Supplementary Online Content

Miller L, Bansal R, Wickramaratne P, et al. Neuroanatomical correlates of religiosity and spirituality: a study in adults at high and low familial risk for depression [published online December 11, 2012]. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2013.3067.

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Analyzing Magnetic Resonance Imaging Data

Image Processing

Morphometric analyses were conducted on Sun Ultra 10 workstations using ANALYZE 8.0 (Rochester, MN). The nonuniformities in image intensity caused by inhomogeneities in RF pulse were corrected using an algorithm developed at the Montreal Neurological Institute.[1] Extracerebral tissues were removed using an isointensity contour function that thresholds cortical gray matter from overlying cerebrospinal fluid. Connecting dura and fat were removed manually on each slice in sagittal, coronal, and axial views. The brainstem was transected at the pontomedullary junction. The brains were positioned into a standard orientation by first rotating them to provide true midline sagittal images and then rotating the brains to provide axial slices that were parallel to the AC-PC line. Rotation of the brains into standard orientation permit reliable parcellation of the cerebrum, cortex, and ventricles (below) using stereotactic coordinates. The brain tissue was then segmented as white matter and gray matter using semi-automated procedures.[2] The hippocampus and the amygdala were manually delineated using detailed protocols that have been previously published.[3] The interrater reliabilities, computed using intraclass correlation coefficients,[4] were 0.89 and 0.88 for the right and left amygdala and 0.91 and 0.92 for the right and left hippocampus, respectively.

Selection of the Template Brain

We selected the template brain as the brain of a single healthy individual by a two-step procedure: First, we selected as a template a participant who demographically as representative as possible of the participants being studied. The brains for all remaining healthy participants were coregistered and nonlinearly warped to this preliminary template. The point correspondences on the surfaces of their cortex were determined, and we computed distances between the corresponding points. Second, the brain that was closest, in terms of least squares, to the average of the computed distances was selected as the final template brain. Relative to this final template, we repeated the registration process, the determination of point correspondences, and the calculation of distances across surfaces were then repeated for all participants in our cohort.

Mapping Cortical Thickness Measures

The cortical thickness for each participant were mapped onto the surface of a template brain using techniques of surface analysis.[5] The participant brains were first coregistered to the template brain using a similarity transformation (3 translations, 3 rotations, and global scaling) such that the mutual information[6] was maximized across the brains. The global scaling of the cerebrum scaled the thickness of the cortical mantle and therefore accounted for the scaling differences across participants. We applied a 3D morphological operator to compute cortical thickness measure at each point on the surface of the brains. The coregistered brains were warped to the template brain using high-dimensional, nonlinear warping algorithms[7] to establish point-by-point correspondence across the surface of the template and each subject brains, thereby mapping the measures of cortical thickness for each participant onto the template surface.

eResults

Stable-high and unstable adults had thicker cortical mantle across the same regions of the brain (see main **Figure 2**), and therefore, we combined the participants in these two groups to form a group of adults who reported high importance at either one or both time points. The larger number of adults in the combined group increased the statistical power to detect correlations between importance and brain measures. Our results showed that the adults with high importance at any one or both time points had thicker cortex in the left and the right occipital cortex and the superior parietal lobes, the precuneus and the mesial frontal lobe in the right hemisphere, and the inferior left parietal lobe (see **eFigure 3**). In addition, in our cohort of 68 adults with either high or low stable importance for religion, the cortical thickness was not significantly associated with the frequency of church attendance (see **eFigure 4**) even though the frequency of attendance was correlated ($r=0.58$, P-value<0.0001) with the personal importance. Therefore, the associations between cortical thickness and personal importance (see main **Figure 1**) were not driven by the frequency of church attendance. Furthermore, their correlations with z-scores of anxiety and/or depression measures differed between the HR and LR groups (see **eFigure 5**). In the HR group, more severe symptoms were associated with thinner cortex in the occipital, parietal, temporal, and cingulate cortices bilaterally (see **eFigure 5**), whereas correlations were less prominent in the LR group across the same brain regions (see **eFigure 5**). The maps of average differences and variance in the difference in the cortical thickness between participants with high, compared to those with low, importance for religion (see **eFigure 6**) demonstrates that the significant differences (see main **Figure 1**) in the cortical thickness are driven by differences rather than variances in the thickness measures.

