DTI Working Group

Proposal to Harmonize DTI Measures for Genetic Analysis

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Diffusion tensor imaging (DTI) is a variant of standard brain magnetic resonance imaging (MRI) that is sensitive to fiber integrity and white matter microstructure. One of the most widely used and accepted DTI measures, fractional anisotropy (FA), evaluates the extent to which water diffusion is directionally constrained. FA, along with other DTI-based measures of fiber integrity has been consistently found to be highly heritable across several cohorts (CHIANG *et al*. 2009; JAHANSHAD *et al*. 2010a; JIN *et al*. 2011; KOCHUNOV *et al*. 2010; LEE *et al*. 2009).

DTI-based white matter abnormalities are widely reported in developmental and degenerative brain diseases (THOMASON and THOMPSON 2010) including Alzheimer's disease and mild cognitive impairment (FELLGIEBEL *et al*. 2004; NAGGARA *et al*. 2006), schizophrenia (CLARK *et al*. 2011), bipolar disorder (MAHON *et al*. 2010; SPROOTEN *et al*. 2011a), and autism (ALEXANDER *et al*. 2007; BARNEA-GORALY *et al*. 2004) to name a few.

Several specific genetic variants have also been associated with altered DTI measures throughout various parts of the white matter including *ApoE4* (BROWN *et al*. 2011; NIERENBERG *et al*. 2005; PERSSON *et al*. 2006; SMITH *et al*. 2008), *CLU* (BRASKIE *et al*. 2011), *BDNF* (CHIANG *et al*. 2011), *HFE* (JAHANSHAD et al. 2011), *ErbB4* (ZULIANI et al. 2011)*, NRG1* (SPROOTEN et al. 2009), *DISC1* (SPROOTEN et al. 2011b), among others, making DTI-measures promising endophenotypes for identifying key genetic markers associated with structural differences in white matter pathways that may play a role in development and disease.

However, diffusion tensor images are subject to several sources of noise that can corrupt or bias measures of white matter integrity obtained, lead to uncertainties in measurements (ZHU *et al*. 2009) and cause additional sources of error when combining multisite data (ZHU *et al*. 2011). These can include spatial resolution of the images (ALEXANDER *et al*. 2001; JAHANSHAD *et al*. 2010b; KIM *et al*. 2006), the angular resolution (GIANNELLI *et al*. 2010; ZHAN *et al*. 2010), the ratio of the number of non-diffusion weighted gradients to diffusion-weighted gradients (JONES *et al*. 1999), the sampling scheme (HASAN *et al*. 2001; JONES 2004), the b-value(s) (CORREIA *et al*. 2009), among other sources of variations and artifacts. These parameters have even been shown to affect the correlations with disease progression in Multiple Sclerosis (LAGANA *et al*. 2010).

Without careful planning, combining data and identifying a reliable phenotype across different sites can involve biases, protocol effects, and sources of error beyond those seen in volumetric analysis of standard MRI.

We propose a DTI-working group for *phenotype harmonization* – to determine several measures computed from DTI images to serve as a phenotype for multi-site genetic analyses

- The working group is a methods development group to identify heritable, and reproducible, measures from diffusion images, with an easy-to-follow protocol that other sites can use

In response to substantial interest from David Glahn, Ian Deary, and Andrew McIntosh to develop image analysis protocols that could be applied across many sites to pool DTI datasets for genetic analysis, a preliminary teleconference was held to discuss overall interest, possible processing methods, initial phenotypes, and quality control considerations (November 17th, 2011).
The following people were on the call for the initial teleconference:

- UCLA: Paul Thompson, Neda Jahanshad, Omid Kohannim, Derrek Hibar, Jason Stein
- Edinburgh: Andrew McIntosh, Emma Sprooten
- Yale: David Glahn
- Brisbane: Margie Wright, Sarah Medland

To summarize the conclusions of the teleconference, the following main points were discussed:

