DTI measures predict the performance on cognitive tests in elderly and patients with early Alzheimer's disease

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Introduction

Alzheimer's disease (AD), a neurodegenerative disorder associated with progressive functional decline, is initially diagnosed as a memory disorder accompanied by attentional and perceptual deficits. Perceptual deficits in early AD include impaired visual motion processing with elevated thresholds for optic flow, the patterned visual motion seen during an observer self-movement (1, 2). The neurodegenerative effects of AD are well known and are observed within the somal, dendritic, and axonal compartments. Recently, it has been demonstrated that diffusion tensor imaging (DTI), a relatively new neuroanatomical imaging technique, can be used as a reliable method for identification of white matter (WM) and for detecting changes in WM tracts and subcortical WM. Changes in DTI measurements within the WM have been identified with demyelization, degradation of axonal integrity, and a loss of cortical connections. We predict that WM alterations as assessed by DTI will be reflective of cognitive processes in general and will correlate with cognitive performance in elderly and patients in early stages of AD in particular.

Methods

We performed DTI and neuropsychological testing on 33 subjects: 18 healthy elder normal controls (EN) (mean age = 75.6, age 60 and above; mean MMSE = 29 with range 27 - 30) and 15 mildly impaired AD patients (mean age = 75.4, age > 60; mean MMSE = 21 with range 19 - 24). Elderly and AD patients underwent neuropsychological testing to evaluate their cognitive status.

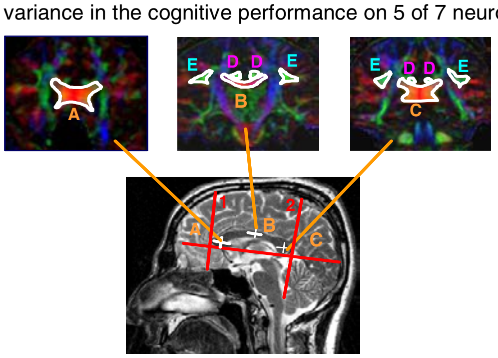
Neuropsychological evaluation: Neuropsychological tests for evaluation of basic cognitive capacities included: 1) The Mini-Mental Status Examination as a measure of overall impairment in AD; 2) The Road Map test was used to assess topographic orientation in simulated route; 3) Two subtests from the Wechsler Memory scale:: the Verbal Paired Associates test was used to assess immediate and delayed verbal memory, and the Figural Memory test was used to assess immediate visual recognition; 4) The Category Name Retrieval test to assess memory retrieval and cognitive flexibility; 5) The Judgment of Line Orientation test to test the ability to judge angular relationships; and 6) The Facial Recognition test to assess visuospatial processing.

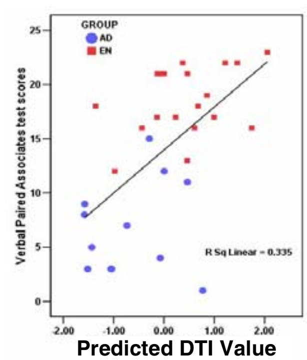
DTI protocol: MRI examinations were performed on a GE Signa 1.5 T MR scanner (LX9.1). In addition to conventional anatomic images, coronal DTI imaging with a single-shot pulsed-gradient spin-echo (PGSE) EPI were performed. Diffusion weightings were applied in 20 different orientations with b value = 0 and 1000 s/mm^2. TR/TE = 8000/85ms, FOV22cm, and matrix128X128. We used 22 contiguous slices perpendicular to the genu-splenium line, approximately 7mm thick, covering WM from the subcortical frontal to posterior parietal and occipital areas. The DTI images were processed using home-built software.

Image analyses: fractional anisotropy (FA), and diffusivity (<D>), were calculated for 13 regions of interest (ROI) (Fig 1): I. Subcortical WM in the prefrontal region (1) and in the parietal-temporal region (2); II. Corpus Callosum (CC): at the anterior (A), middle (B) and posterior (C) sites; III. Limbic System Fibers: bilateral cingulum (D); IV. Association fibers: Superior Longitudinal Fasciculus-SLF (E).