eReferences

1. Sled GJ, Zijdenbos AP, Evans AC. A nonparametric method for automatic correction of intensity nonuniformity in MRI Data. *IEEE Trans. of Medical Imaging.* Feb 1998;17(1):87-97.
2. Peterson BS, Warner V, Bansal R, et al. Cortical thinning in persons at increased familial risk for major depression. *Proc Natl Acad Sci USA.* 2009;106:6273-6278.
3. Kates WR, Abrams MT, Kaufman WE, Breiter SN, Reiss AL. Reliability and validity of MRI measurement of the amygdala and hippocampus in children with fragile X syndrome. *Psychiatry Res: Neuroimaging.* 1997;75:31-48.
4. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull.* 1979;86:420-428.
5. Bansal R, Staib LH, Wang Y, Peterson BS. ROC-based assessments of 3D cortical surface-matching algorithms. *Neuroimage.* 2005;24:150-162.
6. Wells WM, Viola P, Kikinis R. Multi-modal volume registration by maximization of mutual information. *2nd Ann. Int. Symp Med. Robot and Comput. Assisted Surg.* 1995.
7. Christensen GE, Joshi SC, Miller MI. Volumetric transformation of brain anatomy. *IEEE Transactions on Medical Imaging.* 1997;16(6):1369-1383.

eTable 1. Demographic, Clinical, and Religious Characteristics of the High and Low Risk Groups at T20

	High Risk (n = 67)		**Low Risk (n = 36)**		Test
	%	n	%	n	
Demographics					
Age, *M* (SD)	34.2 (9.4)	64	31.7 (10.1)	34	$F(1,96) = 1.5, p = .22$
Female	62.7	42/67	58.3	21/36	$\chi^2(1) = 0.2, p = .67$
Education					$\chi^2(1) = 0.4, p = .52$
=< H.S. diploma	40.4	23/57	33.3	10/30	
> H.S. diploma	59.7	34/57	66.7	20/30	
Annual Income ($)					$\chi^2(2) = 0.5, p = .76$
<20,000 (low)	26.0	13/50	20.0	5/25	
20,000–39,999 (medium)	36.0	18/50	44.0	11/25	
=>40,000 (high)	38.0	19/50	36.0	9/25	
Marital Status					$\chi^2(2) = 1.4, p = .51$
Single	31.0	18/58	43.3	13/30	
Married/cohabiting	55.2	32/58	46.7	14/30	
Separated/divorced	13.8	8/58	10.0	3/30	
Clinical Characteristics					
MDD in lifetime (assessed at T20)	62.5	40/64	32.4	11/34	$\chi^2(1) = 8.1, p = .005$
Religiosity					
High personal importance	24.1	14/58	26.7	8/30	$\chi^2(1) = 0.1, p = .80$
Frequent attendance at services	41.4	24/58	48.3	14/29	$\chi^2(1) = 0.4, p = .54$
Denomination					Fisher's exact test: p = .32
Catholic	51.9	28/54	69.0	20/29	
Protestant	9.3	5/54	6.9	2/29	
Jewish	5.6	3/54	10.3	3/29	
Personal spirituality	11.1	6/54	6.9	2/29	
Agnostic/atheist/other	22.2	12/54	6.9	2/29	

eTable 2. Rates of High Personal Importance of Religion or Spirituality and of Frequent Attendance at Religious Services (at T20 and T25) and Mean HAM-D Scores (at T25), by Risk Group (High or Low Risk for Depression)

