

# Genetic Correlates of Spirituality/Religion and Depression: A Study in Offspring and Grandchildren at High and Low Familial Risk for Depression

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The relationship between suffering and spiritual growth is foundational to the treatment literature on spiritually oriented psychotherapy. A common developmental path between suffering and increased spirituality may point to a unified psychological process, which has in turn a common underlying physiology with a genetic foundation. Possible genetic correlates of spirituality and depression have been identified in community samples. We investigate some of the previously identified candidates in a sample of families at both high and low risk for depression. Offspring and grandchildren of individuals at high and low risk for depression, participating in a multiwave 30-year longitudinal study, were assessed for 7 SNPs (single nucleotide polymorphisms) drawn from 4 single gene candidates associated with systems implicated in both depression and spirituality: Serotonin (5-HT1B and 5-HT2A), Dopamine (DRD2), Oxytocin (OT), and Monoamine Vesicular Transporter (VMAT1). Dopamine (DRD2) Serotonin (5-HT1B), their Transporter (VMAT1), and Oxytocin (OXTR) were positively associated with a high level of importance of spirituality or religion (S/R) in the group at low familial risk for depression. DRD2 minor allele was associated with both lifetime major depressive disorder (MDD) and spirituality in the low-risk group for depression. No SNPs were related to S/R in the group at high familial risk for depression. OXTR was associated with lifetime MDD in the full sample. Genes for dopamine, serotonin, their vesicular transporter, and oxytocin may be associated with S/R in people at low familial risk for depression. Genes for dopamine may be associated both with S/R and increased risk for depression in people at low-risk for depression, suggesting a common pathway or physiology to mild to moderate depression. MDD is associated with oxytocin across risk groups. In the high-risk group, phenotypic expression of S/R may be suppressed. The shared association of DRD2 by S/R and depression, generally found to be inversely related, calls for further research on their common physiological pathways, and the phenotypic expression of these pathways based upon use and environment. The findings may be interpreted to offer biological evidence in support of engaging suffering as an opportunity for spiritual growth in treatment, as is foundational to many existing spiritually oriented psychotherapies.

*Keywords:* depression, genetics, intergenerational transmission, single-gene candidate, spirituality

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The relationship between suffering and increased spiritual awareness is foundational in the literature on spiritually oriented psychotherapy (Richards & Bergin, 2014; Sperry & Shafranske, 2005). A potentially interwoven path of suffering and spirituality in healing, growth, recovery, and subsequent resilience may point to a unified psychological process, which implicates a common physiology with a genetic foundation. In support of a common psychological pathway, a large literature over the past 20 years shows protective benefits of spirituality against depression (for reviews, see Koenig, 2009; Van Ness & Larson, 2002). Depression and spirituality have been shown to share multiple physiological risk factors, including the preliminary suggestion of common genetic markers for risk (Smith, McCullough, & Poll, 2003). In this exploratory study we investigate a subset of those genetic markers that in previous studies have been linked both with depression and with spirituality (Perroud, 2009).

Whereas the majority of research has examined genetic links to depression and spirituality in community and convenience samples, the current study investigates these genes in a “high-risk” sample, namely a sample of adult offspring and grandchildren of people who had severe depression and matched controls (Weissman et al., 2016) offering a smaller sample size but a stronger “signal” for a link between any single gene and its phenotype. Previous research has shown that risk for depression differs by parental risk status—that is, individuals with a parent or grandparent diagnosed with depression are at least 2 to 3 times as likely to become depressed than children without a depressed parent (Klein et al., 2002; Lieb et al., 2002; Weissman et al., 2006). Further, this intergenerational risk is greatest for children with both a depressed grandparent and parent (Weissman et al., 2016).

As a field of inquiry single gene analysis has burgeoned over the past 15 years (Ropers, 2010), offering etiological clues and markers for pathogenic processes but relatively small magnitude of an association with diagnosis. The largest effect sizes of genome-wide association studies (GWAS) account for a relatively small portion of the variance in both diagnosis of psychopathology and psychological traits (Park et al., 2011). That said, single gene analyses

often indicate pathways that might be examined and common ground between seemingly divergent diagnoses or conditions. Likewise, the study of the genetic underpinnings of positive traits has thus far stemmed largely from candidate gene analysis (Moore et al., 2015). Variation examined among candidate genes is investigated at the level of the single-nucleotide polymorphism (SNP), specifically variation in a single nucleotide that occurs at a specific position in the genome.

The candidate genes that we investigate for a relationship between depression and spirituality in this high-risk sample were drawn from the previously published research on single gene candidates. Here we briefly review the literature associated with each single gene candidate that we assessed as potentially related to depression and spirituality and then present the results of the assessment that are driven by three research questions:

1. What are the single-gene correlates of spirituality?
2. What are the single-gene correlates of depression?
3. Are there differential associations by risk status?

### Potential Candidate Single Genes for Spirituality and Depression

#### Oxytocin

Oxytocin (OT) is a nonapeptide signaling molecule that assists with human neuromodulation of social behavior, bonding, adaptation to stress, and reproduction. A large body of research exists on the oxytocin receptor gene (OXTR) and its association with social function, capacity for bonding, and related dysfunction indicated in pathology such as autism, depression, and schizophrenia (see Feldman, Monakhov, Pratt, & Ebstein, 2016 for review). The OXTR SNP rs2254298 (9073A>G), in particular, has been examined, with several studies demonstrating the link between its allelic variation and autism in Japanese, Israeli, and Caucasian samples (Jacob et al., 2007; Lerer et al., 2008; Liu et al., 2010). Costa et al. (2009) examined genotypic distributions of rs2254298 and found that in a group of individuals with unipolar depression, there were a re-

duced number of A-allele carriers. In this same study, GG homozygotes showed high scores on subscales of need for approval, self-esteem, and adult separation anxiety, previously associated with depression.

As with other OXTR SNPs, the minor A allele of rs2254298 has also been associated with increased severity of symptoms in patients with anorexia nervosa and bulimia nervosa, as compared with healthy controls (Acevedo, Valencia, Lutter, & McAdams, 2015). In addition to allelic variation of the SNP, haplotypes with rs2254298 have shown associations with positive and negative affect and emotional loneliness in adults (Lucht et al., 2009), and high callous-unemotional traits, a developmental precursor to psychopathy, in children (Dadds et al., 2014).

OT has been associated with social behavior such as social affiliation, empathy, parental bonding, and stress regulation (for a review, see Aspé-Sánchez, Moreno, Rivera, Rossi, & Ewer, 2016). Because of its apparent role in social affiliation and behavior, rs2254298 has also been examined as a moderator in the relation between religiosity and psychological distress, with the homozygote GG genotype driving an association between religiosity and increased psychological distress in a European American sample (Sasaki, Kim, & Xu, 2011). In another study by Sasaki and colleagues (2015), genetic moderation of the OXTR polymorphism influenced the impact of religious priming on self-control, such that individuals with the homozygote GG genotype showed greater increases in self-control than individuals with AA or AG genotypes after receiving religious cues in a social context. Finally, in a recent study on the effects of intranasal OT administration and self-reported spirituality, OT administration was shown to increase spirituality in males and this effect was moderated by OT-related genotypes (Van Capellen, Way, Isgett, & Fredrickson, 2016).

### Serotonin

To attract ongoing attention within psychopharmacologic research, the serotonergic system has been implicated in both pathology and personality, albeit the mechanisms of its role in the development of either are not straightforward. In imaging studies, it has been established that

serotonin receptor binding potential is reduced in the brains of depressed individuals as compared with controls (Bhagwagar, Rabiner, Sargent, Grasby, & Cowen, 2004; Drevets et al., 1999, 2007; Murrough et al., 2011), reduced serotonin binding potential has been associated with serotonin receptor gene polymorphisms (Baldinger et al., 2015), and serotonin polymorphisms are associated with Major Depressive Disorder (Kishi et al., 2013). However, the inverse of these findings has recently been supported (for review, see Kaufman, DeLorenzo, Choudhury, & Parsey, 2016), making apparent the complexity of the relationship between serotonin, 5-HT receptors, and depression, yet still lending support to the centrality of the system.

One SNP of interest, 5-HT<sub>2A</sub> receptor gene polymorphism rs6311, modulates HTR<sub>2A</sub> promoter activity, such that activity is greater in the presence of the A allele relative to the G allele (Parsons, D'Souza, Arranz, Kerwin, & Makoff, 2004), and leads to greater transcriptive efficiency (Smith et al., 2013). Candidate gene-based and transmission disequilibrium association studies have shown that rs6311 may also have clinical significance and is associated with psychiatric disorders and related phenotypes, such as panic disorder (Unschuld et al., 2007), obsessive-compulsive disorder in individuals with Tourette's Disorder (Dickel et al., 2007), and early onset Obsessive Compulsive Disorder in children and adolescents (Walitza et al., 2012). Giegling, Hartmann, Möller, and Rujescu (2006) observed that haplotypes with the T allele of rs6311 and single functional (T) markers at rs6311 were protective against suicidal behavior, and CC-homozygotes reported more anger and aggression-related behavior. The association between genotypic variation and phenotypic expression of suicide, anger, and aggressive behavior was further supported in Saiz and colleagues' (2008) study in which the A allele was overrepresented in nonimpulsive suicide attempters, as compared to impulsive suicide attempters and healthy controls.

Although meta-analyses have conflicting conclusions on the association between rs6311 and unipolar and bipolar depression (Gu et al., 2013; Jin, Xu, Yuan, Wang, & Cheng, 2013; Lin, Jiang, Kan, & Chu, 2014; Zhao et al., 2014), there has been metaanalytical support for other 5-HTR<sub>2A</sub> variants and MDD (Lin et al.,

2014), risk for schizophrenia conferred by the -1438A/G polymorphism of rs6311 (Gu et al., 2013) and pilot data support for association with post-partum depression (El-Ibiary et al., 2013).

