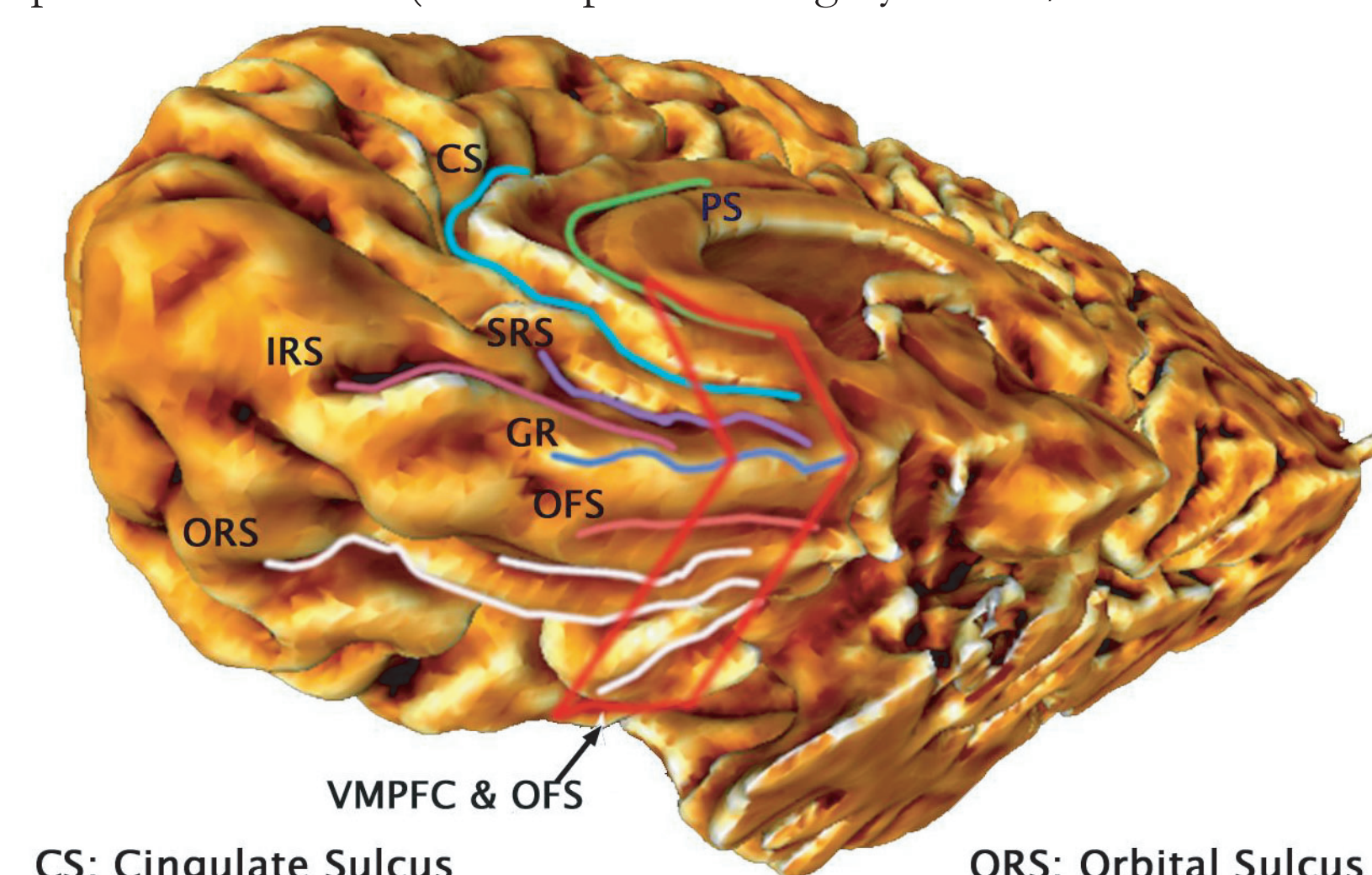


# Analysis of Ventral Medial Prefrontal Cortex Metrics for Depression in Twins

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## Introduction

Structural and functional imaging studies have shown that the medial prefrontal cortex is associated with Major Depressive Disorder (MDD) [1,2]. Automated methods of analysis presented here demonstrate the implementation of statistical tests on pooled (by group) and censored Labeled Cortical Mantle Distance Maps in the Ventral Medial Prefrontal Cortex (VMPFC) to quantify cortical changes. Pooled distances indicate the structural changes in VMPFC and censored distances suggest possible locations (with respect to the gray matter/white matter interface) of changes in VMPFC.



