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Serotonin signaling modulates the effects of familial risk for depression on cortical thickness

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ABSTRACT

Depression is a highly familial and a heritable illness that is more prevalent in the biological offspring of the depressed individuals than in the general population. In a 3-generation, 30-year, longitudinal study of individuals at either a high(HR) or a low(LR) familial risk for depression, we previously showed cortical thinning in the right hemisphere was an endophenotype for the familial risk. In this study, we assessed whether the effects of familial risk were modulated by the serotonin-transporter-linked polymorphic region (5-HTTLPR). We measured cortical thickness using MRI of the brain and associated it with 5-HTTLPR polymorphism in 76 HR and 53 LR individuals. We studied the effects of genotype and gene-by-risk interaction on cortical thickness while controlling for the confounding effects of age and gender, and for the familial relatedness by applying a variance component model with random effects for genotype. The results showed significant effects of gene-by-risk interaction on thickness: The "s" allele was associated with thinner cortex in the LR individuals whereas with thicker cortex in the HR individuals. The opposing gene effects across the two risk groups were likely due to either epistatic effects and/or differing modulation of the neural plasticity by the altered 5-HT signaling *in utero*.

1. Introduction

Heterogeneous symptom presentations of depression across individuals are likely caused by pathological environmental factors interacting with genetic and/or epistatic factors interacting with. To understand the moderating effects of genetic factors, we associated serotonin-linked, functional polymorphism with cortical thickness in 129 individuals who were at either at a high or a low familial risk for depression and were recruited as a part of an ongoing, 3-generation, 30-year, longitudinal study (Weissman et al., 2005a; Weissman et al., 2006). The probands in this study formed the generation 1 (G1) who either had severe, debilitating Major Depressive Disorder (MDD) or did not have any lifetime history of MDD. In the following we interchangeably used "depression" with MDD. The children (generation 2, G2) and grandchildren (generation 3, G3) of the probands with depression were at a high familial risk (HR) whereas those of the probands without depression were at a low familial risk (LR) for depression. Previously (Peterson et al., 2009) we had identified thinner cortex in the HR individuals across large portions of right lateral (post and precentral gyrus, inferior parietal lobe, middle and inferior occipital lobe, middle and inferior frontal gyrus, and posterior regions of the superior and middle temporal gyrus) and the left mesial (subgenual cortex, cuneus, precuneus, posterior cingulate, post and precentral gyrus, anterior cingulate, and superior frontal gyrus) hemispheres as a risk endophenotype (Peterson et al., 2009) because cortical thinning was present in the HR individuals irrespective of their lifetime history of depression. Similar spatial pattern of cortical thinning were recently reported in children prenatally exposed to depression (Sandman et al., 2015). However, the effects of genetic and/or epistatic factors and moderation of the effects of familial risk by these factors on brain circuits of mood and cognition remain unknown.

Genetic factors that modulate or moderate risk for depression can be identified by assessing their effects on brain abnormalities

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that have been previously implicated in depression. Previous neuroimaging studies of depression have implicated abnormalities in the morphology, activity, and connectivity within and across brain circuits that regulate mood, cognition, sleep, and behavior. Reductions in gray matter volumes have been reported in the amygdala (Hamilton et al., 2008; Altshuler et al., 2010), frontal cortex, orbitofrontal cortex, cingulate cortex (Bora et al., 2012), hippocampus (Cole et al., 2011), striatum (Choi et al., 2008; Lorenzetti et al., 2009), and right lateral and left mesial hemispheres (Peterson et al., 2009). Resting state BOLD fMRI studies in depression have found decreased functional connectivity between the anterior cingulate cortex (ACC) and the thalamus (Anand et al., 2005), decreased corticolimbic connectivity (Anand et al., 2007), decreased connectivity between the anterior cingulate cortex and the amygdala (Anand et al., 2009), increased functional connectivity in the dorsomedial prefrontal cortex (DMPFC) (Sheline et al., 2010), and decreased connectivity with the caudate nucleus (Bluhm et al., 2009). Taken together, imaging studies have identified disturbances in brain circuits of mood and cognition that underlie pathophysiology of depression. Associating these disturbances with functional polymorphism of genes linked to depression would identify genetic and/or epigenetic factors that moderate individual's risk for depression.

Several genes have been associated with depression, especially those that alter serotonin signaling, including serotonin-transporter-linked polymorphic region (5-HTTLPR) of the serotonin (5-HT) gene SLC6A4 that codes the serotonin transporter(5-HTT) (Caspi et al., 2003), brain-derived neurotrophic factors (BDNF) (Lee and Kim, 2010; Masi and Brovedani, 2011), tryptophan hydroxylase-2 (TPH2) (Gao et al., 2012), monoamine oxidase A (MAO-A) (Tzeng et al., 2009), and serotonin receptor 2A (HTR2A) (Antypa et al., 2013). These genes either directly modulate serotonin(Mann, 1999) signaling or interact with other genes to alter neuroplastic response of the brain. The long "*L*" and the short "*s*" functional variants (Heils et al., 1995) of the 5-HTTLPR have received great attention because the "*s*" allele has been associated with decreased transcription efficiency of the 5-HTT gene(Lesch and Mossner, 1998), thereby decreasing the density of 5-HTT in presynaptic neurons and increasing the intensity and duration of the serotonin signaling (Glatz et al., 2003). However, because several large studies have failed to associate the 5-HTTLPR polymorphism with depression (Caspi et al., 2003), this polymorphism may only moderate the influence of stressful life events and when exposed to stressful life events, individuals with the "s" allele could be at a greater risk for developing depression than those with the "L" allele (Caspi et al., 2003; Eley et al., 2004; Kendler et al., 2005; Wilhelm et al., 2006; Zalsman et al., 2006).