Like the 5-HT<sub>2A</sub> receptor gene, 5HT<sub>1B</sub> receptor genes modulate activity in the promoter region through influence on transcription of the gene. They do so by increasing the binding of transcription factors, thereby increasing the transcription of the downstream coding region (Huang, Grailhe, Arango, Hen, & Mann, 1999). 5-HT<sub>1B</sub> receptor genes have been extensively studied and are associated with depression (Huang et al., 2003), impulsivity (Stoltenberg, Christ, & Highland, 2012; Varga et al., 2012), ADHD (for review, see Caylak, 2012), aggression (Hakulinen et al., 2013), and alcoholism and substance use disorders (Fehr et al., 2000; Huang et al., 2003), particularly antisocial alcoholism (Lappalainen et al., 1998; Lee et al., 2009; Soyka, Preuss, Koller, Zill, & Bondy, 2004).

Because of their role in transcription and expression of serotonin and its receptors, rs130058, rs11568817, and rs6298 have been examined as 5-HTR<sub>1B</sub> functional variants showing association with psychiatric disorder and maladaptive behaviors. In a Chinese Han population, rs11568817 was significantly associated with suicidal behavior in individuals experiencing major depression (Wang et al., 2009). Although conflicting findings exist, a recent meta-analysis concludes that there is a statistically significant association between rs130058 and rs11568817 and alcohol, cocaine, and heroin dependence (Cao, LaRocque, & Li, 2013).

Rs130058 has also been associated with phenotypes related to addiction and suicide, such as impulsive-aggressive behavior and anger and hostility in men (Conner et al., 2010; Zouk et al., 2007). In Conner et al.'s, 2010 study, the T allele of rs130058 was overrepresented among suicide completers, suggesting that risk for suicide is conferred through the minor allele. Additionally, rs130058 and rs11568817 acted as a functional combination in the promoter region, accounting for significant variance in men's anger and hostility. Interestingly, in this 4-year longitudinal study, the genetic differences in haplotype variances and hostility and anger peaked at age 18 in men, declining thereafter. Age-related or developmental effects on this

phenotypic manifestation might be of interest, as an additional study by Shoval, Bar-Shira, Zalsman, John Mann, and Chechik (2014) showed that the expression levels of participants in the serotonergic system, 5-HTR<sub>1B</sub>, increase sharply in adolescence.

Robust findings have been published that also identify both rs6298 and rs130058 as having respective roles in depressed patients' responses to antidepressant medication. Both SNPs interact with antidepressant type to show a differential association with side effects such as suicidal ideation as well as response time and efficacy (Lenze et al., 2013; Perroud et al., 2011; Villafuerte et al., 2009; Xu et al., 2012).

The serotonin system has also been implicated in studies of spirituality. Although evidence exists that expression levels of 5-HTR<sub>1B</sub> receptors peak in adolescence (Shoval et al., 2014), studies show that spirituality surges in adolescence as well. Particular attention has been paid to the relation between self-transcendence and spiritual acceptance with reduced serotonin binding potential (Borg, Andree, Soderstrom, & Farde, 2003), reduced serotonin transporter availability (resulting in elevated serotonin levels) in specific raphe nuclei (Kim et al., 2015), the short allele of the serotonin transporter gene 5-HTTLPR (Nilsson et al., 2007), and the polymorphism 5HT<sub>1A</sub> in patients with mood disorders (Lorenzi et al., 2005). The -1438A/G polymorphism of rs6311 has also shown association with self-transcendence in a Korean population (Ham et al., 2004).

Other personality traits, such as openness to experience, have also been shown to be associated with spirituality (Henningsgaard & Arnau, 2008; Saroglou, 2002). Not only have cerebral levels of serotonin been associated with openness to experience and cognitive flexibility (Kalbitzer et al., 2009), but researchers are also beginning to examine 5-HTR<sub>2A</sub> polymorphisms as a means to understand the effect of gene and environment interaction on personality traits associated with spirituality. Rs6311 specifically has been shown to interact with the serotonin transporter gene (5-HTTLPR) and education level to predict novelty-seeking in a Spanish sample (Saiz et al., 2010). In a study among Russian wrestlers, rs6311 interacted with gender to predict openness to experience, as measured by the NEO-5 (Butovskaya et al., 2015). Additionally, an understanding of para-

doxical expression—that a condition such as potentiation of serotonin transmission can both increase sensitivity to stressful experiences as well as increase openness to experiences—is important to understanding the relation among serotonin gene receptors, spirituality, and pathology.

## Dopamine

Indicated in both psychopathology and well-being, the dopaminergic system is integral in motivation, learning, and reward processing. Of the dopamine receptor genes (DR), the D<sub>2</sub> dopamine receptor gene (DRD2) is one of the most widely studied, and abnormalities in the DRD2 gene have been implicated in Reward Deficiency Syndrome (Blum et al., 1990, 1996, 2012, 2014). Reward Deficiency Syndrome refers to a dearth of usual feelings of satisfaction that is a result of a disruption in the “brain reward cascade” brought about by a reduced number of dopamine receptors leading to insufficient binding and reduced extracellular dopamine, thus affecting mood and cravings in humans (Blum & Kozlowski, 1990). In addition to addiction, pathological gambling and other reward-seeking behaviors, DRD2 has also shown associations with suicidal behaviors (Mandelli & Serretti, 2013), Posttraumatic Stress Disorder (Voisey et al., 2009), higher levels of rumination in depressed individuals (Whitmer & Gotlib, 2012), and schizophrenia (Yao, Pan, Ding, Pang, & Wang, 2014).

The most widely studied of the DRD2 SNPs, the Taq1A (rs1800497), is now known to be located in the nearby ANKK1 gene, approximately 10 kb downstream from the DRD2 gene, and results in an amino acid substitution (Neville, Johnstone, & Walton, 2004). Several studies have shown that individuals with the Taq1A minor A1 allele exhibit reduced striatal DRD2 binding when compared with subjects without the A1 allele (Eisenstein et al., 2016; Gluskin & Mickey, 2016; Noble, 2003), suggesting that it is indirectly involved in DRD2 expression or interacts with another DRD2 SNP. As with other DRD2 mutations, A1 allele carriers exhibit reduced receptor density, as compared with noncarriers (Nemoda, Szekely, & Sasvari-Szekely, 2011). These existing functional differences in A1 allele carriers are suggested to confer risk for related psychopathology that has

been identified in candidate gene-based association tests, such as depression in men (Roetker et al., 2012), increased risk for mood disorders (Zhang, Hu, Li, Zhang, & Chen, 2014), borderline traits and impulsive self-damaging behaviors (Nemoda et al., 2010), PTSD (Li et al., 2016), alcohol dependence and alcoholism (Munafò, Matheson, & Flint, 2007; Smith et al., 2008), and opioid dependence (Chen et al., 2011).

In a review of the neurobiology of spirituality, Perroud (2009) suggests that similarities in the functional activity in spiritual and religious experience and the dopaminergic system indicate a relation between the two. Candidate gene and imaging studies are consistent with this idea. Using the TCI, Comings et al. (2000) showed an association between DRD4 and spiritual acceptance, and suggested that this was a function of increased concentration of DRD4 receptors in cortical areas. In another sample, individuals with homozygous AA genotype experienced greater stress induced dopamine release and reported lower levels of openness to experience, reflecting what the authors interpreted to be a sensitive, vulnerable phenotype (Peciña et al., 2013). In the effort to understand gene-environment interactions, religiosity has also been identified as a moderator of the relation between the minor A1 allele of rs1800497 and delinquent/antisocial behavior in adolescents, such that individuals with the minor allele reported increased delinquency but only among males without religious belief (Beaver, Gibson, Jennings, & Ward, 2009).

Given the connection between receptor density, extracellular dopamine, and the neural network including the prefrontal cortex and the dorsal striatum, further support for the link between dopamine and spirituality is offered through imaging studies. A PET study of Yoga Nidra meditation demonstrated a significant increase of dopamine levels during the meditation practice (Kjaer et al., 2002). Additionally, the authors reported a significant decrease in binding in the ventral striatum. In another PET study, dysfunctions in the dopaminergic system coincided with impairment in activating religious concepts among Parkinson’s patients whose onset began on the left side of the body/right forebrain (Butler, McNamara, & Durso, 2010). The result of this PET study is consistent with dopaminergic disruption in the right striatum.

tal prefrontal networks that occurs in Parkinson's disease. Also linking S/R and dopamine, it has been argued that the impetus for meditation and religious activities may be related to the activation of the dopaminergic system during these types of activities (Newberg & Iversen, 2003). However, the relation among surfeit dopamine, receptor deficiency, and binding potential remains unclear (Blum et al., 2014), particularly when considering the counterintuitive findings between healthy and clinical populations.

### Vesicular Monoamine Transporters

Unlike the other SNPs examined, vesicular monoamine transporter (VMAT) genes are functionally related to proteins responsible for the transfer of monoamines such as dopamine, epinephrine, and serotonin to synaptic vesicles. In particular, VMAT1 (SLC18A1) is exclusively found in neuroendocrine cells (Erickson, Schafer, Bonner, Eiden, & Weihe, 1996).

In Lohoff et al. (2014), fMRI data showed that the minor A allele altered amygdala and medial prefrontal cortex functioning as well as increased presynaptic transport of monoamines in vitro. Lohoff concluded that VMAT1 variants play a role in emotional processing as well as risk for psychopathology. These findings buttress association studies showing that the minor A allele of VMAT1 variant rs1390938 has been associated with lower risk of alcohol use dependence (Dutta et al., 2016; Vaht, Kiive, Veidebaum, & Harro, 2016), anxiety-related personality traits (Lohoff et al., 2008), maladaptive impulsivity, anxiety, depressiveness, and neuroticism (Vaht et al., 2016). Closely related VMAT2 (SLC18A2) SNPs have been associated with phenotypes such as depression in elderly men (Christiansen et al., 2007), alcohol dependence (Schwab et al., 2005), and posttraumatic stress disorder (Solovieff et al., 2014). The VMAT2 gene has also been implicated in discussion as "the God gene" (Hamer, 2005), because of the C allele's association with higher self-transcendence scores as compared with homozygous AA genotypes, and the relation of VMAT to the packaging and transportation of multiple monoamines, including dopamine and serotonin.