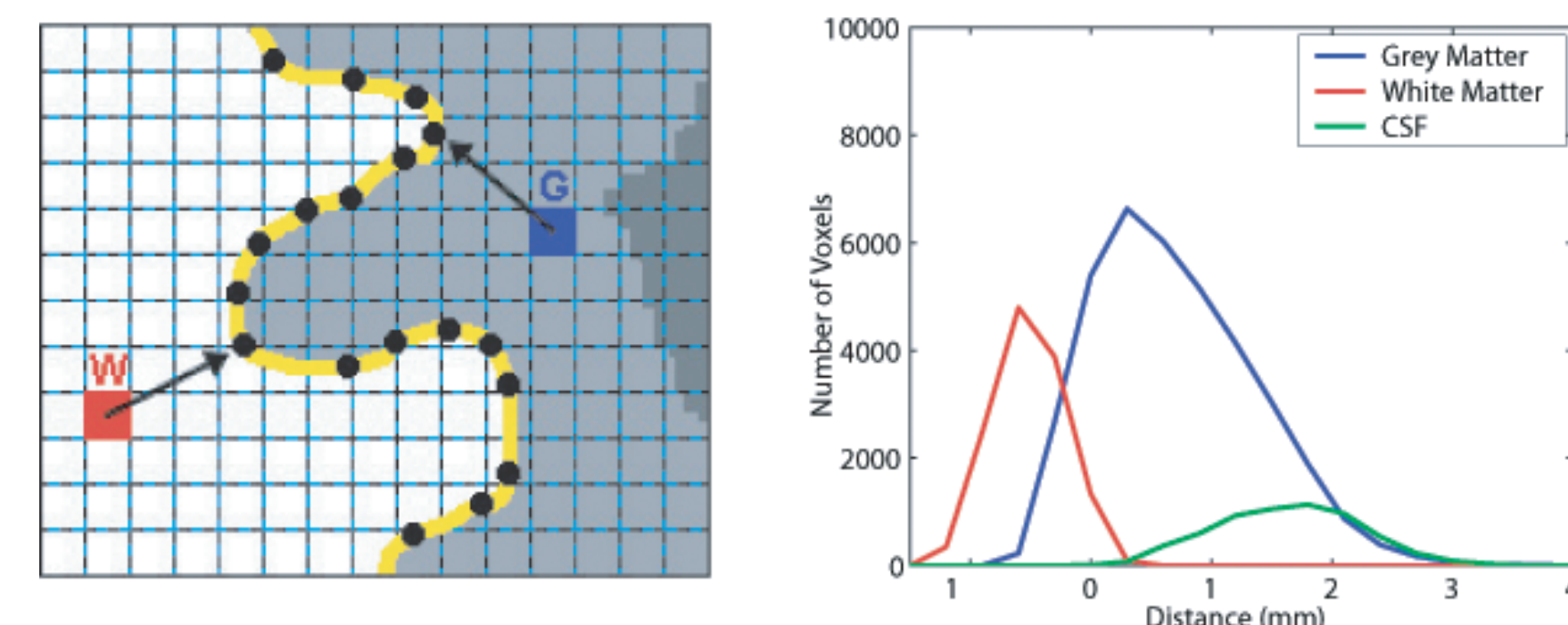
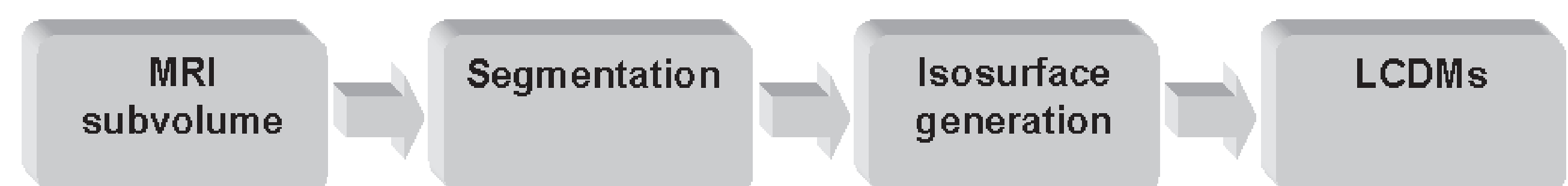
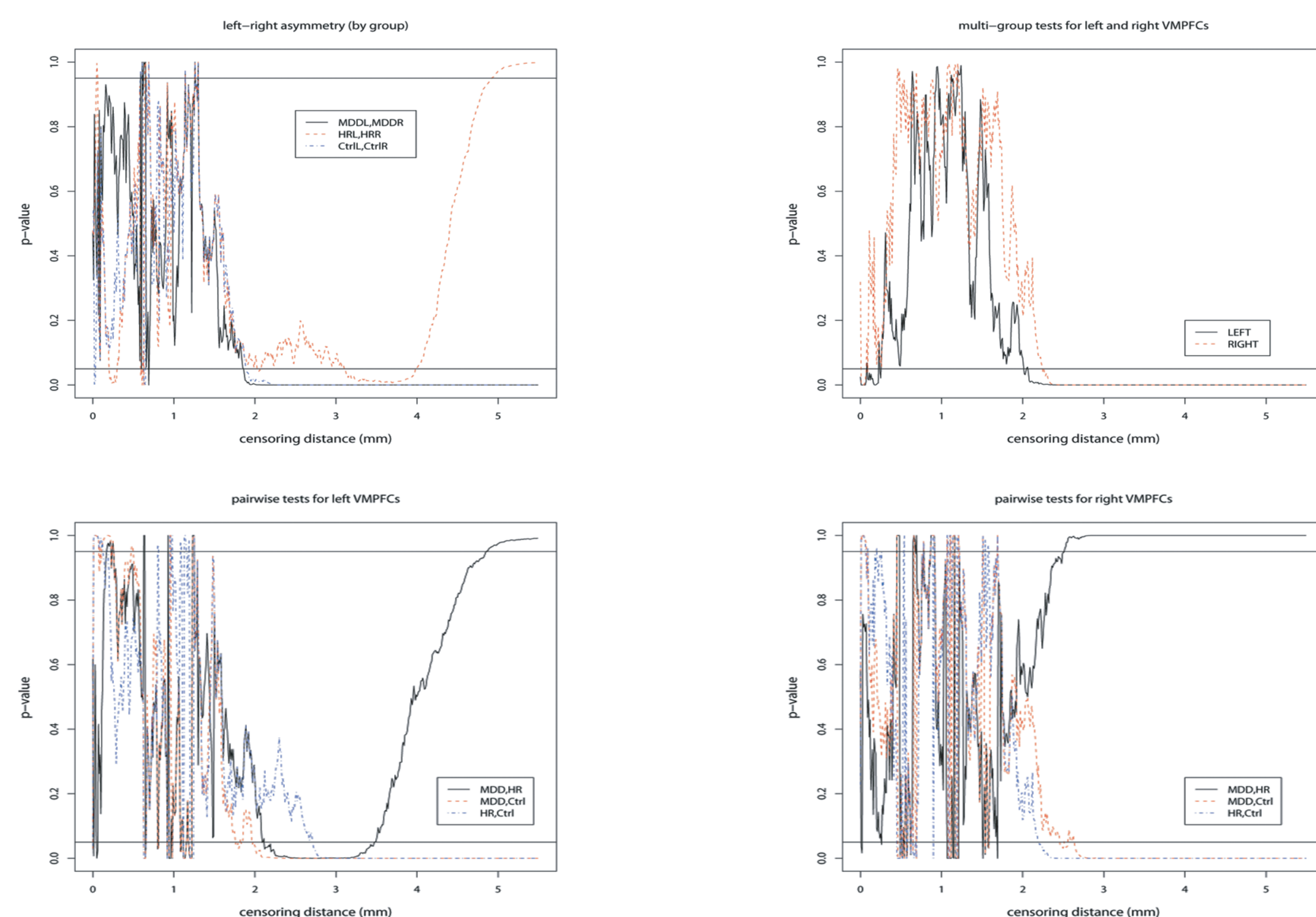
CS: Cingulate Sulcus  
GR: Gyrus Rectus  
IRS: Inferior Rostral Sulcus  
OFS: Olfactory Sulcus  
ORS: Orbital Sulcus  
PS: Pericallosal Sulcus  
SRS: Superior Rostral Sulcus  
VMPFC: Ventral Medial Prefrontal Cortex

