The European DTI Study on Dementia – a multicenter DTI and MRI study on Alzheimer's disease and Mild Cognitive Impairment

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Highlights

- The multicenter EDSD dataset contains 493 DTI and 512 T1-weighted MRI scans
- Encompasses 139 AD patients, 160 MCI patients and 194 Healthy Controls
- Retrospective data collection from 11 centers and 13 scanners
- Extensive demographic/clinical/neuropsychological characterization of subjects

Abstract

The European DTI Study on Dementia (EDSD) is a multicenter framework created to study the diagnostic accuracy and inter-site variability of DTI-derived markers in patients with manifest and prodromal Alzheimer's disease (AD). The dynamically growing database presently includes 493 DTI, 512 T1-weighted MRI, and 300 FLAIR scans from patients with AD dementia, patients with Mild Cognitive Impairment (MCI) and matched Healthy Controls, acquired on 13 different scanner platforms. The imaging data is publicly available, along with the subjects' demographic and clinical characterization. Detailed neuropsychological information, cerebrospinal fluid information on biomarkers and clinical follow-up diagnoses are included for a subset of subjects. This paper describes the rationale and structure of the EDSD, summarizes the available data, and explains how to gain access to the database. The EDSD is a useful database for researchers seeking to investigate the contribution of DTI to dementia diagnostics.

Keywords: Alzheimer's Disease; Mild cognitive impairment; Diffusion tensor imaging; multicenter study; data sharing

1. Introduction

The European DTI Study on Dementia (EDSD) is a framework created to study the multicenter variability and diagnostic accuracy of DTI-derived markers in patients with manifest and prodromal Alzheimer's disease (AD). The potential contribution of DTI (diffusion tensor imaging) to an early and more accurate diagnosis of neurodegenerative diseases has received increasing attention over the last years. In AD, histologic evidence shows early microstructural white matter changes (Brun and Englund, 1986). DTI allows the assessment of microstructural tissue integrity, which may be detected earlier than macrostructural changes (Amlien and Fjell, 2014; Le Bihan et al., 1992). The most commonly used DTI indices include fractional anisotropy (FA), a measure of the directionality of water diffusion, and mean diffusivity (MD), a measure of the absolute magnitude of diffusion (Teipel et al., 2014c). The EDSD framework not only allows evaluating the contribution of DTI to early and accurate dementia diagnostics, but also provides the opportunity to examine the multicentric stability of potential DTI-derived diagnostic markers; a prerequisite for any biomarker that is to be used within a wider clinical setting (Teipel et al., 2011).

The EDSD was founded in 2010 and is coordinated by the German Center for Neurodegenerative Diseases (DZNE) in Rostock (Germany). Initially, DTI and MRI data from healthy control subjects (HC) and AD patients were retrospectively collected from 10 European centers. In 2013, the EDSD was expanded to include subjects with Mild Cognitive Impairment (MCI). Since then, the EDSD database is continuously growing by dynamically adding new centers and subjects, as well as adding supplementary imaging, biomarker, and clinical data for existing subjects in the database. Currently, the EDSD has 18 partner centers, of which 11 have contributed imaging data by now. These include centers in Amsterdam (Netherlands), Brescia (Italy), Cambridge (The UK), Dublin (Ireland), Frankfurt (Germany), Freiburg (Germany), Mainz (Germany), Mannheim (Germany), Milano (Italy), Munich (Germany), and Rostock (Germany). Most of the data (from 9 centers) is already publicly available on the data sharing platform Neugrid N4U (https://neugrid4you.eu/). Recently, access via the Global Alzheimer's Association Interactive Network (GAAIN) (http://gaain.org/) was initiated, from where the user is redirected to Neugrid N4U.