- *Initial data:*
  - Queensland Twin Registry (PIs: Wright/Thompson) - ~700 Caucasian young adult (age 20-29) twins and siblings imaged with 27 directional gradients and ~550 of those also imaged with 94 directional high angular resolution diffusion imaging (HARDI)
  - ~840-850 large extended pedigrees of Mexican-American descent (PIs: Glahn/Blangero), wide age range imaged with 55 directional DTI
  - Lothian cohort (PI: I. Deary) LBC1936: >650 people scanned with DTI at 70 years of age imaged with 64 directional gradients
  - Bipolar Study (PI: Andrew McIntosh): Family based study of ~200 people (age 16-26) at high/low risk for BP based on family history scanned with 64 directional gradients.
- *Initial phenotypes to test:* It was decided to start cross-site comparisons by testing the stability of the following phenotypes, which have shown promise in terms of their heritability, reproducibility, and ease of measurement:
  - Full brain mean-FA from skeleton derived from the Tract-Based Spatial Statistics (SMITH *et al*. 2006) analysis
    - Emma Sprooten provided a TBSS protocol for the other sites to follow, if they have not already run TBSS
  - Mean FA from ROIs defined using the Johns Hopkins University white matter atlas (MORI *et al*. 2008)
    - Genu of the corpus callosum
    - Anterior internal capsule
    - The full corpus callosum (splenium, body and genu)

    - Midsagittal corpus callosum mean FA, and mean diffusivity (MD)
- *Quality Control measures to be aware of:*
    - Intensity dropouts in images
    - Motion/ Eddy current or EPI distortions
    - Micro-strokes
    - Non-white matter regions artifactually skeletonized in TBSS

A full outline of minutes of the teleconference can be provided on request.

Parties interesting in joining the working group are welcome to contact **Neda Jahanshad** neda.jahanshad@loni.ucla.edu who will forward any related email to all group members. In addition to a significant time commitment dedicated to discovery of stable and heritable phenotypes, we ask the following of any groups interested in joining:

- Diffusion tensor imaging and GWAS in a sizeable cohort, ideally 200+ individuals
- Images taken all with the same scanner/protocol and ideally at the same site.
- Images usable for test-retest reliability measures:
    - Either having subjects scanned twice, with a short time interval
    - Or subjects scanned multiple times at different scanning parameters

Interested parties with smaller datasets, or those unable to dedicate significant amounts of time and personnel to protocol development are welcome to sign-up for regular updates from the working group, and are encouraged to test any consensus protocol for feedback on ease of phenotype extraction, and reproducibility.

All groups interested in joining a full ENIGMA-DTI GWAS-MA (scheduled to start in a few months after protocol development efforts by the working group) are asked to email Neda (neda.jahanshad@loni.ucla.edu) with projected number of DTI scans, scanning parameters, and basic subject demographics

ALEXANDER, A. L., K. M. HASAN, M. LAZAR, J. S. TSURUDA and D. L. PARKER, 2001 Analysis of partial volume effects in diffusion-tensor MRI. Magn Reson Med **45:** 770-780.

ALEXANDER, A. L., J. E. LEE, M. LAZAR, R. BOUDOS, M. B. DUBRAY *et al.*, 2007 Diffusion tensor imaging of the corpus callosum in Autism. Neuroimage **34:** 61-73.

BARNEA-GORALY, N., H. KWON, V. MENON, S. ELIEZ, L. LOTSPEICH *et al.*, 2004 White matter structure in autism: preliminary evidence from diffusion tensor imaging. Biol Psychiatry **55:** 323-326.

BRASKIE, M. N., N. JAHANSHAD, J. L. STEIN, M. BARYSHEVA, K. L. MCMAHON *et al.*, 2011 Common Alzheimer's Disease Risk Variant Within the CLU Gene Affects White Matter Microstructure in Young Adults. J Neurosci **31:** 6764-6770.

BROWN, J. A., K. H. TERASHIMA, A. C. BURGGREN, L. M. ERCOLI, K. J. MILLER *et al.*, 2011 Brain network local interconnectivity loss in aging APOE-4 allele carriers. Proc Natl Acad Sci U S A.

