# Archival Report

# Stability of Cortical Thinning in Persons at Increased Familial Risk for Major Depressive Disorder Across 8 Years

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## ABSTRACT

**BACKGROUND:** A biological marker of vulnerability should precede onset of illness and be independent of disease course. We previously reported that cortical thinning may serve as a potential biomarker for risk for familial depression. We now test stability of cortical thinning across 8 years, and whether thinning mediates associations between familial risk and depressive traits.

**METHODS:** Participants were from a three-generation family study of depression, where second- and third-generation offspring were characterized as being at high or low risk for depression based on the presence/absence of major depressive disorder in the first generation. The analysis includes 82 offspring with anatomical magnetic resonance imaging scans across two assessment waves conducted 7.8 years apart (SD = 1.3 years; range, 5.2–10.9 years).

**RESULTS:** High-risk offspring had thinner bilateral superior and middle frontal gyri and left inferior parietal lobule at both time points. High intrasubject correlation ($.60 < r < .91$) and intraclass correlation (0.72–0.78) of thickness measures across time points was detected within the above regions; rank order by effect size and region was also preserved across time. The thinning was stable despite changes in scanning platform (Siemens Sonata vs. GE Signa), field strength (1.5T vs. 3T), and participant age and clinical course. Thinning at the first time point predicted anger and hostility at the second time point and mediated the relationship between familial risk and these traits.

**CONCLUSIONS:** The study provides evidence for cortical thinning as a stable biomarker for familial vulnerability for depressive illness, which supports the ability to detect persistent and clinically relevant anatomical findings regardless of magnetic resonance imaging platform.

*Keywords:* Biomarker, Depression, FreeSurfer, High-risk, MRI, Stability

http://dx.doi.org/10.1016/j.bpsc.2017.04.009

A central goal in psychiatric neuroscience is to identify abnormalities in brain structure and function that predispose to mental illnesses. To represent true markers of risk, such anomalies [also referred to as "endophenotypes" (1,2)] should precede onset of the disorder itself, be distinct from changes in the brain that occur as a result of the illness, and be stable over time. This last criterion is cumbersome to demonstrate, as it requires that individuals be scanned at more than one time point while keeping methodological variation to a minimum. Most longitudinal studies have focused on tracking changes in the brain as a function of illness; few have explicitly tested the stability of brain phenotypes.

We previously reported on a potential biomarker for depression vulnerability in a three-generation family study of major depressive disorder (MDD) (3). We found that second- and third-generation offspring at high compared to low familial risk for depression (where we defined familial risk based on the presence or absence of MDD in the first-generation probands)

had thinner cortices, particularly in the lateral surface of the right hemisphere. The thinning was present even in offspring who were at risk but who had never had an episode of MDD, suggesting that it was unlikely to be a consequence of the illness. We hypothesized that cortical thinning may represent an endophenotype for the familial form of MDD.

What we could not test in our previous report was whether the thinning represented a stable trait, as participants had only been imaged at one time point. We have since rescanned the population, on average 7.8 (range, 5.2–10.9) years later, which allowed us to examine the extent to which differences in cortical morphology between the high- and low-risk groups were conserved over time. In testing this, we addressed three goals. First, we tested if cortical thinning was still present 8 years later. If so, this stability would increase confidence that cortical thinning reflects a stable biomarker rather than a transient phenotype or a clinical state. Second, we tested whether the cortical thinning was robust to methodological

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ISSN: 2451-9022    Biological Psychiatry: Cognitive Neuroscience and Neuroimaging October 2017; 2:619–625   www.sobp.org/BPCNNI

variation, such as the magnetic resonance imaging (MRI) scanning site, platform, and magnetic field strength. For the development of biomarkers, it is critical to test potential effects of methodological advances and to disentangle heterogeneity attributable to biologically relevant processes from that caused by methodological sources. Third, our original findings were reported using proprietary anatomical MRI methods that are not widely available. To foster greater reproducibility, we now use FreeSurfer (4,5), a freely available, open-source software that is among the most frequently used techniques for examining cortical morphology. FreeSurfer is also optimized for longitudinal analyses because its algorithms allow for greater control over segmentation differences across scans than do other software packages (6).

The primary goal of this study was to test whether differences in cortical thickness related to familial risk for depression are stable over an 8-year period, where stability was defined by test–retest consistency of anatomy (i.e., Do brain regions showing significant differences in cortical thickness at the first time point also do so at the second?) and rank order (i.e., Do participants with the greatest degree of thinning at the first time point continue to do so at the second?). Finally, to better understand the clinical implications of cortical thinning, we explored whether cortical thinning identified at the first scan predicted clinical phenotypes relevant to depression approximately 8 years later.