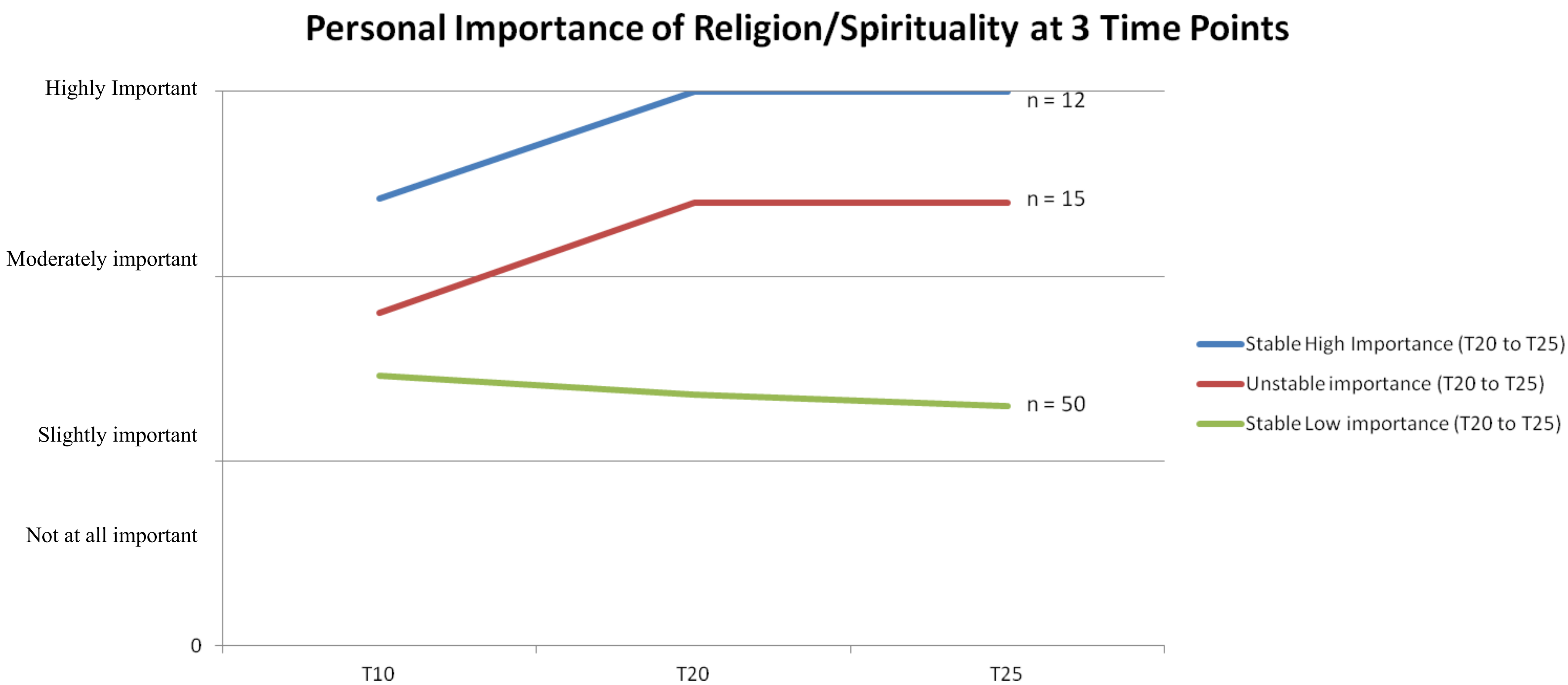
	T20				T25						
	High Importance		Frequent Attendance		High Importance		Frequent Attendance		HAM-D Score		
Group	%	n	%	n	%	n	%	n	M	SD	n
High Risk	24.1	14/58	41.4	24/55	19.4	13/67	22.7	15/66	6.1	7.3	63
Low Risk	26.7	8/30	48.3	14/29	33.3	12/36	47.2	17/36	4.5	5.9	34
Statistic	$\chi^2(1) = 0.1$		$\chi^2(1) = 0.4$		$\chi^2(1) = 2.5$		$\chi^2(1) = 6.5$		$t(1) = 1.1$		
P	.80		.54		.12		.01		.30		

eTable 3. Demographic, Clinical, Religious, and Brain Characteristics at T20 Among 3 Groups Defined by Stability (Between T20 and T25) of Personal Importance of Religion or Spirituality

