. Head movement was minimized using foam cushions and the participants were instructed not to

move the head during the whole session. There were no hardware updates during the study period. For the current data analyses we used a sagittal 3DT1 Turbo field echo (TFE) sequence (repetition time (TR) = 7.6 ms, echo time (TE) = 3.5 ms, flip angle (FA) = 8 degrees, inversion time (TI) = 939.5 ms, turbo factor (TF) = 237, 180 slices, slice thickness = 1 mm, field of view (FOV) = 240 mm, voxel size 1 x 1 x 1 mm³, time of acquisition (TA) was 6 min 20 s) and a transversal 3D Fluid attenuated inversion recovery (FLAIR) sequence (TR = 4800 ms, TE = 356 ms, FA = 90 degrees, TI = 1660 ms, TF = 202, 240 slices, slice thickness = 1.2 mm, voxel size 1.15 x 1.15 x 1.2 mm³, TA = 5 min 50 s).

Cortical reconstruction and volumetric segmentation were performed with the FreeSurfer image analysis suite version 6.0 using the aseg atlas (Massachusetts General Hospital, Boston, MA). [30] This includes segmentation of the subcortical white matter, detection of white matter hypointensities and deep gray matter volumetric structures, and parcellation of the cortical surface according to a previously published parcellation scheme [31, 30]. The cortical regions and thickness values are calculated in regions of interest (ROIs); 3 subcortical volumes= white matter hypointensities and left and right hippocampus and 30 cortical thickness ROIs. In addition, intracranial volume based on FreeSurfer estimations were calculated.

Other variables considered for the analysis were sociodemographic factors (age, sex, years of schooling, and marital status) and body mass index (BMI). Depressive symptoms were assessed using The Geriatric Depression Scale (GDS) 15 items, with a cut point of 6 for at least mild depression. The number of comorbidities (evaluated employing a summary score, summing up hypertension, diabetes, COPD, stroke, myocardial infarction, arthritis, and cancer) were recorded.[32]

Statistical analysis:

The variables were described using means with standard deviations or frequencies with percentages, as appropriate. Participants were classified into HC and SCD groups, and baseline characteristics were compared using a t-test for means and a chi-squared or Fisher

exact test for frequencies. To assess the longitudinal effect of TUG in the progression of MMSE and CERAD, linear mixed-effect models with a random intercept were conducted. For modelling, the squared root of 30 - MMSE was used to obtain a better approximation to the normality assumption, while the CERAD-MC measure was used in its original scale. As adjustment variables we performed a stepwise procedure based on the AIC criteria and the likelihood ratio test, considering initially gender, age, BMI, year of education, marital status, number of comorbidities, and the GDS score for depression, adjusting finally only by years of education. All models considered the variability between subjects as a random intercept. We graphed results of the adjusted models for HC and SCD using the original scale for the MMSE and the CERAD-MC at 1.5 years average of follow-up.

In addition, linear regression models were performed to explore potential associations between TUG and regional cortical thickness adjusting by age and sex and subcortical brain volumes adjusting by age, sex, and intracranial volume. These models included each normalized brain volume at baseline as the dependent variable and TUG at baseline as the independent variable. P-values lower than 0.05 were considered statistically significant for this analysis. No corrections of the p-values were carried out since multiple comparisons were not made within the different models. All statistical analysis was performed using R version 4.0.3.[33]

Ethics

The regional medical research ethics committee approved the study. Participants gave their written informed consent before taking part in the study. The study was in line with the guidelines provided by the Helsinki declaration of 1964, revised 2013, and the Norwegian Health and Research act.

Results:

Baseline characteristics of the sample

The final sample consisted of 19 SCD and 16 healthy controls (HC). Both groups were comparable and there were no significant differences in the CERAD-MC or MMSE at baseline. Baseline characteristics of the sample are displayed in Table 1. The mean follow-up period was 1.50 ± 0.70 years (HC 1.59 ± 0.64 and SCD 1.39 ± 0.78 p-value 0.4562). The time performing the TUG at baseline was longer in SCD; 8.35 ± 1.34 vs HC 7.42 ± 1.05 (p-value 0.028).