Results

We used multiple regression analyses to determine which FA and <D> measures from the ROIs would predict performance on neuropsychological tests. Regression analyses using stepwise method showed that the DTI measures significantly predicted the performance of elderly and AD patients on the Mini-Mental Status Examination test (R^2 = 19%, p = .01), the Verbal Paired Associates test (R^2 = 34%, p = .003; Fig 2), the Delayed Verbal Memory test (R^2 = 19%, p = .01), the Figural Memory test (R^2 = 55%, p < .0005; Fig 3), the Judgment of Line Orientation test (R^2 = 13%, p = .05), and the Facial Recognition test (R^2 = 19%, p = .001). Regression analyses also showed that several of the FA and <D> measures form different ROI were linked to cognitive performance. In general, DTI measures from the posterior subcortical regions and the middle and posterior CC were selected as the most predictive. Anisotropy measure FA from the posterior subcortical region was selected as a significant predictor on performance on the MMSE (β = .43, p = .01), the Verbal Memory test (β = 38, p = .02), the Delayed Verbal Memory test (β = .44, p = .01), and the Judgment of Line Orientation test (β = .44, p = .05). Anisotropy measure FA from the middle CC was also selected as a significant predictor for performance on the Figural Memory test from CCM (β = -.34, p =.03). Diffusivity measure <D> from the middle CC was selected as a significant predictor test for performance on the Facial Recognition test (-.57, p =.001), and for the Figural Memory test (β = -.48, p =.006), while <D> from the posterior CC was selected as a predictor of performance on the Verbal Memory test: CCPTR from the middle CC (β = -.44, p = 01). In summary, the results showed that the DTI measures can predict 13 % to 55 % of variance in the cognitive performance on 5 of 7 neuropsychological tests.





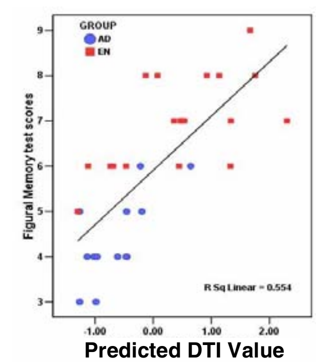


Fig 1 (Left) ROIs for subcortical WM (1,2), CC at the anterior (A), middle (B), and posterior (C) sites, cingulum (D), and SLF (E). **Fig 2** (Middle) Scatter plot of Verbal Paired Associates test scores (ordinate) by composite multiple linear regression DTI predictors (abscissa) for all AD (blue circles) and EN (red squares) subjects. Stepwise regression selected the <D> (β = -.44), from the posterior CC and FA from the posterior subcortical ROI (β = .38) as significant predictors yielding a composite R^2=. 34**.** **Fig 3** (Right) Scatter plot of Figural Memory test scores (ordinate) by composite multiple linear regression DTI predictors (abscissa) for all AD (blue circles) and EN (red squares) subjects. Stepwise regression selected the <D> (β = -.48), and FA (β = -.34) from the middle CC as significant predictors yielding a composite R^2=. 55**.**

Discussion

Our results from 18 healthy elder normal controls and 15 mildly impaired AD showed that DTI measures can reliably predict performance on several neuropsychological tests. Measures of anisotropy and diffusivity, primarily from the CC (middle and posterior ROIs) and the posterior subcortical region, significantly predicted performance on tests measuring verbal memory capacity (e.g., Verbal Paired Associates test, and Delayed Verbal Memory test), nonverbal memory capacity (e.g., Figural Memory test), as well as performance on visuospatial perceptual tests (e.g., Judgment of Line Orientation test and Facial Recognition test). These results clearly demonstrate that cognitive performance as measured by standard neuropsychological tests does not depend only on the intact cortex but also on preserved and functionally viable WM structures. Greater involvement of more posterior WM structures in predicting cognitive performance may reflect the early spread of the AD neurodegeneration into the interhemispheric (i.e., callosal) and intrahemispheric WM fibers in the temporal and parietal cortices.

Reference: (1) Tetewsky,S, Duffy C. J, Neurology, 52, 958-965 (1999). (2) Kavcic V., Duffy C.J., Brain, 126, 1173-1181 (2003).