2. Available data in the database

2.1. *Sample characteristics*

As of March 2016, the EDSD study sample consists of 139 AD patients, 160 MCI patients and 194 HC. Dementia patients were diagnosed with clinically probable AD according to the NINCDS-ADRCA criteria (McKhann et al., 1984) and were required to be free of any other significant neurological, psychiatric, or medical conditions. Patients with MCI were diagnosed according to the Petersen criteria, exhibiting subjective and objective cognitive impairment (exceeding –1.5 standard deviations in the Consortium to Establish a Registry of Alzheimer's Disease (CERAD) testing battery, controlled for age and education) and being free of dementia (Petersen, 2004). Some MCI patients (N = 19) exhibited past or current psychiatric symptoms such as depressive or anxiety symptoms, which were recorded in the clinical data. Cerebrospinal fluid (CSF) information on biomarkers of amyloid and tau pathology is available for 76 MCI subjects, allowing a classification according to the revised diagnostic criteria (Albert et al., 2011). HC were required to be free of cognitive complaints and to have performed according to the age and education adjusted norms in all subtests of the CERAD testing battery (Morris et al., 1989). According to the declaration of Helsinki, written informed consent was provided by all participants or their legal representatives. The study was approved by the local ethics committees at each site. The subjects' main demographic data are summarized in Table 1. Additional clinical and neuropsychological data could retrospectively be collected for a subsample (Table 2).

Table 1 Subjects' demographic data

	AD (N = 139)	MCI (N = 160)	HC (N = 194)
Age, mean (SD)	73 (8)	73 (7)	69 (6)
Gender female/male	79/60	69/91	99/95
Education years, mean (SD)	10.2 (3.4) (N = 136)	12.5 (3.5) (N = 157)	13.1 (3.7) (N = 173)
MMSE, mean (SD)	20.7 (5.3)	26.5 (2.4)	28.9 (1.1) (N = 184)

Table 2 Number of subjects for whom clinical and neuropsychological data is available

	AD (N = 139)	MCI (N = 160)	HC (N = 194)
Converter to AD at clinical follow-up (N)	-	46 (out of N = 106)	-
APOE status (N)	52	77	75
CSF (amyloid-beta and tau) (N)	2	76	0
CERAD information (N)	97	129	117

2.2. Imaging data

Available imaging data include 493 DTI scans, 512 T1-weighted MRI data, and 300 FLAIR images, after quality control (see 2.2.2.). The diverging number of FLAIR images is due to the fact that FLAIR images were only provided for a subsample. The numbers of available DTI scans from each scanner are reported in Table 3. The anonymized images are provided in raw format (DICOM and NIFTI) as well as preprocessed format (NIFTI). The preprocessing procedure is described below. As there is no commonly agreed gold standard for image preprocessing routines in clinical studies, provision of the raw imaging data allows users to process the scans using their preferred settings.

Table 3 Numbers of DTI scans available from each scanner

Center	Scanner type	AD (N = 139)	MCI (N = 160)	HC (N = 194)
I	GE Signa HDxt	0	18	0
II	Siemens Allegra	17	0	16
III	Siemens Trio	0	22	24
IV	Siemens Achieva	9	11	20
V	Siemens Trio	16	0	8
VI	Siemens Trio	4	11	9
VII	Siemens Sonata	16	27	16
VIII	Siemens TrioTim	1	25	17
IX	Siemens Avanto	15	0	14
IX	Philips Intera	0	17	10
X	Siemens TrioTim	26	0	20
XI	Siemens Avanto	20	0	20
XI	Siemens Verio	15	29	20

2.2.1. Image acquisition

Images were obtained from 1.5 and 3.0 Tesla MRI scanners, including 9 scanner models from 3 vendors. The number of gradient directions of the DTI scans varied between 6 and 61, and slice spacing varied between 2 and 2.4mm across the different scanners. In addition, anatomical 3D gradient echo T_1-weighted MRI scans of approximately 1 mm^3 resolution were obtained from all scanners (Table 4).