A population of 34 right-handed female twin pairs between the age 13-23 years were included in this study, of which 14 pairs were control and 20 pairs were affected with MDD. Both monozygotic and dizygotic twins were included. The inclusion criteria for the affected twin pairs were onset prior to age 16 and the DSM IV criteria for Major Depression being greater than a duration of 4 weeks.

Control twin pairs had no personal or first degree family history of MDD.

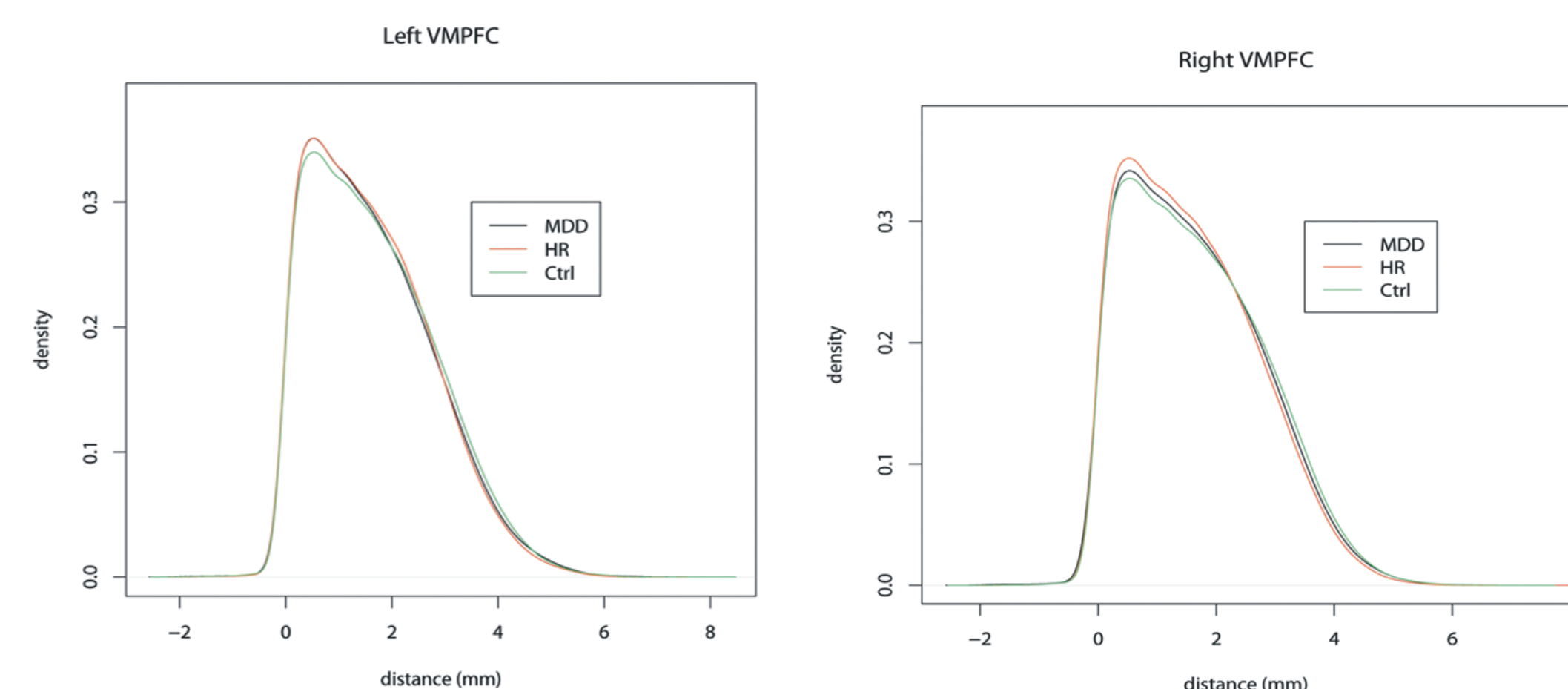
## Results and Discussion

- Analysis of gray matter volumes demonstrate that left Ventral Medial Prefrontal Cortex of MDD subjects is larger than right ( $p=.0360$ ). There is no significant volumetric lateralization difference in High Risk (HR) and Control subjects.
- However when examining pooled LCDM distances (after outliers are removed), left VMPFC of both MDD and Control subjects tend to be significantly thinner than right VMPFC, and in the HR group, left VMPFC tends to be thicker than right VMPFC. See Table 2 in the right panel.
- In left VMPFC, LCDM distances of Control subjects have larger variance than those of MDD subjects which have larger variance than those of HR subjects (larger variance implies more shape variation). Likewise in right VMPFC. See Tables 1 and 3 in the right panel.
- In left VMPFC, (pooled) LCDM distances of Control subjects tend to be larger than those of MDD subjects whose LCDM distances tend to be larger than those of HR subjects (larger distances imply more thickness in mantle and/or variation in shape). Likewise in right VMPFC. See Tables 1 and 3 in the panel right.
- To find the LCDM distance values (with respect to the GM/WM interface) at which the significant differences occur, we censor the distances at increments of .01 mm. Censoring distance analysis for left-right asymmetry by group is presented in the (second figure in the panel below, for multi-group comparisons is presented in the second figure, pairwise comparisons for left VMPFC is presented in the third figure, and pairwise comparisons for right VMPFC is presented in the fourth figure. In two-group comparisons, p-values less than .05 are significant for  $1^{st} < 2^{nd}$ , while greater than .95 are significant for  $1^{st} > 2^{nd}$  alternatives.



