Int. J. Devl Neuroscience 46 (2015) 125–131

Contents lists available at ScienceDirect

International Journal of Developmental Neuroscience

journal homepage: www.elsevier.com/locate/ijdevneu

# Cortical thickness predicts the first onset of major depression in adolescence

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ARTICLE INFO

*Article history:*
Received 26 May 2015
Received in revised form 18 July 2015
Accepted 20 July 2015
Available online 24 August 2015

*Keywords:*
Depression
Cortical thickness
Emotion regulation
Machine learning

ABSTRACT

Given the increasing prevalence of Major Depressive Disorder and recent advances in preventative treatments for this disorder, an important challenge in pediatric neuroimaging is the early identification of individuals at risk for depression. We examined whether machine learning can be used to predict the onset of depression at the individual level. Thirty-three never-disordered adolescents (10–15 years old) underwent structural MRI. Participants were followed for 5 years to monitor the emergence of clinically significant depressive symptoms. We used support vector machines (SVMs) to test whether baseline cortical thickness could reliably distinguish adolescents who develop depression from adolescents who remained free of any Axis I disorder. Accuracies from subsampled cross-validated classification were used to assess classifier performance. Baseline cortical thickness correctly predicted the future onset of depression with an overall accuracy of 70% (69% sensitivity, 70% specificity; $p = 0.021$). Examination of SVM feature weights indicated that the right medial orbitofrontal, right precentral, left anterior cingulate, and bilateral insular cortex contributed most strongly to this classification. These findings indicate that cortical gray matter structure can predict the subsequent onset of depression. An important direction for future research is to elucidate mechanisms by which these anomalies in gray matter structure increase risk for developing this disorder.



## 1. Introduction

Major Depressive Disorder (MDD) is the most common psychiatric illness in the United States (Kessler et al., 2003) and accounts for almost half of all disability-adjusted life years worldwide (Whiteford et al., 2013). Although the onset of major depression can occur at any age, most adults living with the disorder experienced their first episode during their teenage years (Lewinsohn et al., 1998). Late adolescence is a period of considerable vulnerability for depression: one-quarter of all youth will experience an episode of MDD by the end of their teenage years, a figure that is increasing over time (Kessler et al., 2001). Despite over two decades of research examining the neural and molecular bases of depression, fewer than one-quarter of depressed adolescents respond to an initial course of antidepressant medication. Half of those who do respond to treatment continue to have disturbances in sleep and mood, fatigue, and concentration difficulties (Tao et al., 2010).

Given the enormous personal and societal costs and the high prevalence of MDD, and the difficulty in treating depression once it has developed, early detection and prevention is crucial. Prevention programs that are implemented before the first onset of disorder should significantly reduce the societal burden of adolescent and adult depression. Such programs, however, require that we accurately identify children at greater risk for the disorder (Gladstone et al., 2011), a goal that continues to be elusive as the etiology of major depression is poorly understood. Therefore, an important challenge in pediatric neuroimaging is to identify brain measures that are useful for predicting the onset of MDD. In this study, we used machine learning methods to test the hypothesis that structural patterns in cortical gray matter can distinguish adolescents who go on to develop clinically significant depression within five years of their initial assessment from adolescents who remain free of any Axis I disorder. As in previous studies (Grotegerd et al., 2013;

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http://dx.doi.org/10.1016/j.ijdevneu.2015.07.007
0736-5748/

**Table 1**
Demographic variables.

| Demographic variable | Converted ($N = 18$) | Non-converted ($N = 15$) | $p$ |
|---|---|---|---|
| Age at baseline (SD), years | 13.0 (1.8) | 13.7 (1.2) | 0.25[a] |
| Baseline CDI-S score (SD) | 0.83 (1.5) | 0.73 (0.8) | 0.81[a] |
| Baseline MASC score (SD) | 39.3 (9.8) | 40.5 (13.8) | 0.77[a] |
| Baseline WISC-III vocabulary score (SD) | 46.8 (5.1) | 50.4 (6.7) | 0.11[a] |
| Baseline SES | 3.8 (1.5) | 4.2 (0.7) | 0.11[b] |
| Maternal history of MDD (%) | 9 (50.0) | 11 (73.3) | 0.28[b] |
| Number of traumatic events experienced before scanning | 1.2 (0.9) | 0.9 (1.1) | 0.36[a] |
| Number of traumatic events experienced between baseline and follow-up assessment | 1.6 (1.0) | 1.9 (1.6) | 0.84[a] |

Values indicate the mean ± SD unless otherwise noted.
Abbreviations: CDI-S, Child Depression Inventory–Short Form; MASC, Multidimensional Anxiety Scale for Children; WISC-III, Wechsler Intelligence Scale for Children–III; SES, socioeconomic status; MDD, Major Depressive Disorder.
[a] Statistic computed using two-sample $t$-tests.
[b] Statistic computed using $\chi^2$ test, Trauma was assessed using Post Traumatic Stress Disorder (PTSD) section of the K-SADS-PL. SES was coded using annual household income (US dollars) as follows: 0 = less than 10,000, 1 = 10,000–25,000, 2 = 25,000–50,000, 3 = 50,000–75,000, 4 = 75,000–100,000, 5 = more than 100,000.