CHIANG, M. C., M. BARYSHEVA, D. W. SHATTUCK, A. D. LEE, S. K. MADSEN *et al.*, 2009 Genetics of brain fiber architecture and intellectual performance. J Neurosci **29:** 2212-2224.

CHIANG, M. C., M. BARYSHEVA, A. W. TOGA, S. E. MEDLAND, N. K. HANSELL *et al.*, 2011 BDNF gene effects on brain circuitry replicated in 455 twins. Neuroimage **55:** 448-454.

CLARK, K. A., K. H. NUECHTERLEIN, R. F. ASARNOW, L. S. HAMILTON, O. R. PHILLIPS *et al.*, 2011 Mean diffusivity and fractional anisotropy as indicators of disease and genetic liability to schizophrenia. J Psychiatr Res **45:** 980-988.

CORREIA, M. M., T. A. CARPENTER and G. B. WILLIAMS, 2009 Looking for the optimal DTI acquisition scheme given a maximum scan time: are more b-values a waste of time? Magn Reson Imaging **27:** 163-175.

FELLGIEBEL, A., P. WILLE, M. J. MULLER, G. WINTERER, A. SCHEURICH *et al.*, 2004 Ultrastructural hippocampal and white matter alterations in mild cognitive impairment: a diffusion tensor imaging study. Dement Geriatr Cogn Disord **18:** 101-108.

GIANNELLI, M., M. COSOTTINI, M. C. MICHELASSI, G. LAZZAROTTI, G. BELMONTE *et al.*, 2010 Dependence of brain DTI maps of fractional anisotropy and mean diffusivity on the number of diffusion weighting directions. J Appl Clin Med Phys **11:** 2927.

HASAN, K. M., D. L. PARKER and A. L. ALEXANDER, 2001 Comparison of gradient encoding schemes for diffusion-tensor MRI. J Magn Reson Imaging **13:** 769-780.

JAHANSHAD, N., O. KOHANNIM, D. P. HIBAR, J. L. STEIN, K. L. MCMAHON *et al.*, 2011 Brain structure in healthy adults is related to serum transferrin and the H63D HFE polymorphism. Proc Natl Acad Sci U S A **Accepted**.

JAHANSHAD, N., A. D. LEE, M. BARYSHEVA, K. L. MCMAHON, G. I. DE ZUBICARAY *et al.*, 2010a Genetic influences on brain asymmetry: a DTI study of 374 twins and siblings. Neuroimage **52:** 455-469.

JAHANSHAD, N., L. ZHAN, M. A. BERNSTEIN, B. J. BOROWSKI, C. R. JACK *et al.*, 2010b Diffusion tensor imaging in seven minutes: determining trade-offs between spatial and directional resolution. , pp. 1161-1164 in *ISBI*, Rotterdam, The Netherlands.

JIN, Y., Y. SHI, S. JOSHI, N. JAHANSHAD, L. ZHAN *et al.*, 2011 Heritability of White Matter Fiber Tract Shapes: A HARDI Study of 198 Twins.

JONES, D., M. HORSFIELD and A. SIMMONS, 1999 Optimal strategies for measuring diffusion in anisotropic systems by magnetic resonance imaging. Magnetic Resonance in Medicine **42:** 515-525.

JONES, D. K., 2004 The effect of gradient sampling schemes on measures derived from diffusion tensor MRI: a Monte Carlo study. Magn Reson Med **51:** 807-815.

KIM, M., I. RONEN, K. UGURBIL and D. S. KIM, 2006 Spatial resolution dependence of DTI tractography in human occipito-callosal region. NeuroImage **32:** 1243-1249.

KOCHUNOV, P., D. C. GLAHN, J. L. LANCASTER, A. M. WINKLER, S. SMITH *et al.*, 2010 Genetics of microstructure of cerebral white matter using diffusion tensor imaging. Neuroimage **53:** 1109-1116.

LAGANA, M., M. ROVARIS, A. CECCARELLI, C. VENTURELLI, S. MARINI *et al.*, 2010 DTI parameter optimisation for acquisition at 1.5T: SNR analysis and clinical application. Comput Intell Neurosci**:** 254032.