## Labeled Cortical Distance Maps (LCDMs)

The flow chart above describes the sequence of methods to quantify the thickness of cortices with LCDM. Following Ratnanather et al. [3], a Bayesian segmentation performed on the magnetic resonance images (MRI) classifies each image voxel as Gray Matter (GM), White Matter (WM), and cerebrospinal fluid (CSF). Isosurfaces representing the 2-D cortical sub-manifold are generated at the GM/WM interface. LCDMs form a histogram consisting of labeled tissue compartments of GM, WM, and CSF computed as a function of distance from the GM/WM interface as illustrated in panels 1 and 2 above. The kernel density estimates (normalized histograms) of LCDMs by subject is investigated for left and right VMPFC to determine the outliers (subjects with extremely different VMPFC) in each group. After outliers are removed, the LCDMs are pooled by each group for both left and right VMPFCs. The kernel density estimates of the pooled distances are plotted below.



	Descriptive Statistics of LCDM distances (in mm)					
	Left			Right		
Group	Mean	Median	Std dev	Mean	Median	Std dev
MDD	1.621	1.459	1.129	1.628	1.493	1.101
HR	1.606	1.461	1.107	1.586	1.455	1.075
Ctrl	1.658	1.503	1.140	1.662	1.529	1.116

Table 1

p-values for left-right distance asymmetry by group		
MDD (left < right)	HR (left > right)	Ctrl (left < right)
<.0001	.0015	<.0001

Table 2

	p-values for pairwise comparisons ( $1^{st} < 2^{nd}$ ) of			
	Pooled LCDM distances		Variances of pooled LCDM distances	
Pair	Left	Right	Left	Right
HR vs MDD	.0084	<.0001	<.0001	<.0001
MDD vs Ctrl	<.0001	<.0001	<.0001	<.0001
HR vs Ctrl	<.0001	<.0001	<.0001	<.0001

Table 3

### References:

- [1] Miller, M. I. et al. 2003 *Proc. Nat'l Acad. Sci* **100**: 15172-15177.
- [2] Botteron, K. L., et al. 2002 *Biological Psychiatry* **51**: 342-344.
- [3] Ratnanather, J. T. et al. (2001) *NeuroImage* **14**: 1058-1069.

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