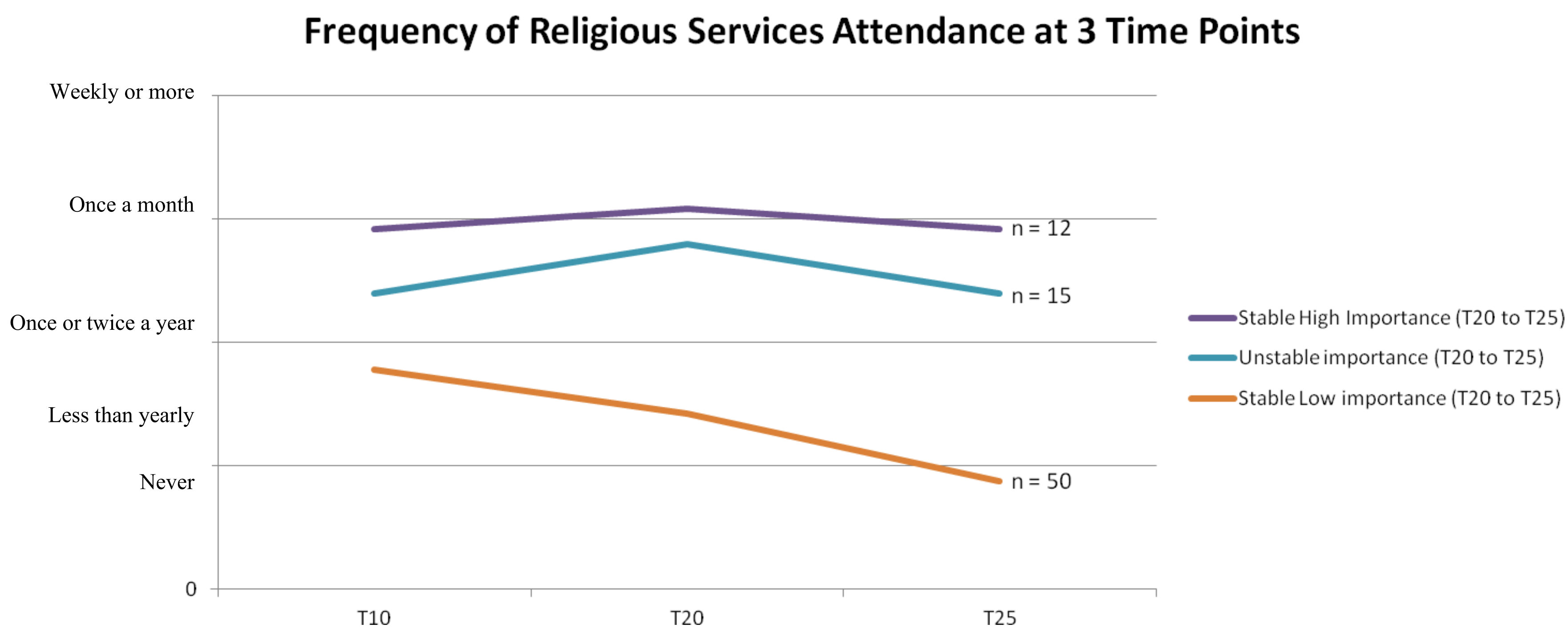
	Stability of Personal Importance of Religion or Spirituality						
	High Stable (n = 12)		**Low Stable (n = 56)**		**Unstable (n = 20)**		
	%	n	%	n	%	n	Test
Demographics							
Age, *M* (SD)	38.5 (4.7)	12	35.4 (8.1)	56	33.7 (8.7)	20	F(2,85) = 1.4, p = .25
Female	66.7	8/12	58.9	33/56	75.0	15/20	$\chi^2(2) = 1.7$, p = .43
Education							
=< H.S. diploma	33.3	4/12	34.6	19/55	50.0	10/20	$\chi^2(2) = 1.6$, p = .45
> H.S. diploma	66.7	8/12	65.5	36/55	50.0	10/20	
Annual Income ($)							
<20,000 (low)	18.2	2/11	22.9	11/48	31.3	5/16	Fisher's exact test: p = .39
20,000–39,999 (medium)	18.2	2/11	43.8	21/48	37.5	6/16	
=>40,000 (high)	63.6	7/11	33.3	16/48	31.3	5/16	
Marital Status							
Single	0.0	0/12	39.3	22/56	45.0	9/20	Fisher's exact test: p = .02
Married/cohabiting	91.7	11/12	48.2	27/56	40.0	8/20	
Separated/divorced	8.3	1/12	12.5	7/56	15.0	3/20	
Clinical Characteristics							
Family risk (high)	58.3	7/12	69.6	39/56	60.0	12/20	$\chi^2(2) = 1.0$, p = .62
Major depressive disorder (lifetime)	75.0	9/12	50.0	28/56	45.0	9/20	$\chi^2(2) = 3.0$, p = .22
Religiosity							
Frequent attendance at services	83.3	10/12	28.6	16/56	63.2	12/19	$\chi^2(2) = 15.8$, p = .0004
Denomination							
Catholic	66.7	8/12	48.1	25/52	79.0	15/19	Fisher's exact test: p = .10
Protestant	8.3	1/12	11.5	6/52	0.0	0/19	
Jewish	0.0	0/12	9.6	5/52	5.3	1/19	
Personal spirituality	0.0	0/12	9.6	5/52	15.8	3/19	
Agnostic/atheist/other	25.0	3/12	21.2	11/52	0.0	0/19	
Brain							
Whole brain volume, *M* (mm^3), SD	1282574	141575.0	1313535	153638.6	1250618	156293.4	P = .52*