## Method

### Study Samples

Study participants were 334 subjects (156 female and 178 male; mean age = 31.5,  $SD = 16.0$ ) comprising offspring and grandchildren drawn from an ongoing 30-year, three generational study of individuals at high and low-risk for depression. Mean ages for the two generations of study participants were as follows: Generation 2 (G2),  $M = 47.5$   $SD = 7.9$  and Generation 3 (G3),  $M = 19.3$ ,  $SD = 7.4$  years.

Probands in Generation 1 (G1) had been originally recruited for the study of major depressive disorder and followed up for 30 years at six longitudinal waves. The study cohort has been described previously elsewhere (Weissman, Berry, et al., 2016; Weissman, Wickramaratne, et al., 2016). Subjects were diagnosed with major depression using the age-appropriate version of the semistructural diagnostic Schedule for Affective Disorders and Schizophrenia (Kaufman et al., 1997; Mannuzza, Fyer, Klein, & Endicott, 1986). Individuals with any history of bipolar, schizophrenia spectrum, or antisocial personality disorders were excluded. Altogether 450 individuals were available for the present study. Written informed consent was obtained from all subjects and the study protocol was approved by the Institutional Review Board at New York State Psychiatric Institute/Columbia University.

In the final study sample of 334 participants, 99.1% were Caucasian. Distribution of annual income ranged as follows: \$5,000 (7.1%), \$15,000 (7.8%), \$25,000 (10.6%), \$35,000 (12.1%), \$45,000 (12.8%), \$55,000 (11.4%), \$65,000 (7.8%), \$80,000 (12.1%), \$90,000 (18.4%). Education levels ranged as follows: 18.6% had less than high school, 32.6% had high school, 48.8% had more than high school.

### Religion and Spirituality

Religious denomination ranged as follows: 52.8% were Catholic, 21.3% Protestant, 6.0% belonged to other religious denominations, 7.1% were Agnostic/Atheist, 12.4% were personal religious, 3.6% were Jewish, and 0.4% were Buddhist/Hindu/Muslim.

Measures on personal experience and practice of S/R included two questions. First, "How

important to you is religion or spirituality?" with responses ranging from 1 (*not important at all*) to 4 (*very important*). Second, "How often, if at all, do you attend church, synagogue, or other religious or spiritual services?" with responses ranging from 1 (*once a week or more*) to 5 (*never*). The average rating within the study sample on the personal importance of S/R was  $M = 2.74$ ,  $SD = 1.02$  (approximating a rating of moderate importance), and the average rating on frequency of attendance was  $M = 2.91$ ,  $SD = 1.50$  (with the average rate of church attendance approximating once or twice a year).

### Rates of Depression

Of the 334 participants, 37.7% had a diagnosis of Life-Time MDD and 17.0% had an episode of MDD at most recent follow-up.

### Genotyping

We genotyped in total 7 SNPs in five genes: HTR2A, HTR1B, OXTR, VMAT1, and DRD2 genes across the 2-generation samples (334 individuals). Genomic DNA was extracted from a saliva sample collected using Oragene DNA Self Collection Kit following the protocol provided by the manufacture (Oragene Genotek, Ontario, Canada). SNPs were genotyped using Taqman SNP Genotyping assays with TaqMan Genotyping Master Mix (Applied Biosystems, Foster City, CA) on an ABI 7900HT Fast Real-Time PCR System and analyzed using SDS 2.1 software (Applied Biosystems, Foster City, CA).

### Analysis

The main analyses (Tables 2 and 3) were performed using methods for family based association tests within the framework of Generalized Estimating Equation models similar to that described in Chen and Yang (2010) using SAS (SAS Software Version 9.2, Cary, NC, Copyright, 2008). Linear regression models were fitted to quantitative traits such as personal importance of S/R and logistic regression models were fitted to binary traits such as MDD. Personal importance of S/R and MDD are the respective outcomes; importance is treated as a continuous variable, with values from 1–4. Higher score indicates greater personal importance of S/R. MDD is a binary variable with the

values 0 (absence of Lifetime MDD) and 1 (presence of Lifetime MDD), respectively. For each of the 7 SNPs, the corresponding genotypes were coded as  $-1$ ,  $0$ ,  $1$  and treated as a linear predictor. All analyses were adjusted by age and gender. All models were assumed to be additive genetic models, with the homozygous minor allele genotype coded as  $-1$ , the heterozygous genotype coded as  $0$ , and the homozygous major allele genotype coded as  $1$ . Lack of independence among observations in the same pedigree was accounted for by treating each pedigree as a cluster, with an independence working correlation matrix used in the robust variance estimator.

### Results

Study participants ( $N = 334$ ) were stratified into a high-risk group ( $N = 109$ ) and a low-risk group ( $N = 225$ ). The distribution of genotypes in the sample by risk status is summarized in Table 1. Rates of major and minor alleles for 5 of the 6 SNPs did not differ significantly between the low and high-risk groups. There was a significant difference in rates of major and minor alleles between the high and low risk group for DRD2 SNP rs1800497 ( $p = .054$ ).

The results show that, adjusted by age and gender, there is a significant association between high personal importance of S/R and OXTR SNP rs2254298 ( $p = .024$ ), 5HTR1B SNPs rs130058 ( $p = .001$ ), and rs11568817 ( $p = .029$ ), VMAT1 SNP rs1390938 ( $p = .033$ ) and DRD2 SNP rs1800497 ( $p = .026$ ) in the low-risk group. For rs130058 genotype, the minor A allele is associated with decreased personal importance of S/R (Table 4). For the other four SNPs that were found to be associated with personal importance of S/R in the low risk group the minor allele was found to be associated with increased personal importance of S/R. In the high-risk group, rs2254298 is significantly associated with lifetime MDD ( $p = .049$ ). In the low-risk group, rs1800497 ( $p = .012$ ) is significantly associated with lifetime MDD and genotype GG is associated with lower risk of lifetime MDD (Table 5).

The interaction term of rs2254298\*risk (OXTR by Risk Status) is not significant ( $p = .839$ ) whereas rs1800497\*risk (HTR1B by Risk Status) is significant ( $p = .041$ ). So for

Table 1  
*Genotype Frequencies of Selected SNPs at High and Low Familial Risk for Major Depressive Disorder*

		Rs2254298				
Total		AA (%) -1	AG (%) 0	GG (%) 1	Unknown (%) missing	Chi-square test
High risk	225	2 (.89)	53 (23.56)	158 (70.22)	12 (5.33)	$\chi^2 = .09$
Low risk	109	1 (.92)	24 (22.02)	78 (71.56)	6 (5.50)	$p = .954$
		Rs6298				
Total		AA (%) -1	AG (%) 0	GG (%) 1	Unknown (%) missing	Chi-square test
High risk	225	12 (5.33)	75 (33.33)	137 (60.89)	1 (.44)	$\chi^2 = .93$
Low risk	109	4 (3.67)	41 (37.61)	63 (57.80)	1 (.92)	$p = .629$
		Rs130058				
Total		AA (%) -1	AT (%) 0	TT (%) 1	Unknown (%) missing	Chi-square test
High risk	225	21 (9.33)	98 (43.56)	101(44.89)	5 (2.22)	$\chi^2 = 1.44$
Low risk	109	8 (7.34)	42 (38.53)	56 (51.38)	3 (2.75)	$p = .488$
		Rs11568817				
Total		CC (%) -1	CA (%) 0	AA (%) 1	Unknown (%) missing	Chi-square test
High risk	225	49 (21.78)	115 (51.11)	56 (24.89)	5 (2.22)	$\chi^2 = 2.09$
Low risk	109	31 (28.44)	54 (49.54)	22 (20.18)	2 (1.83)	$p = .352$
		Rs1390938				
Total		AA (%) -1	AG (%) 0	GG (%) 1	Unknown (%) missing	Chi-square test
High risk	225	8 (3.56)	94 (41.78)	110(48.89)	13 (5.78)	$\chi^2 = 1.67$
Low risk	109	5 (4.59)	53 (48.62)	46 (42.20)	5 (4.59)	$p = .434$
		Rs1800497				
Total		AA (%) -1	AG (%) 0	GG (%) 1	Unknown (%) missing	Chi-square test
High risk	225	11 (4.89)	64 (28.44)	145 (64.44)	5 (2.22)	$\chi^2 = 5.84$
Low risk	109	7 (6.42)	43 (39.45)	54 (49.54)	5 (4.59)	$p = .054$
		Rs6311				
Total		CC (%) -1	CT (%) 0	TT (%) 1	Unknown (%) missing	Chi-square test
High risk	225	69 (30.67)	114 (50.67)	37 (16.44)	5 (2.22)	$\chi^2 = 2.80$
Low risk	109	33 (30.28)	48 (44.04)	26 (23.85)	2 (1.83)	$p = .247$

rs2254298 (OXTR), we combine the two risk groups. The estimated parameter of rs2254298 is 0.7799 and its 95%CL is (0.045, 1.510). Therefore, there is still a significant association between lifetime MDD and rs2254298 (OXTR) in the whole sample ( $p = .036$ ).