Cognitive performance associations with TUG

After adjustments, higher TUG was associated with faster cognitive decline in subjects with SCD and HC. For the MMSE (Est. 0.14 Std. Err. 0.06 p-value 0.039) there was an average decrease in the score of 0.21 for SCD and 0.17 for HC by each second that the TUG increased. For the CERAD-MC (Est.-3.66, Std. Err. 1.24, p-value 0.006) there was an average decrease in the score of 3.66 for each second that TUG increased for SCD and HC. The higher TUG at baseline the lower the MMSE and CERAD-MC performance in the follow-up. See Table 2 and Figure 1.

Cortical volume associations with TUG

After adjustments, in SCD the TUG test had a negative association with cortical thickness in the left superior frontal gyrus, left lateral orbitofrontal cortex, left precentral gyrus, left pars triangularis, right and left paracentral lobule, right and left Rostral Middle Frontal Gyrus and right medial orbitofrontal cortex. In HC, a longer time to complete the TUG test was negatively associated with cortical thickness in the left precentral gyrus and the left caudal anterior cingulate cortex. See Table 3 and Figure 2.

Discussion:

In this study, we found that motor slowing, measured by longer time to perform the TUG test was associated with faster cognitive decline in both groups of participants; SCD and HC during a mean follow-up of 1.5 years. In addition, we report that longer time performing the TUG especially in SCD was negatively associated with cortical thickness in several brain regions.

This research provides evidence suggesting that measuring gait speed and mobility using the TUG can be a useful measure that might predict a subsequent faster decline in cognitive performance in subjects with SCD and HC.

The performance in TUG has been reported to be also affected in people with MCI [10].

However, the evidence of the TUG is limited concerning the risk of faster cognitive decline in persons living with SCD. People with SCD have no objective cognitive decline in neuropsychological tests and have preserved function in activities of daily living. However, persons with SCD are at an increased risk of cognitive decline and dementia. SCD is considered a pre-Mild Cognitive Impairment or predementia stage [34, 35]. Thus, identifying factors that can help to detect those subjects with SCD with a greater risk of dementia is clinically relevant.

While no baseline difference in cognitive performance was shown between HC and SCD, we found that TUG performance was slower in SCD cases. However, when assessing TUG and cognition during the follow-up, reduced performance on CERAD-MC and MMSE was associated with slower baseline TUG in both groups. CERAD has been related to higher sensitivity for small changes compared to MMSE, [36] although in this study both tests were affected in both groups which strengthen the utility of TUG to predict cognitive decline in early stages

Recent studies have reported relevant associations between TUG and cognitive decline, including associations with dementia diagnosis; Lee JE et al, found an association of TUG with dementia incidence in a national registry in Korea. Moreover, Katsumata et al. reported that TUG was associated with global cognitive function in Japanese community-dwelling older adults.[9] Also, slower TUG performance has been associated with poor performance in domains such as memory and executive function [37-39].

Research is growing regarding physical measures and the prediction of risk of cognitive impairment [15]. There is evidence that slowing of gait speed (GS) occurs early in the disease course and may precede declines on cognitive tests[40]. A previous study by our group found a cross-sectional association of walking speed with cognitive testing using the

Trail Making (TMT) A and B tests and a gradual worsening in the GS starting from the normal controls, SCD, and to MCI[41].

Additionally, the GS and the TUG have been combined with cognitive tasks in the dual-task paradigm. Research in this area has shown that the dual-task can reveal subtle motor impairments that are not detected during single-task test conditions, and that these motor impairments represent a higher risk for cognitive deterioration in healthy older adults[42]. Montero-Odasso reported that in subjects with MCI, the dual-task gait test predicted the risk of dementia incidence [43].

Further, the Motor-cognitive risk syndrome (MCR) is also considered a condition of increased risk for dementia development defined as impaired gait speed in subjects with SCD[44]. There is evidence that this condition is a risk factor not only for cognitive decline but also for falls, disability, frailty, and increased mortality has been found in different populations [44-46]

GDS depression score at baseline was higher in the SCD group (but below the cut-off of mild depression ($GDS > 6$): mean 2.63 ± 2.5). Depression may relate to cognitive and motor deficits, therefore it was considered as a possible confounder.[47, 48]. However, it was discarded in the final model after a stepwise procedure of variable selection.