*After controlling for age and sex, whole brain volume (WBV) did not differ across stability groups.

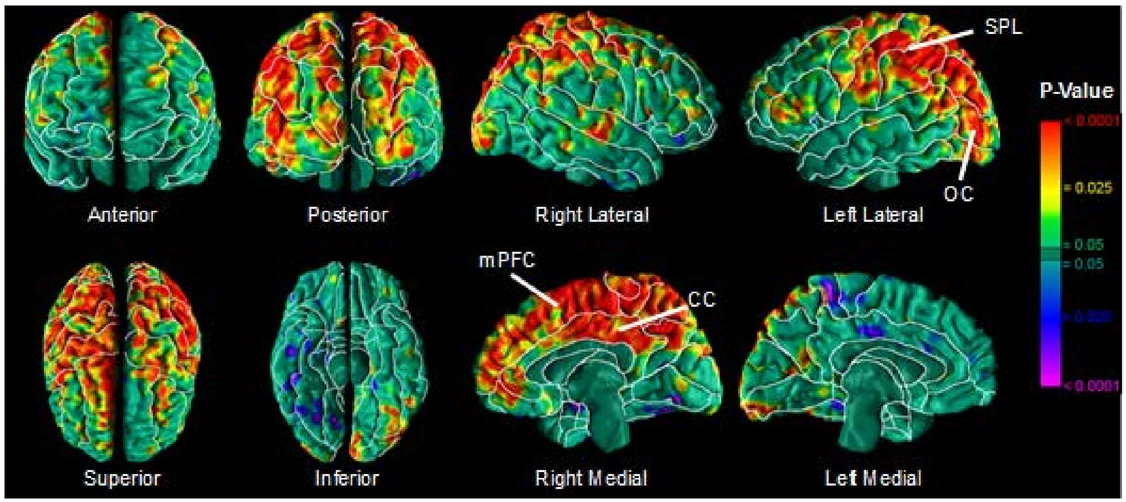
eFigure 1


Personal Importance of Religion/Spirituality at 3 Time Points
Highly Important
Moderately important
Slightly important
Not at all important
0
n = 12
n = 15
n = 50
T10
T20
T25
Stable High Importance (T20 to T25)
Unstable importance (T20 to T25)
Stable Low importance (T20 to T25)