LEE, A. D., N. LEPORE, C. BRUN, Y. Y. CHOU, M. BARYSHEVA *et al.*, 2009 Tensor-based analysis of genetic influences on brain integrity using DTI in 100 twins. Med Image Comput Comput Assist Interv **12:** 967-974.

MAHON, K., K. E. BURDICK and P. R. SZESZKO, 2010 A role for white matter abnormalities in the pathophysiology of bipolar disorder. Neurosci Biobehav Rev **34:** 533-554.

MORI, S., K. OISHI, H. JIANG, L. JIANG, X. LI *et al.*, 2008 Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. Neuroimage **40:** 570-582.

NAGGARA, O., C. OPPENHEIM, D. RIEU, N. RAOUX, S. RODRIGO *et al.*, 2006 Diffusion tensor imaging in early Alzheimer's disease. Psychiatry Res **146:** 243-249.

NIERENBERG, J., N. POMARA, M. J. HOPTMAN, J. J. SIDTIS, B. A. ARDEKANI *et al.*, 2005 Abnormal white matter integrity in healthy apolipoprotein E epsilon4 carriers. Neuroreport **16:** 1369-1372.

PERSSON, J., J. LIND, A. LARSSON, M. INGVAR, M. CRUTS *et al.*, 2006 Altered brain white matter integrity in healthy carriers of the APOE epsilon4 allele: a risk for AD? Neurology **66:** 1029-1033.

SMITH, C. D., H. CHEBROLU, A. H. ANDERSEN, D. A. POWELL, M. A. LOVELL *et al.*, 2008 White matter diffusion alterations in normal women at risk of Alzheimer's disease. Neurobiol Aging **31:** 1122-1131.

SMITH, S. M., M. JENKINSON, H. JOHANSEN-BERG, D. RUECKERT, T. E. NICHOLS *et al.*, 2006 Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. Neuroimage **31:** 1487-1505.

SPROOTEN, E., G. K. LYMER, S. MUNOZ MANIEGA, J. MCKIRDY, J. D. CLAYDEN *et al.*, 2009 The relationship of anterior thalamic radiation integrity to psychosis risk associated neuregulin-1 variants. Mol Psychiatry **14:** 237-238, 233.

SPROOTEN, E., J. E. SUSSMANN, A. CLUGSTON, A. PEEL, J. MCKIRDY *et al.*, 2011a White matter integrity in individuals at high genetic risk of bipolar disorder. Biol Psychiatry **70:** 350-356.

SPROOTEN, E., J. E. SUSSMANN, T. W. MOORHEAD, H. C. WHALLEY, C. FFRENCH-CONSTANT *et al.*, 2011b Association of white matter integrity with genetic variation in an exonic DISC1 SNP. Mol Psychiatry **16:** 685, 688-689.

THOMASON, M., and P. THOMPSON, 2010 Diffusion Imaging, White Matter and Psychopathology. Annual Review of Clinical Psychology **in press, Oct. 2010**.

ZHAN, L., A. D. LEOW, N. JAHANSHAD, M. C. CHIANG, M. BARYSHEVA *et al.*, 2010 How does angular resolution affect diffusion imaging measures? NeuroImage **49:** 1357-1371.

ZHU, T., R. HU, X. QIU, M. TAYLOR, Y. TSO *et al.*, 2011 Quantification of accuracy and precision of multi-center DTI measurements: a diffusion phantom and human brain study. Neuroimage **56:** 1398-1411.

ZHU, T., X. LIU, M. D. GAUGH, P. R. CONNELLY, H. NI *et al.*, 2009 Evaluation of measurement uncertainties in human diffusion tensor imaging (DTI)-derived parameters and optimization of clinical DTI protocols with a wild bootstrap analysis. J Magn Reson Imaging **29:** 422-435.

ZULIANI, R., T. W. MOORHEAD, M. E. BASTIN, E. C. JOHNSTONE, S. M. LAWRIE *et al.*, 2011 Genetic variants in the ErbB4 gene are associated with white matter integrity. Psychiatry Res **191:** 133-137.