Table 4 Acquisition parameters of T1-weighted MRI and DTI scans

Center	Scanner type	Tesla	T1-weighted MRI					DTI							FLAIR			
			TR	TE	TI	Fa	Voxel size (mm)	TR	TE	Fa	Gradients	b-values	Voxel size	Gap (mm)	TR	TE	TI	Voxel size (mm)
I	GE Signa HDxt	3.0	7836	3.0	450	12	1x0.9x0.9	13000	91	90	30	0, 1000	1x1x2.4	0.4	N/A	N/A	N/A	N/A
II	Siemens Allegra	3.0	2300	3.9	1100	12	1x1x1	5000	118	90	30	0, 1000	2x2x6	1.0	6000	353	2200	0.5x0.5x1.1
III	Siemens Trio	3.0	2300	2.9	900	9	1.25x1.25x1.25	9300	102	90	12	0, 1000	2x2x2.4	0.4	N/A	N/A	N/A	N/A
IV	Siemens Achieva	3.0	1512	3.9	518	8	0.9x0.9x0.9	11450	52	90	15	0, 800	2x2x2	0	N/A	N/A	N/A	N/A
V	Siemens Trio	3.0	792	2.5	910	16	1x1x1	146	100	90	60	0, 1000	2x2x2	0	6000	353	2200	1x1x2
VI	Siemens Trio	3.0	2200	2.2	1100	12	1x1x1	11800	94	90	61	0, 1000	2x2x2	0	N/A	N/A	N/A	N/A
VII	Siemens Sonata	1.5	2160	3.9	1100	15	1x1x1	8000	105	90	6	0, 1000	2x2x3	0	9000	108	2500	0.4x0.4x6
VIII	Siemens TrioTim	3.0	2300	3.0	900	9	1x1x1	9300	102	90	12	0, 1000	2x2x 2.4	0.4	8980	99	2500	0.9x0.9x4
IX	Siemens Avanto	1.5	2000	2.9	1100	12	0.5x0.5x0.9	6500	95	90	12	0, 1000	2x2x2.5	0	10000	115	2500	0.9x0.9x2.5
IX	Philips Intera	3.0	2500	4.6	N/A	30	0.8x0.9x0.9	8931	58	90	35	0, 900	1.9x1.9 x2.3	0	11000	120	2800	0.45x0.45x3
X	Siemens TrioTim	3.0	2400	3.1	900	9	1x1x1	9300	102	90	12	0, 1000	2x2x2	0	9000	117	2500	0.9x0.9x5
XI	Siemens Avanto	1.5	1900	2.9	1100	15	1x1x1	5100	85	90	30	0, 1000	2x2x2.4	0.4	9000	123	2500	0.6x0.6x5
XI	Siemens Verio	3.0	1900	2.5	900	9	1x1x1	8200	93	90	20	0, 1000	1x1x2.4	0.4	9000	94	2500	0.5x0.5x5

TR, Repetition time (ms); TE Echo time (ms); TI, Inversion time (ms); Fa, Flip angle (degrees)

2.2.2. Data quality

Image quality of each scan was visually controlled by a trained expert at the coordinating center. Scans were excluded if they showed strong ghosting effects, blurring, motion, or

susceptibility artefacts. In addition, covariance homogeneity of all MRI and DTI indices (FA, MD, GM, WM) was checked across the sample using VBM8 and scans with deviant values were carefully examined. Images marked as "dropout" were removed from the common database and are not included in this report, but are available upon request. Multicenter IDs were assigned by the coordinating center.

2.2.3. Preprocessing of DTI and MRI data

DTI data was preprocessed at the coordinating center using the FSL diffusion toolbox (Version 4.1, FMRIB, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl/) (Smith et al., 2004). For automatic batch processing of DTI data in FSL we used FSL-Control, an in-house software that is particularly suited for processing large multicenter datasets. The program is available upon request from the coordinating site (edsd@dzne.de). The images were corrected for eddy currents and head motion, and skull stripping was performed using the Brain Extraction Tool. Diffusion tensors were fitted to the data by means of DTIfit. Further spatial processing was performed using SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK, http://www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab (Mathworks, Natwick). All DTI maps were rigidly aligned to the corresponding T1-weighted MRI scans using the B0 image as reference and applying the transformations to the other DTI maps. Spatial normalization was performed using the normalization parameters derived from the corresponding T1-weighted MRI scan. These were estimated using a high-dimensional non-linear registration (DARTEL algorithm (Ashburner, 2007)) of segmented gray and white matter tissue maps of the T1-weighted MRI scan to a customized MNI space template by means of the VBM8 toolbox (Version 414, http://dbm.neuro.uni-jena.de/vbm8/). The customized template was created on the basis of N = 54 MRI scans, including 6 randomly selected scans (three AD patients and three HC) per center from the initial AD/HC cohort (Teipel et al., 2012). Assuming that anatomical characteristics of MCI patients lie on a continuum in between HC and AD patients, normalizing MRI scans from MCI subjects to this customized template should not be prone to registration bias. Finally, all scans were smoothed using an 8 mm full width at half maximum (FWHM) isotropic Gaussian kernel.