## Discussion

We found associations between the personal importance of S/R and genes for dopamine (DRD2 SNP rs1800497), oxytocin (OXTR SNP rs2254298), serotonin (5HT1B SNPs rs130058 and rs11568817), and their vesicular transporter (VMAT1 SNP

rs1390938) uniquely in the low-risk group. DRD2 was associated with both risk for depression and positively associated with S/R in the low-risk group. OXTR was associated with lifetime depression across both the high risk and the low risk group.

## Research Question 1: What Are the Single-Gene Correlates of Spirituality?

Findings on VMAT1, 5HT1B, OXTR, and DRD2 in the low-risk sample are consistent with previous literature that relates these genes with spirituality or closely related constructs. Interestingly, these genetic associations and

Table 2  
Association Between Importance of S/R and SNP (N = 291)

SNP	Low-risk (N = 96) Estimate (95% CI)	p	High-risk (N = 96) Estimate (95% CI)	p
rs2254298	.527 (.069, .985)	.024	.056 (-.220, .331)	.693
rs6298	.093 (-.311, .498)	.652	.113 (-.139, .365)	.380
rs130058	-.493 (-.781, -.206)	.001	.061 (-.229, .351)	.680
rs11568817	.258 (.026, .491)	.029	.066 (-.191, .323)	.614
rs1390938	.268 (.022, .515)	.033	-.145 (-.408, .118)	.281
rs1800497	.433 (.051, .816)	.026	.194 (-.128, .515)	.238
rs6311	-.231 (-.479, .018)	.069	.058 (-.174, .290)	.626

their expression map onto three distinct domains related to spirituality: *mood*, *bonding*, and *transcendence*. As with VMAT and 5HT1B, which are linked to *mood*, spirituality has been linked with positive mood and thriving and as both conferring protective benefit against depression and other forms of psychopathology (Akrawi, Bartrop, Potter, & Touyz, 2015; Lucette, Ironson, Pargament, & Krause, 2016; Miller, 1998; in this sample, Miller et al., 2014; Miller, Davies, & Greenwald, 2000; Miller, Weissman, Gur, & Adams, 2001). Spirituality, like OXTR, has been implicated in outcomes of *bonding* including pro-social behavior and empathy (Giordano, Prosek, & Lankford, 2014; Rew & Wong, 2006). Dopamine receptor genes (here DRD2), like spirituality, have been linked to *transcendence* through previous studies (Comings et al., 2000; Comings, Saucier, & MacMurray, 2002).

**Research Question 2: What Are the Single-Gene Correlates of Depression?**

DRD2 minor allele was found to be both a risk factor for depression and positively associated with higher levels of importance of S/R in

the low-risk sample. Additionally, rates of minor allele frequency were significantly greater in the low-risk group than the high-risk group, suggesting the presence of a minor allele is more normative in the low-risk sample. This finding on DRD2 may lend support to previous research around a common pathway or physiology underlying both existentially oriented depression and spirituality (Barton, Barkin, & Miller, in press; Miller & Barton, 2015; Miller et al., 2014). Experiential trait correlates that mirror this finding include the positive associations to both depression and spirituality found in openness to experience (Henningsgaard & Arnau, 2008; Trull & Sher, 1994; Wolfstein & Trull, 1997) and self-transcendence (for a review, see Cloninger, 2008).

DRD2 minor allele may increase risk for either depression or spirituality based upon environment, both that environment external to us and the internal environment that is in the use and practice of inner life (prayer, meditation, reflection, habitual inner ways of living). The physiological pathway supported by the DRD2 minor allele may show functional or morphological change as a result of spiritual practice.

Table 3  
Association Between Lifetime MDD and SNP (N = 334)

SNP	Low-risk (N = 96) Estimate (95% CI)	p	High-risk (N = 96) Estimate (95% CI)	p
rs2254298	1.034 (-.776, 2.844)	.263	.831 (.003, 1.658)	.049
rs6298	-.221 (-.834, .393)	.480	-.106 (-.903, .691)	.795
rs130058	-.005 (-.575, .564)	.985	.103 (-.347, .553)	.654
rs11568817	.037 (-.567, .641)	.905	-.076 (-.601, .450)	.778
rs1390938	-.203 (-.898, .492)	.567	.217 (-.502, .936)	.554
rs1800497	-1.022 (-1.818, -.226)	.012	.055 (-.589, .700)	.867
rs6311	-.121 (-.744, .503)	.704	-.058 (-.568, .452)	.823

Table 4  
*Mean, Standard Deviation, and Analysis of Variance of Importance of S/R by Genotype and Risk Group*

		Rs2254298 <i>M (SD)</i> of importance				
Total		AA (%) -1	AG (%) 0	GG (%) 1	Unknown missing	ANOVA
High risk	195	3.00 (.)	3.31 (.94)	3.26 (1.06)	3.38 (1.19)	$F = .81$
Low risk	96	4.00 (.)	3.62 (1.02)	3.07 (.98)	3.33 (1.21)	$p = .584$
		Rs6298 <i>M(SD)</i> of importance				
Total		AA (%) -1	AG (%) 0	GG (%) 1	Unknown missing	ANOVA
High risk	195	3.67 (.89)	3.32 (1.01)	3.23 (1.05)	2.00 (.)	$F = .58$
Low risk	96	3.25 (.50)	3.28 (1.16)	3.18 (.96)	3.00 (.)	$p = .769$
		Rs130058 <i>M (SD)</i> of importance				
Total		AA (%) -1	AT(%) 0	TT(%) 1	Unknown missing	ANOVA
High risk	195	3.05 (.97)	3.45 (1.01)	3.16 (1.03)	3.00 (1.41)	$F = 2.40$
Low risk	96	2.86 (1.07)	2.92 (.81)	3.54 (1.07)	2.33 (.58)	$p = .021$
		Rs11568817 <i>M(SD)</i> of importance				
Total		CC (%) -1	CA (%) 0	AA (%) 1	Unknown missing	ANOVA
High risk	195	3.32 (1.06)	3.27 (1.04)	3.25 (.98)	3.25 (1.50)	$F = .38$
Low risk	96	3.40 (1.10)	3.22 (1.00)	2.95 (.97)	3.00 (0)	$p = .916$
		Rs1390938 <i>M (SD)</i> of importance				
Total		AA (%) -1	AG (%) 0	GG (%) 1	Unknown missing	ANOVA
High risk	195	3.38 (1.19)	3.17 (1.03)	3.35 (1.02)	3.40 (1.07)	$F = .85$
Low risk	96	4.00 (1.00)	3.13 (1.06)	3.17 (1.00)	3.60 (.55)	$p = .549$
		Rs1800497 <i>M (SD)</i> of importance				
Total		AA (%) -1	AG (%) 0	GG (%) 1	Unknown missing	ANOVA
High risk	195	4.00 (.94)	3.32 (1.01)	3.21 (1.03)	2.50 (.71)	$F = 2.45$
Low risk	96	4.14 (.69)	3.35 (1.03)	2.96 (.98)	3.40 (.89)	$p = .019$
		Rs6311 <i>M (SD)</i> of importance				
Total		CC (%) -1	CT (%) 0	TT (%) 1	Unknown missing	ANOVA
High risk	195	3.25 (1.02)	3.31 (1.11)	3.24 (.83)	3.25 (.50)	$F = .58$
Low risk	96	3.00 (.95)	3.18 (1.05)	3.52 (1.05)	3.50 (.71)	$p = .770$

Offering some support for this hypothesis, neuroimaging shows common regions of parietal, precuneus, and occipital cortex to be thicker in people with a *sustained* spirituality over five years and thinner in people with depression (Liu et al., in press; Miller et al., 2014). Within the NIH pediatric imaging study, among those adolescents with mild-moderate levels of depression, those who also were high in transcendence (as measured by the Cloninger Self-Transcendence Scale) showed a differential cluster of depressive symptoms (less disrupted sleep and less anhedonia) and differential comorbidity (less substance abuse and conduct disorder)

then those low in self-transcendence (Miller & Barton, 2015).

The possibility that a subtype of mild to moderate depression is associated with specifically the dopaminergic pathway mirrors a great body of clinical literature on the existential struggle (reward or lack of reward; ability to perceive transcendence and sense value) around developmental transitions and life events to find a felt sense of ultimate connection, meaning and purpose (Benson, Scales, Syvertsen, & Roehlkepartain, 2012; Gottlieb, Still, & Newby-Clark, 2007). It is possible that the epigenetic interaction of the minor allele of DRD2, with fellow

Table 5  
Frequency and Rate of MDD by Genotype and Risk Group

		Rs2254298				
Total		AA (%) -1	AG (%) 0	GG (%) 1	Unknown	Chi-square test
High Risk	225	2 (100.00)	18 (33.96)	78 (49.37)	2 (16.67)	$\chi^2 = 2.71$
Low Risk	109	0 (.00)	4 (16.67)	20 (25.64)	2 (33.33)	$p = .439$
		Rs6298				
Total		AA (%) -1	AG (%) 0	GG (%) 1	Unknown	Chi-square test
High Risk	225	3 (25.00)	36 (48.00)	60 (43.80)	1 (100.00)	$\chi^2 = 2.44$
Low Risk	109	0 (.00)	13 (31.71)	13 (20.63)	0 (.00)	$p = .487$
		Rs130058				
Total		AA (%) -1	AT (%) 0	TT (%) 1	Unknown	Chi-square test
High Risk	225	7 (33.33)	44 (44.90)	46 (45.54)	3 (60.00)	$\chi^2 = 1.38$
Low Risk	109	1 (12.50)	11 (26.19)	14 (25.00)	0 (.00)	$p = .708$
		Rs11568817				
Total		CC (%) -1	CA (%) 0	AA (%) 1	Unknown	Chi-square test
High Risk	225	23 (46.94)	57 (49.57)	17 (30.36)	3 (60.00)	$\chi^2 = 1.41$
Low Risk	109	6 (19.35)	17 (31.48)	3 (13.64)	0 (.00)	$p = .702$
		Rs1390938				
Total		AA (%) -1	AG (%) 0	GG (%) 1	Unknown	Chi-square test
High Risk	225	1 (12.50)	49 (52.13)	47 (42.73)	3 (23.08)	$\chi^2 = 2.12$
Low Risk	109	1 (20.00)	15 (28.30)	9 (19.57)	1 (20.00)	$p = .548$
		Rs1800497				
Total		AA (%) -1	AG (%) 0	GG (%) 1	Unknown	Chi-square test
High Risk	225	4 (36.36)	28 (43.75)	66 (45.52)	2 (40.00)	$\chi^2 = 12.75$
Low Risk	109	2 (28.57)	13 (30.23)	8 (14.81)	3 (60.00)	$p = .005$
		Rs6311				
Total		CC (%) -1	CT (%) 0	TT (%) 1	Unknown missing	Chi-square test
High Risk	225	32 (46.38)	46 (40.35)	20 (54.05)	2 (40.00)	$\chi^2 = .72$
Low Risk	109	9 (27.27)	11 (22.92)	6 (23.08)	0 (.00)	$p = .868$

bonding and mood related genes, is essential for report of spirituality (by conferring a greater capacity for transcendence). The fellow genes associated with spirituality (VMAT1, OXTR, and 5HT1BR) without the presence of minor allele DRD2 instead may confer a likelihood for a subtype identified by positive psychology as secular “virtuous humanists” (Miller & Barton, 2015).