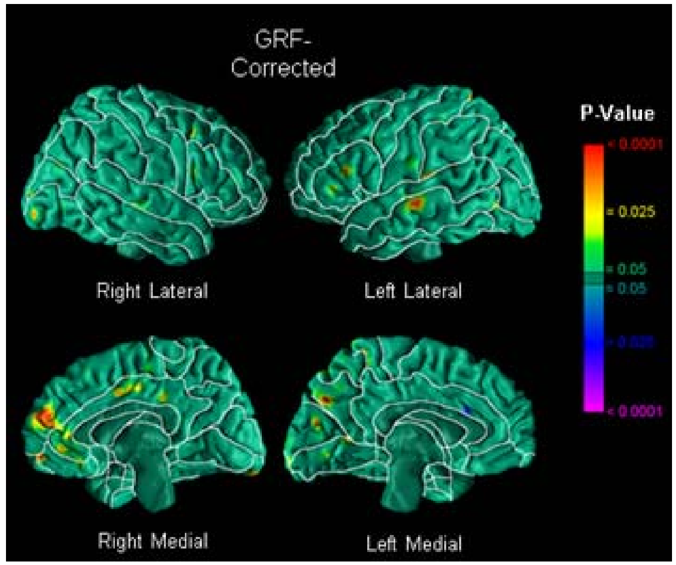
eFigure 2


Frequency of Religious Services Attendance at 3 Time Points
Weekly or more
Once a month
Once or twice a year
Less than yearly
Never
0
T10
T20
T25
n = 12
n = 15
n = 50
Stable High Importance (T20 to T25)
Unstable importance (T20 to T25)
Stable Low importance (T20 to T25)

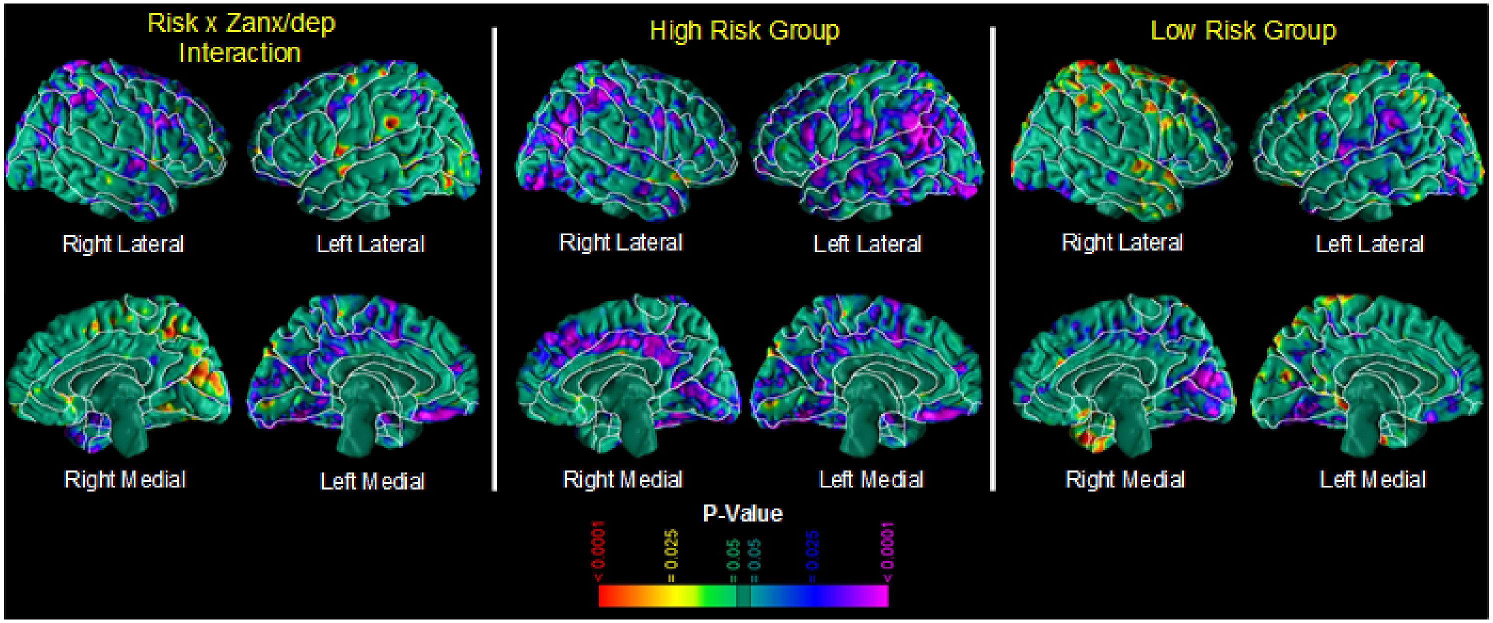
eFigure 3


SPL
P-Value
< 0.0001
= 0.025
= 0.05
= 0.05
< 0.0001
OC
Anterior
Posterior
Right Lateral
Left Lateral
mPFC
CC
Superior
Inferior
Right Medial
Left Medial