3. Accessing the data

The data may be used by anyone with a scientific interest in it. The demographic, clinical and neuropsychological metadata are summarized in a spreadsheet. All data are anonymized. DICOM data from 9 centers can be downloaded from the portal Neugrid N4U (https://neugrid4you.eu/), where users are required to register and sign a Data Usage Agreement. After having logged in, the data can be found at 'Science gateway/Virtual laboratory/Grid browser/data/EDSD'. Large data requests (exceeding 2 gigabytes) may be downloaded using gLITE commands in a command-line interface. Alternatively, all data including the raw data (DICOM) as well as preprocessed images (NIFTI) can be downloaded from the DZNE Rostock server. In order to gain access, users should contact the DZNE Rostock via email (edsd@dzne.de), briefly stating their objectives. They will be sent a Data Usage Agreement for signature, and the coordinating center will store their contact details in case there is a need to communicate updated information about the dataset. On the DZNE Rostock server a protocol is provided, documenting the time points when data is modified or added to. In case of an interrupted connection, a synchronization mechanism supports resuming and synchronizing downloads.

4. Conclusion and future directions

The EDSD was the first large multicenter DTI dataset publicly available. The dataset is a growing collection of DTI and MRI data of MCI and AD patients and matched healthy controls. As of March 2016, it encompasses data from 13 scanners. EDSD data has already been used in numerous studies, assessing research questions such as the multicentric variability of DTI parameters derived from heterogeneous acquisition schemes, the diagnostic and prognostic potential of specific DTI parameters, as well as the utility of post-acquisition processing approaches that may improve these parameters by reducing multicentric variability (Brueggen et al., 2015; Dyrba et al., 2015; Dyrba et al., 2014; Dyrba et al., 2012; Dyrba et al., 2013; Fischer et al., 2012; Kljajevic et al., 2014; Teipel et al., 2014a; Teipel et al., 2014b; Teipel et al., 2011; Teipel et al., 2012). In the future, the data set will be continuously expanded through ongoing support from the existing partner centers as well as the steady inclusion of new centers. More partners recently joined the EDSD group, and new members

are welcome to participate and contribute data. The data is required to include DTI and anatomical T1-weighted MRI scans, as well as clinical and neuropsychological characterization, and a matched control group of healthy individuals. Regarding MCI subjects, clinical follow-up (conversion to dementia) or cerebrospinal fluid (CSF) information is required. This is due to the high pathological heterogeneity associated with a clinical diagnosis of MCI. Optionally, FLAIR images and specific pheno- and genotypic variables may be added. To become a partner, the respective center should contact the DZNE Rostock (edsd@dzne.de). The formal process includes signing a Data Sharing Agreement, and ethical approval is to be obtained at the respective site. Data is centrally uploaded on the FTP server of the DZNE. New members will also be asked to sign a Neugrid N4U Data Sharing Agreement, and the coordinating site will manage the upload onto the platform.

In summary, the EDSD allows investigating hypotheses concerning the contribution of DTI in dementia diagnostics. Furthermore, its multicenter structure permits validating the use of DTI across different scanners and clinical settings; an important but often neglected aspect of the development of biomarkers that are to be used in a clinical context. The availability of clinical follow-up and CSF information provides the possibility to investigate the utility of DTI-based imaging markers for prediction of the underlying pathology and conversion to dementia in subjects with MCI. The constant expansion of the data set ensures its continuing significance.

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