In addition, we found a negative association between cortical thickness and time to complete TUG. Thinner cortex in some ROIs was associated with a longer time to complete TUG, these areas are associated with working memory, motor, somatosensorial, executive, and integration tasks. [49] A previous publication in persons with documented cognitive decline and gait impairment have reported volume loss in the superior frontal gyrus, superior parietal gyrus, precuneus, thalamus, and cerebellum.[50] The evidence regarding changes in people with SCD in gait or motor tasks is scarce. We here provide new evidence of reduced integrity in brain areas related to very early TUG alterations.

Some cross-sectional studies studying MCR, (which by definition includes SCD), have shown that MCR is associated with lower gray matter primarily in the prefrontal cortex, and supplementary motor area[51-53, 50] results that also support our current findings. Like

some of the other studies, we did not find associations between TUG and hippocampal volume [51]. However, hippocampal degeneration may occur later in the degeneration process, reported mainly when cognitive symptoms are more pronounced.[54]

Some possible mechanisms behind the associations described in our study include the following: First, high-level cognitive abilities are associated with specific brain regions with the capacity to regulate motor activities such as those involved in the TUG[55]. We found associations in specific areas that seem to support this mechanism.

For example, cortical thickness of the left precentral gyrus was related to longer time for TUG completion on both HC and SCD and is central for the execution of voluntary movement. Previous studies have shown thinning of this area in people diagnosed with Parkinson's disease with freezing of gait.[56]

Second, factors like mobility, muscle mass, and strength are also involved in motor performance. These factors change in the course of normal aging and especially in neurodegeneration, having the potential to interfere with normal motor performance.[57] Muscle function (gait) is a proxy measure of good muscular status. Muscle tissue is central e.g. in glucose and insulin metabolism and may reduce inflammation with possible links to metabolic and inflammatory changes associated with brain neurodegeneration.[58] [59, 60]. Thus, for example, physical inactivity can potentiate muscle loss and increase inflammation by interfering with the anti-inflammatory properties of the muscle. In fact, interventions such as physical activity and nutritional supplementation targeting muscle, mobility, and sarcopenia have shown positive effects on cognition and brain structure [61, 62]

This research has some limitations. Due to the small sample size and short follow-up duration, the statistical power is relatively low and we could not establish the risk of progression to MCI and Dementia. Also, the number of variables to include in the models was limited.[63]. Therefore, we did not adjust for multiple comparisons, thus we consider this an exploratory study. Available multicenter data from the DDI study was not used at this stage of analysis, to avoid scanner variability. The Cognitive-TUG was not used in the study. Instead, we assessed cognitive performance using a different validated and

comprehensive neuropsychological protocol. However, it would be relevant to use Cognitive-TUG in future studies in order to have a dual-task dynamic measure.

Conclusion:

Using longer time when performing the TUG test was associated with faster cognitive deterioration in the participants with SCD and HC. In addition, in HC and SCD there was a negative association between TUG and cortical thickness. This research provides evidence that measuring mobility using the TUG could be a marker of risk of progression in subjects with SCD.

Statements

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Statement of Ethics

This study was approved by the regional ethics committee (approval code: REK 2013/150) for the collection of medical data. All data was handled and kept under national health and data privacy protocols. All participants signed an informed consent form before inclusion in the study.

Conflict of Interest Statement:

The authors have no potential conflicts of interest to declare regarding research, authorship, and/or publication of this article.

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Author Contributions

Miguel Germán Borda: Conception of work, Formal analysis, Methodology, Visualization, Writing- Reviewing and Editing.

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Data Availability Statement

The data that support the findings of this study are not publicly available for containing information that could compromise the privacy of research participants but can be provide upon reasonable request to the PI DA dag.aarsland@kcl.ac.uk.

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Fig. 1. MMSE AND CERAD-MC progression according to TUG

MMSE and Baseline TUG, c. CERAD-MC and Baseline TUG. SCD: Subjective cognitive decline, HC: healthy controls. Marginal estimation at 1.5 years of follow-up.

Fig. 2. TUG and MRI measures

Adjusted models * SCD: Subjective cognitive decline, HC: healthy controls.