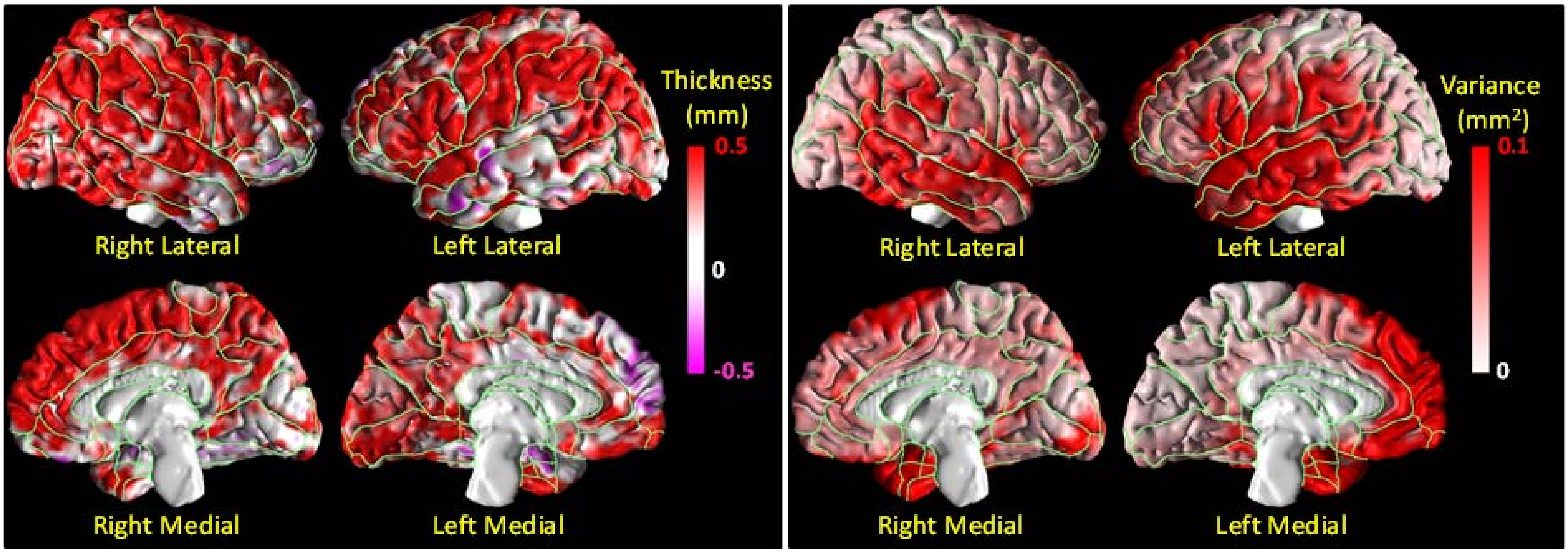
eFigure 4


GRF-
Corrected
P-Value
< 0.0001
= 0.025
= 0.05
= 0.05
< 0.0001
Right Lateral
Left Lateral
Right Medial
Left Medial

eFigure 5


Risk x Zanx/dep
Interaction
Right Lateral
Left Lateral
Right Medial
Left Medial
High Risk Group
Right Lateral
Left Lateral
Right Medial
Left Medial
Low Risk Group
Right Lateral
Left Lateral
Right Medial
Left Medial
P-Value
< 0.0001
= 0.025
= 0.05
= 0.05
= 0.025
< 0.0001

eFigure 6



Right Lateral
Left Lateral
Thickness (mm)
0.5
0
-0.5
Right Medial
Left Medial
Right Lateral
Left Lateral
Variance (mm^2)
0.1
0
Right Medial
Left Medial