Lending some support, a differential susceptibility and resilience of the dopaminergic system based upon environment was explored through a recent meta-analysis. Children with the “at-risk” DRD2 genotype (with the minor

allele) fared worse in adverse environments but benefitted most in positive environments (Bakermans-Kranenburg & van Ijzendoorn, 2011). Similar findings supporting differential susceptibility have been found in studies examining the relation between DRD2 and aggression, intergenerational transmission of parenting, and response to prevention programs (Beaver & Belsky, 2012; Brody, Chen, & Beach, 2013; Simons et al., 2011). More generally, differential susceptibility also remains congruent with the theory of Reward Deficiency Syndrome (Comings & Blum, 2000), which suggests that the same individual at risk for addiction due to

a less efficient dopaminergic system is responsive to spiritual intervention, perhaps due to the stimulation of the dopaminergic system. In light of surrounding research on openness to experience and self-transcendence, it may be susceptibility and sensitivity to the environment—a capacity for spiritual perception—that drives the relationship between depression and spirituality in the association with DRD2 SNP rs1800497. In this case, perhaps either depression or spirituality may be the resulting phenomenology of DRD2. Further research conducted at multiple levels of analysis is required to understand whether functional differences attributable to dopamine gene receptor polymorphic variation underlie a phenotype that is both susceptible to depression and yet protected through spirituality.

A more commonly researched association between depression and bonding is reflected across the full sample, in both the high-risk and low-risk group (with particular strength in the high risk group), in the association between the oxytocin receptor gene (OXTR) rs2254298 and depression. This finding potentially suggests that the extensively researched pathway of OXTR to depression is a differential pathway to that of DRD2. To this body of research on OXTR, the current study replicates that OXTR interacts with familial risk for depression to predict psychopathology including depression and anxiety (Thompson, Parker, Hallmayer, Waugh, & Gotlib, 2011). Difference by risk group could not be definitively be established because of a nonsignificance interaction term (OXTR x risk-group). That in the low-risk group alone OXTR was not significant, however, gains support from previous work by Brune (2012) who suggests a distinct physiological profile based upon environment to diverge from the OXTR gene over the course of the life span. Drawing on a thorough review of existing literature on specifically the SNP rs2254298 (OXTR), Brune applies Belsky and Pluess (2009) theory of *differential susceptibility*, to suggest that the phenotypic expression of genetic variants of rs2254298, whether favorable or unfavorable, are dependent on early environmental factors. The OXTR-specific gene-environment interaction has been directly tested in at least two studies. In a study by Thompson et al. (2011), children with a heterozygous rs2254298 SNP in a high-risk

group (with familial risk for depression) and children with the same variant in a low-risk group varied significantly in measures of psychopathology, in that children in the high-risk group had significantly more depressive symptoms than those in the low-risk group. Further, when compared with children who were homozygous GG carriers in the low-risk group, low-risk children with a minor allele had the fewest depressive symptoms, suggesting that the GG carriers were less responsive to context than were the AG carriers.

In a low-income, African American sample, Bradley and colleagues (2011) showed that OXTR SNP rs53576 moderated the relationship between childhood maltreatment and both attachment style and emotional dysregulation. In the sample, male and female G allele carriers were at increased risk for emotional dysregulation and attachment problems after experiencing childhood abuse. However, in other studies, these same vulnerable G allele carriers also sought out social support in times of stress (Kim et al., 2010). In fact, the G allele had, in less adverse conditions (not including maltreatment), been associated with higher levels of empathy and sensitive parenting (Bakermans-Kranenburg & van Ijzendoorn, 2008; Rodrigues, Saslow, Garcia, John, & Keltner, 2009). Thus, Bradley suggested that the counterintuitive finding, that G allele individuals were at most risk in this sample, aligned with the findings that the G allele conferred resilience in other studies, by application of Belsky's model.

### **Research Question 3: Are There Differential Associations Based on Risk Status?**

There appears to be a suppression of the phenotypic expression of spirituality in people at high risk for depression. In the high-risk group none of the candidate genes were associated with personal importance of S/R, despite consistent positive findings across four genes in the low-risk group. Differential risk and protective factors by familial risk for depression is consistent with other studies on clinical outcomes from this longitudinal sample. In Fendrich, Warner, and Weissman (1990), family risk factors of poor marital adjustment, divorce, parent-child discord, affectionless control and

*DSM-III* diagnoses were predictive of depression and other diagnoses in offspring only in the low-risk group. In the high-risk group none of these usual family risk factors conferred risk for offspring diagnoses. In a 2006 study, Pilowsky and colleagues replicated this null finding in a subsequent generation of the same the study, among the children of these depressed parents 20 years later, showing that affectionless control remains predictive of MDD only in the low-risk group (Pilowsky, Wickramaratne, Nomura, & Weissman, 2006). These findings suggest that the impact of parental depression may outweigh other risk and protective factors in predicting clinical outcomes. In this study, it appears that in the high-risk group, familial ecology may in part suppress the phenotypic expression of genes otherwise associated with spirituality.

Our findings on potential suppression of the phenotype of spirituality speak to the intergenerational conference of risk for depression, and seem to point to opportunity for prevention and intervention in offspring. Previous prevention-intervention research shows that the intergenerational transmission of depression can be disrupted by preemptively supporting protective factors in offspring. (Beardslee, Gladstone, & O'Connor, 2011; Verdelli et al., 2004), raising the possibility that the fostering of spirituality in offspring of depressives might be preventative against a subsequent offspring depression.

Development of spirituality in offspring is partially dependent on the lived spirituality of a parental figure, as well as his or her tendency to clearly articulate and support spiritual beliefs and values (Boyatzis, Dollahite, & Marks, 2006). Parental expression and transmission of spirituality may be mitigated by a mood disorder generating a depressogenic outlook (Gur, Miller, Warner, Wickramaratne, & Weissman, 2005). However, previous research on this same sample shows that the intergenerational transmission of religious denomination, (whether or not there is high level of parental spirituality) decreases the likelihood of transmission of depression and anxiety in offspring (in both high and low-risk groups) by 91% (Jacobs et al., 2012). Offspring of depressed parents, who are exposed in childhood to religious community, may find other adults who exhibit a strong spirituality, support for their own spirituality, and a "road map" to spiritual life derive the customary protective benefits of spirituality. Se-

lective spiritual socialization (Miller et al., 2001), previously to have been identified in offspring of Opiate addicts, shows that youth tend to become concordant with the spirituality held by the healthiest committed parent figure in their lives, and in turn derive the protective benefits of spirituality. From a developmental perspective, evidence converges to suggest that prevention against the intergenerational transmission of severe recurrent depression may be derived from fellow healthy adults and a community that supports offspring spirituality.

**Limitations.** The study design has the chief limitation of a single time assessment of religion and spirituality, drawn from the available data in this 30-year longitudinal design. The single-item measure further conflates religion and spirituality, which are two distinct but related constructs and ways of living. A second customary limitation in single-gene research is that identification of single genes can point to pathways but does not fully explain the relationship between gene and behavior.

**Clinical implications.** Spiritually oriented psychotherapies often hold that suffering and symptoms of depression are an opportunity for spiritual growth (Richards & Bergin, 2014; Sperry & Shafranske, 2005). Identification of a common physiology, including a common genetic foundation between transcendence and depression (in DRD2), offers some biologically based evidence to support the engagement of suffering as an opening for a deepening of spirituality. In other words, the current existing body of psychotherapies that engage suffering and symptoms of depression as an opportunity for an increased spiritual awareness may be embracing an innate developmental or regulatory process with a genetic foundation. Future innovations in treatments might further harvest this innate human potential for healing and growth in the form of intensified transcendent awareness through suffering.

## Conclusion

Spirituality and/or its expression as religiousness (S/R) may be a phenotype of DRD2, HT1B, VMAT1 and OXTR, in people at low risk for depression. Uniquely the minor allele of DRD2 (previously linked with reward and transcendence) is associated with both importance of S/R and increased risk for depression in people at low familial risk for depression, perhaps implicating a

common pathway or mechanism dependent on environment (outer environment or practice of inner life). High familial risk for depression may suppress the phenotypic expression of these genes otherwise associated with spirituality. The association between MDD and bonding is associated with OXTR and found across both high and low risk for depression, suggesting a potentially differential pathway of depression.