## METHODS AND MATERIALS

### Participants

The sample has been detailed in several publications (2,7–9). Briefly, the study began in 1982 with the simultaneous recruitment of two groups of probands (generation 1 [G1]). Depressed probands were selected from outpatient psychiatric clinics for the treatment of mood disorders in the New Haven, Connecticut, area and were required to have moderate to severe MDD. Nondepressed probands were selected concurrently from the same community and were required to have no lifetime history of psychiatric illness, based on several interviews. All probands were of European ancestry. Their biological children (G2) and subsequently grandchildren (G3) were followed prospectively over time. The offspring of the depressed probands formed the "high-risk" group, and those of the nondepressed probands formed the "low-risk" group (8,9).

### Assessments

Diagnostic interviews were conducted using the adult (10) or child (6–17 years) (11) version of the semistructured Schedule for Affective Disorders and Schizophrenia–Lifetime interview by doctoral and masters level mental health professionals [reliability was high, as documented elsewhere (8,9)]. The first interview assessed the lifespan to that point; follow-up interviews assessed catch-up periods; diagnoses are therefore cumulative until the latest interview. Each family member was interviewed independently and blinded to the clinical status of other family members. Final diagnoses were made by one or more experienced clinicians, using the best-estimate procedure (12). Current depressive symptoms at the time of each

scan were measured using the Hamilton Depression Rating Scale (13) or Children's Depression Rating Scale, Revised (14) (for adults and children, respectively); anxiety symptoms were measured with the Hamilton Anxiety Rating Scale (15) and revised Children's Manifest Anxiety Scale (16), respectively. Child and adult scores were first each converted to z scores, which were then combined to create a single measure. In addition to state measures, we also collected trait measures of impulsivity [Barratt Impulsiveness Scale version 11 (17)], and anger and hostility [Buss–Perry Aggression Questionnaire (18,19)]. These measures were assessed because our primary hypothesis suggests that cortical thinning represents a stable biomarker of risk for depression, and thus its clinical correlates should likewise be stable, trait markers of depression risk.

### Analytic Sample

We obtained MRI scans from 158 G2 and G3 offspring between 7 and 55 years of age at wave 5 (W5) and from 114 offspring between 11 and 68 years of age at wave 6 (W6). MRI scans from 8 individuals at W5 and 1 individual at W6 were excluded because of severe head motion. Of 150 usable W5 scans and 113 usable W6 scans, there were 82 common individuals (43 from high-risk families and 39 from low-risk families). The interval between W5 and W6 scans for the same individual varied from 5.2 to 10.9 years, with a mean of 7.8 and SD of 1.3 years. Interscan intervals were similar for G2 (7.6 ± 1.4 years) and G3 (8.1 ± 1.2 years) individuals.

Analyses on clinical correlates of cortical thinning were based on the 110 (of 150) individuals with a usable MRI scan at W5 who also had clinical measures at W6. These 110 participants did not differ on measures of age, sex, or risk status from the primary sample of $n = 82$ with usable brain scans at both waves (not shown).

### MRI Scanning

W5 MRI scans were obtained using a Siemens Sonata 1.5T scanner (Siemens AG, Munich, Germany) using a three-dimensional magnetization prepared rapid acquisition gradient-echo sequence (repetition time = 24 ms, echo time = 2.96 ms, 45° flip angle, field of view = 30 × 30 cm, phase field of view = 100%, 2 excitations, 1.2-mm slice thickness, 256 × 192 matrix size, 128 slices, 1.17 × 1.17 × 1.2 mm voxel resolution). W6 MRI scans were obtained using a GE Signa 3T whole-body scanner (GE Medical Systems, Milwaukee, WI) equipped with an 8-channel, phased array head coil using three-dimensional fast spoiled gradient recall sequence (repetition time = 4.7 ms, echo time = 1.3 ms, 110° flip angle, bandwidth = 41.67 MHz, field of view = 25 × 25 cm, array spatial sensitivity encoding technique factor = 2, 1-mm slice thickness, 256 × 256 matrix size, 128 slices, 0.98 × 0.98 × 1.0 mm voxel resolution, 1 NEX images × 2).

### Processing Pipeline

Methods for estimating cortical thickness can be broadly categorized as surface- or voxel-based. We used FreeSurfer (4,5), a surface-based approach to estimate cortical thickness at each point on the pial surface. The use of explicit surface models enables subvoxel accuracy, high sensitivity, and