Redlich et al., 2014), our SVM analysis was conducted using a mask that included areas of the cortex that have been widely implicated in neuroanatomical models of depression and of emotion regulation (e.g., ventral and superior frontal cortex, anterior cingulate cortex, insula).

## 2. Methods

### 2.1. Participants

The study was approved by Stanford University's institutional review board. All adolescent participants provided written assent, and their mothers provided written informed consent. Participants in the current study sample included 33 adolescent girls, ages 10–15 years. We restricted our sampling to young adolescent girls to avoid the confound of sex differences on brain structure and depression vulnerability (Nolen-Hoeksema & Hilt, 2010) and because of previous findings indicating that the average age for first onset of adolescent depression is 15 years (Lewinsohn et al., 1994). Participants were recruited through advertisements posted in numerous locations (e.g., internet bulletin boards, university kiosks, supermarkets, etc.) describing a research study on depression in mothers. The mothers' responses to a telephone interview provided initial selection information. This phone screen established that both mothers and daughters were fluent in English and that daughters were between 10 and 15 years of age. Participants were excluded if they had experienced severe head trauma, learning disabilities, current or past depression or other Axis I disorders, current or past substance abuse, or if they were taking psychotropic medications. The telephone interview was also used to identify mothers who were likely either to have no psychiatric history or to meet criteria for recurrent depression during their daughter's lifetime. Those mother-daughter pairs who were considered likely to be eligible for participation were invited to come to the laboratory.

Baseline diagnostic status of participants was assessed by administering the structured Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL; Kaufman et al., 1997) to both the girls and their mothers (regarding the girls). In addition, the Structured Clinical Interview for the DSM-IV was administered to participants' mothers to assess history of maternal depression (for more information about the use of these measures in this study, see Joormann et al., 2007; Gotlib et al., 2010; Chen et al., 2012). To monitor the course of depressive symptoms and the possible onset of depression, girls and their mothers returned to the laboratory for diagnostic reassessment every 18 months for up to 5 years, or until the onset of depression. Importantly, although investigators have estimated that between 12% (Merikangas et al., 2010) and 35% (Weissman et al., 1997) of adolescents will experience an initial onset of depression by the end of their teenage years, just over 50% of the participants in the current study had developed a depressive disorder by follow-up (see Section 3). This high incidence rate was due to our sampling approach: many of the adolescents were at familial risk for depression by virtue of having a mother with repeated episodes of depression during her lifetime (Table 1). More importantly, however, to qualify for inclusion in the converted group, participants needed to be followed only until the onset of a depressive episode; this took considerably less time from the baseline scan date than the time needed to qualify as for inclusion in the non-converted group (i.e., had not developed a depressive episode in the five years following the baseline scan date).

#### 2.1.1. Magnetic resonance imaging data acquisition

Within one week of the baseline interview assessments, participants were scanned on a 1.5T GE scanner (GE Healthcare Systems, Milwaukee, Wisconsin). Anatomic images were obtained using a T1-weighted spoiled gradient-recalled (SPGR) echo sequence using the following parameters: repetition time (TR) = 8.924 ms, echo time (TE) = 1.792 ms, flip angle = 15°, in-plane resolution = 0.859 × 0.859 $mm^2$, and slice thickness = 1.5 mm.

#### 2.1.2. Magnetic resonance imaging data preprocessing

Scans were processed using FreeSurfer to produce measures of cortical gray matter thickness (Fischl & Dale, 2000; version 5.0, http://surfer.nmr.mgh.harvard.edu; Huang and Du, 2005; Salat et al., 2004). Processing streams included the removal of nonbrain tissue, intensity normalization, the segmentation of gray/white matter, and the alignment of each image volume to a standardized space. To estimate cortical gray matter thickness, a deformable surface algorithm was applied to segmented images to extract the pial and gray/white cortical surfaces (Dale et al., 1999). To ensure the accuracy of gray/white matter segmentation, exclusion of scalp and other non-brain tissue, and the inclusion of brain tissue, cortical surfaces were visually inspected by one rater (B.G.) who was blind to group membership. Manual corrections were performed by this rater where appropriate, in accordance with previously established procedures (Black et al., 2012; Yang et al., 2009). After spatially normalizing the data to an average template space, local cortical thickness was measured by estimating the shortest distance between spatially equivalent surface points on the pial surface and the gray–white matter boundary and vice versa and averaging these 2 values (Fischl and Dale, 2000). The cortical surface was then parcellated into 34 regions per hemisphere, as in Desikan et al. (2006). We chose to use cortical gray matter thickness as our primary measure in the current study, given prior work by our group and