## References

- Acevedo, S. F., Valencia, C., Lutter, M., & McAdams, C. J. (2015). Severity of eating disorder symptoms related to oxytocin receptor polymorphisms in anorexia nervosa. *Psychiatry Research*, *228*, 641–648. <http://dx.doi.org/10.1016/j.psychres.2015.05.040>
- Akrawi, D., Bartrop, R., Potter, U., & Touyz, S. (2015). Religiosity, spirituality in relation to disordered eating and body image concerns: A systematic review. *Journal of Eating Disorders*, *3*, 29. <http://dx.doi.org/10.1186/s40337-015-0064-0>
- Aspé-Sánchez, M., Moreno, M., Rivera, M. I., Rossi, A., & Ewer, J. (2016). Oxytocin and vasopressin receptor gene polymorphisms: Role in social and psychiatric traits. *Frontiers in Neuroscience*, *9*, 510.
- Bakermans-Kranenburg, M. J., & van Ijzendoorn, M. H. (2008). Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting. *Social Cognitive and Affective Neuroscience*, *3*, 128–134. <http://dx.doi.org/10.1093/scan/nsn004>
- Bakermans-Kranenburg, M. J., & van Ijzendoorn, M. H. (2011). Differential susceptibility to rearing environment depending on dopamine-related genes: New evidence and a meta-analysis. *Development and Psychopathology*, *23*, 39–52. <http://dx.doi.org/10.1017/S0954579410000635>
- Baldinger, P., Kraus, C., Rami-Mark, C., Gryglewski, G., Kranz, G. S., Haeusler, D., . . . Lanzenberger, R. (2015). Interaction between 5-HTTLPR and 5-HT1B genotype status enhances cerebral 5-HT1A receptor binding. *NeuroImage*, *111*, 505–512. <http://dx.doi.org/10.1016/j.neuroimage.2015.01.049>
- Barton, Y. A., Barkin, S. H., & Miller, L. (in press). Deconstructing depression: A latent profile analysis of potential depressive subtypes in emerging adults. *Spirituality in Clinical Practice*.
- Beardslee, W. R., Gladstone, T. R., & O'Connor, E. E. (2011). Transmission and prevention of mood disorders among children of affectively ill parents: A review. *Journal of the American Academy of Child & Adolescent Psychiatry*, *50*, 1098–1109. <http://dx.doi.org/10.1016/j.jaac.2011.07.020>
- Beaver, K. M., & Belsky, J. (2012). Gene-environment interaction and the intergenerational transmission of parenting: Testing the differential-susceptibility hypothesis. *Psychiatric Quarterly*, *83*, 29–40. <http://dx.doi.org/10.1007/s11126-011-9180-4>
- Beaver, K. M., Gibson, C. L., Jennings, W. G., & Ward, J. T. (2009). A gene X environment interaction between DRD2 and religiosity in the prediction of adolescent delinquent involvement in a sample of males. *Biodemography and Social Biology*, *55*, 71–81. <http://dx.doi.org/10.1080/19485560903054689>
- Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin*, *135*, 885–908. <http://dx.doi.org/10.1037/a0017376>
- Benson, P. L., Scales, P. C., Syvertsen, A. K., & Roehlkepartain, E. C. (2012). Is youth spiritual development a universal developmental process? An international exploration. *The Journal of Positive Psychology*, *7*, 453–470. <http://dx.doi.org/10.1080/17439760.2012.732102>
- Bhagwagar, Z., Rabiner, E. A., Sargent, P. A., Grasby, P. M., & Cowen, P. J. (2004). Persistent reduction in brain serotonin1A receptor binding in recovered depressed men measured by positron emission tomography with [<sup>11</sup>C]WAY-100635. *Molecular Psychiatry*, *9*, 386–392. <http://dx.doi.org/10.1038/sj.mp.4001401>
- Blum, K., Chen, A. L., Giordano, J., Borsten, J., Chen, T. J., Hauser, M., . . . Barh, D. (2012). The addictive brain: All roads lead to dopamine. *Journal of Psychoactive Drugs*, *44*, 134–143. <http://dx.doi.org/10.1080/02791072.2012.685407>
- Blum, K., Febo, M., McLaughlin, T., Cronjé, F. J., Han, D., & Gold, S. M. (2014). Hatching the behavioral addiction egg: Reward Deficiency Solution System (RDSS) as a function of dopaminergic neurogenetics and brain functional connectivity linking all addictions under a common rubric. *Journal of Behavioral Addictions*, *3*, 149–156. <http://dx.doi.org/10.1556/JBA.3.2014.019>
- Blum, K., & Kozlowski, G. P. (1990). Ethanol and neuromodulator interactions: A cascade model of reward. In H. Ollat, S. Parvez, & H. Parvez (Eds.), *Alcohol and behavior* (pp. 131–149). Utrecht, the Netherlands: VSP Press.
- Blum, K., Noble, E. P., Sheridan, P. J., Montgomery, A., Ritchie, T., Jagadeeswaran, P., . . . Cohn, J. B. (1990). Allelic association of human dopamine D2 receptor gene in alcoholism. *Journal of the American Medical Association*, *263*, 2055–2060. <http://dx.doi.org/10.1001/jama.1990.03440150063027>
- Blum, K., Sheridan, P. J., Wood, R. C., Braverman, E. R., Chen, T. J., Cull, J. G., & Comings, D. E. (1996). The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. *Journal of the Royal Society of Medicine*, *89*, 396–400.

- Borg, J., André, B., Soderstrom, H., & Farde, L. (2003). The serotonin system and spiritual experiences. *The American Journal of Psychiatry*, *160*, 1965–1969. <http://dx.doi.org/10.1176/appi.ajp.160.11.1965>
- Boyatzis, C. J., Dollahite, D. C., & Marks, L. D. (2006). The family as a context for religious and spiritual development in children and youth. In E. C. Roehlkepartain, P. E. King, L. Wagener, & P. L. Benson (Eds.), *The handbook of spiritual development in childhood and adolescence* (pp. 297–309). Thousand Oaks, CA: Sage. <http://dx.doi.org/10.4135/9781412976657.n21>
- Bradley, B., Westen, D., Mercer, K. B., Binder, E. B., Jovanovic, T., Crain, D., . . . Heim, C. (2011). Association between childhood maltreatment and adult emotional dysregulation in a low-income, urban, African American sample: Moderation by oxytocin receptor gene. *Development and Psychopathology*, *23*, 439–452. <http://dx.doi.org/10.1017/S0954579411000162>
- Brody, G. H., Chen, Y. F., & Beach, S. R. (2013). Differential susceptibility to prevention: GABAergic, dopaminergic, and multilocus effects. *Journal of Child Psychology and Psychiatry*, *54*, 863–871. <http://dx.doi.org/10.1111/jcpp.12042>
- Brüne, M. (2012). Does the oxytocin receptor (OXTR) polymorphism (rs2254298) confer ‘vulnerability’ for psychopathology or ‘differential susceptibility’? Insights from evolution. *BMC Medicine*, *10*, 38. <http://dx.doi.org/10.1186/1741-7015-10-38>
- Butler, P. M., McNamara, P., & Durso, R. (2010). Deficits in the automatic activation of religious concepts in patients with Parkinson’s disease. *Journal of the International Neuropsychological Society*, *16*, 252–261. <http://dx.doi.org/10.1017/S1355617709991202>
- Butovskaya, P. R., Lazebnij, O. E., Fekhetdinova, D. I., Vasil’ev, V. A., Prosikova, E. A., Lysenko, V. V., . . . Butovskaya, M. L. (2015). The relationship between polymorphism of four serotonergic genes (5-HTTL, 5-HT1A, 5-HT2A, and MAOA) and personality in wrestlers and control group. *Molecular Genetics, Microbiology and Virology*, *30*, 165–172. <http://dx.doi.org/10.3103/S0891416815040035>
- Cao, J., LaRocque, E., & Li, D. (2013). Associations of the 5-hydroxytryptamine (serotonin) receptor 1B gene (HTR1B) with alcohol, cocaine, and heroin abuse. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *162B*, 169–176. <http://dx.doi.org/10.1002/ajmg.b.32128>
- Caylak, E. (2012). Biochemical and genetic analyses of childhood attention deficit/hyperactivity disorder. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *159B*, 613–627. <http://dx.doi.org/10.1002/ajmg.b.32077>
- Chen, D., Liu, F., Shang, Q., Song, X., Miao, X., & Wang, Z. (2011). Association between polymorphisms of DRD2 and DRD4 and opioid dependence: Evidence from the current studies. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *156B*, 661–670. <http://dx.doi.org/10.1002/ajmg.b.31208>
- Chen, M. H., & Yang, Q. (2010). GWAF: An R package for genome-wide association analyses with family data. *Bioinformatics*, *26*, 580–581. <http://dx.doi.org/10.1093/bioinformatics/btp710>
- Christiansen, L., Tan, Q., Iachina, M., Bathum, L., Kruse, T. A., McGue, M., & Christensen, K. (2007). Candidate gene polymorphisms in the serotonergic pathway: Influence on depression symptomatology in an elderly population. *Biological Psychiatry*, *61*, 223–230. <http://dx.doi.org/10.1016/j.biopsych.2006.03.046>
- Cloninger, C. R. (2008). The psychobiological theory of temperament and character: Comment on Farmer and Goldberg (2008). *Psychological Assessment*, *20*, 292–299. <http://dx.doi.org/10.1037/a0012933>
- Comings, D. E., & Blum, K. (2000). Reward deficiency syndrome: Genetic aspects of behavioral disorders. *Progress in Brain Research*, *126*, 325–341. [http://dx.doi.org/10.1016/S0079-6123\(00\)26022-6](http://dx.doi.org/10.1016/S0079-6123(00)26022-6)
- Comings, D. E., Gade-Andavolu, R., Gonzalez, N., Wu, S., Muhleman, D., Blake, H., . . . MacMurray, J. P. (2000). A multivariate analysis of 59 candidate genes in personality traits: The temperament and character inventory. *Clinical Genetics*, *58*, 375–385. <http://dx.doi.org/10.1034/j.1399-0004.2000.580508.x>
- Comings, D. E., Saucier, G., & MacMurray, J. P. (2002). Role of DRD2 and other dopamine genes in personality traits. *Molecular genetics and the human personality*, *165*.
- Conner, T. S., Jensen, K. P., Tennen, H., Furneaux, H. M., Kranzler, H. R., & Covault, J. (2010). Functional polymorphisms in the serotonin 1B receptor gene (HTR1B) predict self-reported anger and hostility among young men. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *153B*, 67–78.
- Costa, B., Pini, S., Gabelloni, P., Abelli, M., Lari, L., Cardini, A., . . . Martini, C. (2009). Oxytocin receptor polymorphisms and adult attachment style in patients with depression. *Psychoneuroendocrinology*, *34*, 1506–1514. <http://dx.doi.org/10.1016/j.psyneuen.2009.05.006>
- Dadds, M. R., Moul, C., Cauchi, A., Dobson-Stone, C., Hawes, D. J., Brennan, J., . . . Ebstein, R. E. (2014). Polymorphisms in the oxytocin receptor gene are associated with the development of psychopathy. *Development and Psychopathology*, *26*, 21–31. <http://dx.doi.org/10.1017/S0954579413000485>