Imaging genetic studies associated the 5-HTTLPR polymorphism with altered function and morphology of brain regions and circuits that modulate mood and cognition. The fMRI studies showed that individuals with the "s" allele exhibited amygdala hyperactivity in response to threatening stimuli (Hariri et al., 2002; Heinz et al., 2005; Hariri et al., 2005) because of the disrupted regulation (Hariri et al., 2005) of amygdala response by the perigenual anteriror cingulate cortex (pACC) (Hariri et al., 2005). Anatomical MRI studies showed that individuals who had the "s" allele had decreased gray matter volumes in the pACC and the amygdala (Pezawas et al., 2005), regions intimately involved in emotional response (Pezawas et al., 2005) and mood. These alterations in brain function and morphology could be due to the morphological consequences of the altered serotonin signaling in fetus during brain development (Ansorge et al., 2004; Esaki et al., 2005; Homberg et al., 2010). We therefore expected these morphological consequences to be present in individuals who were at a greater risk for developing depression, regardless of their lifetime history for depression. Because the "s" allele has been associated with increased vulnerability for developing depressive symptoms(Caspi et al., 2003) and because the risk endophenotype (Peterson et al., 2009) was not a consequence of illness and/or medication use, we hypothesized that individuals who had at least one "s" allele would have thinner cortex in the brain regions of risk endophenotype compared to those who had the homozygous L/L genotype.

2. Methods

2.1. Participants

We acquired brain MR images in 129 individuals, ages 6 to 54 years, in generation 2 (G2) and generation 3 (G3), who were biological descendents of the probands (generation 1, G1) recruited in an ongoing, 30-year, longitudinal study (Weissman et al., 2005a; Weissman et al., 2006). The probands (G1) were white Caucasians and either had moderate to severe MDD with more than one episode of moderate to severe depression of 4 week duration or had no lifetime history of any psychiatric illness over an eight-year period. The probands with MDD were selected from outpatient clinic for the psychopharmacologic treatment of MDD and the nondepressed probands were selected from the same community (Weissman et al., 1987). The biological descendants of the probands with depression were at a high familial risk (HR) for depression, whereas those of the probands without depression were at a low familial risk (LR) for depression. Since the previous study (Peterson et al., 2009) with 131 individuals, we had processed MRI data for additional 16 individuals in generations 2&3. Of these 147 individuals, present study comprised 129 individuals who had both MRI and genotype data, with 113 individuals in both the previous (Peterson et al., 2009) and the present study. The HR group consisted of 76 individuals (61 adults age $>=$18 years; 43 females; mean age 33.80 years [SD 13.06]; 26 individuals had the homozygous L/L genotype and 38 had the heterozygous s/L genotype) and the LR group consisted of 53 individuals (28 adults age $>=$ 18 years; 26 females; mean age 24.86 years [SD 13.27]; 17 individuals had the homozygous L/L genotype and 35 had the heterozygous s/L genotype). All participants were white Caucasian. Although the HR and LR groups did not differ by gender and the 5-HTTLPR allele frequency, during a 20-year follow-up the HR individuals compared to the LR individuals had threefold higher risk for mood disorder, lower age-at-onset of MDD, (Weissman et al., 2006) and significantly greater frequency of lifetime depression (Table 1). Few participants at scan time had comorbid disorders: 3 LR individuals and 5 HR individuals had Generalized Anxiety disorder, 5 LR and 10 HR individuals had Panic Disorder, 4 LR and 1 HR individual had Attention Deficit Disorder, and 4 LR and 4 HR individuals had Obsessive Compulsive Disorder. However, all participants at the scan time were free of current depression and medication use. The interviews were conducted at each of the five waves in the longitudinal study: At baseline and years 2, 10, 20, and 25 of the study. We currently are completing the 6th wave at 30 year in the study. The diagnostic assessments for the analyses were carried out at the 5th wave within one week of the MRI scan and the lifetime diagnoses used in the analysis were cumulative over all the previous waves. That is, the final diagnosis included diagnoses from all five waves of the longitudinal study and was based on a best-estimate procedure that involved an independent review of all assessments, including the assessment at MRI scan, by 2 experienced clinicians—a child psychiatrist or a psychologist. The expert clinicians were not involved in the interviewing and were blind to the diagnostic status of the previous generations, MRI scan, and genotype of the participants (Leckman et al., 1982).

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