THE JOURNAL OF CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Prediction of Nonremission to Antidepressant Therapy Using Diffusion Tensor Imaging

Author(s): Stuart M. Grieve, MBBS, DPhil; Mayuresh S. Korgaonkar, PhD; Evian Gordon, MD, PhD; Leanne M. Williams, PhD; and A. John Rush, MD

DOI Number: 10.4088/JCP.14m09577

List of Supplementary Material for the article

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Section

Prediction of Non-Remission to Anti-Depressant Therapy Using Diffusion Tensor Imaging.

Running Title: Predicting Depression Nonremission with DTI

Stuart M. Grieve, MBBS, DPhil[*a,b,c], Mayuresh S. Korgaonkar, PhD[a,d] Evian Gordon, MD, PhD[a,f], Leanne M. Williams, PhD[a,d,e] A. John Rush, MD[g]

[a] The Brain Dynamics Centre, Sydney Medical School - Westmead and Westmead Millennium Institute, Sydney, NSW 2145, Australia.

[b] Sydney Translational Imaging Laboratory, Charles Perkins Centre & Sydney Medical School, University of Sydney, Camperdown NSW 2050, Australia.

[c] Department of Radiology, Royal Prince Alfred Hospital, Camperdown NSW 2050, Australia.

[d] Discipline of Psychiatry, University of Sydney Medical School: Western, Westmead Hospital, Sydney NSW 2145, Australia.

[e] Department of Psychiatry and Behavioral Sciences, Stanford University, 401 Quarry Road, Stanford, CA 94305.

[f] Brain Resource, Level 12, 235 Jones Street, Ultimo, Sydney, NSW 2007, Australia; and Suite 200, 1000 Sansome Street, San Francisco 94111, USA.

[g] Academic Medicine Research Institute and Office of Clinical Sciences, Duke-National University of Singapore, Singapore

Methods - MRI acquisition and analysis details

Image acquisition

MRI acquisition was performed at the Westmead Hospital, Sydney, Australia and utilized a 3.0T GE Signa HDx scanner with an 8-channel head coil (GE Healthcare, Milwaukee, Wisconsin). DTI parameters: 70 axial contiguous 2.5mm slices; 1.72mmx1.72mm resolution; 128x128 matrix; TR=17000ms; TE=95ms; Frequency direction=R/L; 42 diffusion orientations; b-value=1250.

Tract-based spatial statistical analysis of DTI data

DTI data was preprocessed and analyzed using the Oxford Centre for Functional MRI of the Brain (FMRIB) Diffusion Toolbox and Tract-Based Spatial Statistical analysis (TBSS) software tools as part of the FMRIB Software Library release 4.1.3 (http://www.fmrib.ox.ac.uk/fsl)[1-4].

The raw DTI data for each participant were first corrected for head movement and eddy current distortions. A binary brain mask was generated using the baseline non-diffusion weighted (b=0) image. Diffusion tensor models were then fitted independently for each voxel within the brain mask and images of fractional anisotropy (FA) were generated for each participant.

FA images from each participant were then aligned to the FMRIB58_FA template and transformed into Montreal Neurological Institute 152 $1mm^3$ standard space using the nonlinear registration tool FNIRT. Next, an average FA image was generated and thinned to

create a white matter skeleton representing the centers of all white matter tracts common to all participants. This FA skeleton was then thresholded to FA ≥0.2 to include the major white matter pathways but avoid peripheral tracts that are more vulnerable to interparticipant variability and/or partial volume effects with grey matter. Each participant's aligned FA image was then projected onto the mean FA skeleton by assigning each skeleton voxel by the maximum FA value found in a direction perpendicular to the tract. This accounts for any residual registration misalignments and variability in exact tract location between participants. The JHU ICBM-DTI-81 white matter labels atlas was used to identify parts of the tract skeleton corresponding to the cingulate portion of the cingulum bundle and the stria terminalis[5]. The mean FA for each tract was used for creating the biomarker.

Results - Cross validation analysis for the pooled (test and replication) MDD cohort:

One thousand random samples were run to provide a distribution and confidence interval of replication accuracy. The remission rates were lower in the replication cohort ($\chi 2$= 8.02; p=0.005): 46% (34/74) of the MDD participants from the test cohort achieved remission, while 24% (20/83) of the MDD participants from the replication cohort achieved remission. To remove any bias of this high proportion of non-remitters in the replication cohort on the predictive value accuracy in this cohort, this cross-validation procedure on MDD participants pooled across the test and replication cohorts was performed. One thousand random groups with 100 MDD participants randomly chosen from the pooled cohorts each time in each group were analyzed for predictive value using the threshold value of $R_{ST\text{-}CB}$ = 1.0. This provided a distribution and confidence interval of the replication accuracy.

The mean specificity from this analysis was 86.9 ± 7.7% (10% centile: 75.0%; 90% centile: 95.2%) and was found to match that obtained from the entire pooled cohort. The actual

accuracy in identifying non-remitters for the pooled groups was 85.7% (30/35) against an overall remission rate of 34.4% (54/157) with an overall selection of 29.1% of non-remitters and 9.3% of remitters selected using the threshold of RST-CB >1.0 ($\chi 2$= 8.07; p=0.004; odds ratio, 4.0; 95%CI, 1.5-11.1).

References:

1. Behrens TEJ, Berg HJ, Jbabdi S, Rushworth MFS, Woolrich MW. Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? *NeuroImage.* 2007;34:144-155.

2. Smith SM. Fast robust automated brain extraction. *Human brain mapping.* 2002;17:143-155.

3. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *NeuroImage.* 2006;31:1487-1505.

4. Smith SM, Jenkinson M, Woolrich MW, et al. Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage.* 2004;23 Suppl 1:S208-219.

5. Mori S, Oishi K, Jiang H, Jiang L, Li X, Akhter K. Stereotaxic White Matter Atlas Based on Diffusion Tensor Imaging in an ICBM Template. *Neuroimage.* 2008;40:570-582.