- Dickel, D. E., Veenstra-VanderWeele, J., Bivens, N. C., Wu, X., Fischer, D. J., Van Etten-Lee, M., . . . Hanna, G. L. (2007). Association studies of serotonin system candidate genes in early-onset obsessive-compulsive disorder. *Biological Psychiatry*, *61*, 322–329. <http://dx.doi.org/10.1016/j.biopsych.2006.09.030>
- Drevets, W. C., Frank, E., Price, J. C., Kupfer, D. J., Holt, D., Greer, P. J., . . . Mathis, C. (1999). PET imaging of serotonin 1A receptor binding in depression. *Biological Psychiatry*, *46*, 1375–1387. [http://dx.doi.org/10.1016/S0006-3223\(99\)00189-4](http://dx.doi.org/10.1016/S0006-3223(99)00189-4)
- Drevets, W. C., Thase, M. E., Moses-Kolko, E. L., Price, J., Frank, E., Kupfer, D. J., & Mathis, C. (2007). Serotonin-1A receptor imaging in recurrent depression: Replication and literature review. *Nuclear Medicine and Biology*, *34*, 865–877. <http://dx.doi.org/10.1016/j.nucmedbio.2007.06.008>
- Dutta, N., Helton, S. G., Schwandt, M., Zhu, X., Momenan, R., & Lohoff, F. W. (2016). Genetic Variation in the Vesicular Monoamine Transporter 1 (VMAT1/SLC18A1) Gene and Alcohol Withdrawal Severity. *Alcoholism: Clinical and Experimental Research*, *40*, 474–481. <http://dx.doi.org/10.1111/acer.12991>
- Eisenstein, S. A., Bogdan, R., Love-Gregory, L., Corral-Frías, N. S., Koller, J. M., Black, K. J., . . . Hershey, T. (2016). Prediction of striatal D2 receptor binding by DRD2/ANKK1 TaqIA allele status. *Synapse*, *70*, 418–431. <http://dx.doi.org/10.1002/syn.21916>
- El-Ibiary, S. Y., Hamilton, S. P., Abel, R., Erdman, C. A., Robertson, P. A., & Finley, P. R. (2013). A pilot study evaluating genetic and environmental factors for postpartum depression. *Innovations in Clinical Neuroscience*, *10*(9–10), 15–22.
- Erickson, J. D., Schafer, M. K., Bonner, T. I., Eiden, L. E., & Weihe, E. (1996). Distinct pharmacological properties and distribution in neurons and endocrine cells of two isoforms of the human vesicular monoamine transporter. *Proceedings of the National Academy of Sciences of the United States of America*, *93*, 5166–5171. <http://dx.doi.org/10.1073/pnas.93.10.5166>
- Fehr, C., Grintschuk, N., Szegedi, A., Angheliescu, I., Klawe, C., Singer, P., . . . Dahmen, N. (2000). The HTR1B 861G>C receptor polymorphism among patients suffering from alcoholism, major depression, anxiety disorders and narcolepsy. *Psychiatry Research*, *97*, 1–10. [http://dx.doi.org/10.1016/S0165-1781\(00\)00215-8](http://dx.doi.org/10.1016/S0165-1781(00)00215-8)
- Feldman, R., Monakhov, M., Pratt, M., & Ebstein, R. P. (2016). Oxytocin pathway genes: Evolutionary ancient system impacting on human affiliation, sociality, and psychopathology. *Biological Psychiatry*, *79*, 174–184. <http://dx.doi.org/10.1016/j.biopsych.2015.08.008>
- Fendrich, M., Warner, V., & Weissman, M. M. (1990). Family risk factors, parental depression, and psychopathology in offspring. *Developmental Psychology*, *26*, 40–50. <http://dx.doi.org/10.1037/0012-1649.26.1.40>
- Giegling, I., Hartmann, A. M., Möller, H. J., & Rujescu, D. (2006). Anger- and aggression-related traits are associated with polymorphisms in the 5-HT-2A gene. *Journal of Affective Disorders*, *96*(1–2), 75–81. <http://dx.doi.org/10.1016/j.jad.2006.05.016>
- Giordano, A. L., Prosek, E. A., & Lankford, C. T. (2014). Predicting empathy: The role of religion and spirituality. *Journal of Professional Counseling, Practice, Theory, & Research*, *41*, 53.
- Gluskin, B. S., & Mickey, B. J. (2016). Genetic variation and dopamine D2 receptor availability: A systematic review and meta-analysis of human in vivo molecular imaging studies. *Translational Psychiatry*, *6*, e747. <http://dx.doi.org/10.1038/tp.2016.22>
- Gottlieb, B. H., Still, E., & Newby-Clark, I. R. (2007). Types and precipitants of growth and decline in emerging adulthood. *Journal of Adolescent Research*, *22*, 132–155. <http://dx.doi.org/10.1177/0743558406298201>
- Gu, L., Long, J., Yan, Y., Chen, Q., Pan, R., Xie, X., . . . Su, L. (2013). HTR2A–1438A/G polymorphism influences the risk of schizophrenia but not bipolar disorder or major depressive disorder: A meta-analysis. *Journal of Neuroscience Research*, *91*, 623–633. <http://dx.doi.org/10.1002/jnr.23180>
- Gur, M., Miller, L., Warner, V., Wickramaratne, P., & Weissman, M. (2005). Maternal depression and the intergenerational transmission of religion. *Journal of Nervous and Mental Disease*, *193*, 338–345. <http://dx.doi.org/10.1097/01.nmd.0000161701.05878.8a>
- Hakulinen, C., Jokela, M., Hintsanen, M., Merjonen, P., Pulkki-Råback, L., Seppälä, I., . . . Keltikangas-Järvinen, L. (2013). Serotonin receptor 1B genotype and hostility, anger and aggressive behavior through the lifespan: The Young Finns study. *Journal of Behavioral Medicine*, *36*, 583–590. <http://dx.doi.org/10.1007/s10865-012-9452-y>
- Ham, B. J., Kim, Y. H., Choi, M. J., Cha, J. H., Choi, Y. K., & Lee, M. S. (2004). Serotonergic genes and personality traits in the Korean population. *Neuroscience Letters*, *354*, 2–5. [http://dx.doi.org/10.1016/S0304-3940\(03\)00753-5](http://dx.doi.org/10.1016/S0304-3940(03)00753-5)
- Hamer, D. H. (2005). *The God gene: How faith is hardwired into our genes*. New York, NY: Anchor.
- Henningsgaard, J. M., & Arnau, R. C. (2008). Relationships between religiosity, spirituality, and personality: A multivariate analysis. *Personality and Individual Differences*, *45*, 703–708.

- Huang, Y. Y., Grailhe, R., Arango, V., Hen, R., & Mann, J. J. (1999). Relationship of psychopathology to the human serotonin 1B genotype and reeceptor binding kinetics in postmortem brain tissue. *Neuropsychopharmacology*, *21*, 238–246.
- Huang, Y. Y., Oquendo, M. A., Harkavy Friedman, J. M., Greenhill, L. L., Brodsky, B., Malone, K. M., . . . Mann, J. J. (2003). Substance abuse disorder and major depression are associated with the human 5-HT1B receptor gene (HTR1B) G861C polymorphism. *Neuropsychopharmacology*, *28*, 163–169. <http://dx.doi.org/10.1038/sj.npp.1300000>
- Jacob, S., Brune, C. W., Carter, C. S., Leventhal, B. L., Lord, C., & Cook, E. H., Jr. (2007). Association of the oxytocin receptor gene (OXTR) in Caucasian children and adolescents with autism. *Neuroscience Letters*, *417*, 6–9. <http://dx.doi.org/10.1016/j.neulet.2007.02.001>
- Jacobs, M., Miller, L., Wickramaratne, P., Gameroff, M., & Weissman, M. M. (2012). Family religion and psychopathology in children of depressed mothers: Ten-year follow-up. *Journal of Affective Disorders*, *136*, 320–327. <http://dx.doi.org/10.1016/j.jad.2011.11.030>
- Jin, C., Xu, W., Yuan, J., Wang, G., & Cheng, Z. (2013). Meta-analysis of association between the –1438A/G (rs6311) polymorphism of the serotonin 2A receptor gene and major depressive disorder. *Neurological Research*, *35*, 7–14. <http://dx.doi.org/10.1179/1743132812Y.0000000111>
- Kalbitzer, J., Frokjaer, V. G., Erritzoe, D., Svarer, C., Cumming, P., Nielsen, F. A., . . . Knudsen, G. M. (2009). The personality trait openness is related to cerebral 5-HTT levels. *NeuroImage*, *45*, 280–285. <http://dx.doi.org/10.1016/j.neuroimage.2008.12.001>
- Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., . . . Ryan, N. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*, 980–988. <http://dx.doi.org/10.1097/00004583-199707000-00021>
- Kaufman, J., DeLorenzo, C., Choudhury, S., & Parsey, R. V. (2016). The 5-HT1A receptor in major depressive disorder. *European Neuropsychopharmacology*, *26*, 397–410. <http://dx.doi.org/10.1016/j.euroneuro.2015.12.039>
- Kim, H. S., Sherman, D. K., Sasaki, J. Y., Xu, J., Chu, T. Q., Ryu, C., . . . Taylor, S. E. (2010). Culture, distress, and oxytocin receptor polymorphism (OXTR) interact to influence emotional support seeking. *Proceedings of the National Academy of Sciences of the United States of America*, *107*, 15717–15721. <http://dx.doi.org/10.1073/pnas.1010830107>
- Kim, J. H., Son, Y. D., Kim, J. H., Choi, E. J., Lee, S. Y., Joo, Y. H., . . . Cho, Z. H. (2015). Self-transcendence trait and its relationship with in vivo serotonin transporter availability in brainstem raphe nuclei: An ultra-high resolution PET-MRI study. *Brain Research*, *1629*, 63–71. <http://dx.doi.org/10.1016/j.brainres.2015.10.006>
- Kishi, T., Yoshimura, R., Fukuo, Y., Okochi, T., Matsunaga, S., Umene-Nakano, W., . . . Iwata, N. (2013). The serotonin 1A receptor gene confer susceptibility to mood disorders: Results from an extended meta-analysis of patients with major depression and bipolar disorder. *European Archives of Psychiatry and Clinical Neuroscience*, *263*, 105–118. <http://dx.doi.org/10.1007/s00406-012-0337-4>
- Kjaer, T. W., Bertelsen, C., Piccini, P., Brooks, D., Alving, J., & Lou, H. C. (2002). Increased dopamine tone during meditation-induced change of consciousness. *Cognitive Brain Research*, *13*, 255–259. [http://dx.doi.org/10.1016/S0926-6410\(01\)00106-9](http://dx.doi.org/10.1016/S0926-6410(01)00106-9)
- Klein, D. N., Lewinsohn, P. M., Rohde, P., Seeley, J. R., & Durbin, C. E. (2002). Clinical features of major depressive disorder in adolescents and their relatives: Impact on familial aggregation, implications for phenotype definition, and specificity of transmission. *Journal of Abnormal Psychology*, *111*, 98–106. <http://dx.doi.org/10.1037/0021-843X.111.1.98>
- Koenig, H. G. (2009). Research on religion, spirituality, and mental health: A review. *Canadian Journal of Psychiatry*, *54*, 283–291.
- Lappalainen, J., Long, J. C., Eggert, M., Ozaki, N., Robin, R. W., Brown, G. L., . . . Goldman, D. (1998). Linkage of antisocial alcoholism to the serotonin 5-HT1B receptor gene in 2 populations. *Archives of General Psychiatry*, *55*, 989–994. <http://dx.doi.org/10.1001/archpsyc.55.11.989>
- Lee, S. Y., Lin, W. W., Huang, S. Y., Kuo, P. H., Wang, C. L., Wu, P. L., . . . Lu, R. B. (2009). The relationship between serotonin receptor 1B polymorphisms A-161T and alcohol dependence. *Alcoholism: Clinical and Experimental Research*, *33*, 1589–1595. <http://dx.doi.org/10.1111/j.1530-0277.2009.00990.x>
- Lenze, E. J., Dixon, D., Nowotny, P., Lotrich, F. E., Doré, P. M., Pollock, B. G., . . . Butters, M. A. (2013). Escitalopram reduces attentional performance in anxious older adults with high-expression genetic variants at serotonin 2A and 1B receptors. *International Journal of Neuropsychopharmacology*, *16*, 279–288. <http://dx.doi.org/10.1017/S1461145712000351>
- Lerer, E., Levi, S., Salomon, S., Darvasi, A., Yirmiya, N., & Ebstein, R. P. (2008). Association between the oxytocin receptor (OXTR) gene and autism: Relationship to Vineland Adaptive Behav-

- ior Scales and cognition. *Molecular Psychiatry*, *13*, 980–988. <http://dx.doi.org/10.1038/sj.mp.4002087>
- Li, L., Bao, Y., He, S., Wang, G., Guan, Y., Ma, D., . . . Yang, J. (2016). The association between genetic variants in the dopaminergic system and posttraumatic stress disorder: A meta-analysis. *Medicine*, *95*, e3074. <http://dx.doi.org/10.1097/MD.0000000000003074>
- Lieb, R., Isensee, B., Höfler, M., Pfister, H., & Wittchen, H. U. (2002). Parental major depression and the risk of depression and other mental disorders in offspring: A prospective-longitudinal community study. *Archives of General Psychiatry*, *59*, 365–374. <http://dx.doi.org/10.1001/archpsyc.59.4.365>
- Lin, J. Y., Jiang, M. Y., Kan, Z. M., & Chu, Y. (2014). Influence of 5-HTR2A genetic polymorphisms on the efficacy of antidepressants in the treatment of major depressive disorder: A meta-analysis. *Journal of Affective Disorders*, *168*, 430–438. <http://dx.doi.org/10.1016/j.jad.2014.06.012>
- Liu, J., Svob, C., Wickmarantre, P., Hao, X., Talati, A., Kayser, J., . . . Weissman, M. R. (in press). Neuroanatomical correlates of familial risk for depression and religiosity/spirituality. *Spirituality in Clinical Practice*.
- Liu, X., Kawamura, Y., Shimada, T., Otowa, T., Koishi, S., Sugiyama, T., . . . Sasaki, T. (2010). Association of the oxytocin receptor (OXTR) gene polymorphisms with autism spectrum disorder (ASD) in the Japanese population. *Journal of Human Genetics*, *55*, 137–141. <http://dx.doi.org/10.1038/jhg.2009.140>
- Lohoff, F. W., Hodge, R., Narasimhan, S., Nall, A., Ferraro, T. N., Mickey, B. J., . . . Doyle, G. A. (2014). Functional genetic variants in the vesicular monoamine transporter 1 modulate emotion processing. *Molecular Psychiatry*, *19*, 129–139. <http://dx.doi.org/10.1038/mp.2012.193>
- Lohoff, F. W., Lautenschlager, M., Mohr, J., Ferraro, T. N., Sander, T., & Gallinat, J. (2008). Association between variation in the vesicular monoamine transporter 1 gene on chromosome 8p and anxiety-related personality traits. *Neuroscience Letters*, *434*, 41–45. <http://dx.doi.org/10.1016/j.neulet.2008.01.024>
- Lorenzi, C., Serretti, A., Mandelli, L., Tubazio, V., Ploia, C., & Smeraldi, E. (2005). 5-HT 1A polymorphism and self-transcendence in mood disorders. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *137B*, 33–35. <http://dx.doi.org/10.1002/ajmg.b.30111>
- Lucette, A., Ironson, G., Pargament, K. I., & Krause, N. (2016). Spirituality and religiousness are associated with fewer depressive symptoms in individuals with medical conditions. *Psychosomatics*, *57*, 505–513. <http://dx.doi.org/10.1016/j.psych.2016.03.005>
- Lucht, M. J., Barnow, S., Sonnenfeld, C., Rosenberger, A., Grabe, H. J., Schroeder, W., . . . Rosskopf, D. (2009). Associations between the oxytocin receptor gene (OXTR) and affect, loneliness and intelligence in normal subjects. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *33*, 860–866. <http://dx.doi.org/10.1016/j.pnpbp.2009.04.004>
- Mandelli, L., & Serretti, A. (2013). Gene environment interaction studies in depression and suicidal behavior: An update. *Neuroscience and Biobehavioral Reviews*, *37*, 2375–2397.
- Mannuzza, S., Fyer, A. J., Klein, D. F., & Endicott, J. (1986). Schedule for Affective Disorders and Schizophrenia—Lifetime Version modified for the study of anxiety disorders (SADS-LA): Rationale and conceptual development. *Journal of Psychiatric Research*, *20*, 317–325. [http://dx.doi.org/10.1016/0022-3956\(86\)90034-8](http://dx.doi.org/10.1016/0022-3956(86)90034-8)
- Miller, L., Bansal, R., Wickramaratne, P., Hao, X., Tenke, C. E., Weissman, M. M., & Peterson, B. S. (2014). Neuroanatomical correlates of religiosity and spirituality: A study in adults at high and low familial risk for depression. *Journal of the American Medical Association Psychiatry*, *71*, 128–135. <http://dx.doi.org/10.1001/jamapsychiatry.2013.3067>
- Miller, L., & Barton, Y. A. (2015). Developmental depression in adolescents: A potential sub-type based on neural correlates and comorbidity. *Journal of Religion and Health*, *54*, 817–828. <http://dx.doi.org/10.1007/s10943-015-0047-0>
- Miller, L., Davies, M., & Greenwald, S. (2000). Religiosity and substance use and abuse among adolescents in the National Comorbidity Survey. *Journal of the American Academy of Child & Adolescent Psychiatry*, *39*, 1190–1197. <http://dx.doi.org/10.1097/00004583-200009000-00020>
- Miller, L., Weissman, M., Gur, M., & Adams, P. (2001). Religiousness and substance use in children of opiate addicts. *Journal of Substance Abuse*, *13*, 323–336. [http://dx.doi.org/10.1016/S0899-3289\(01\)00084-0](http://dx.doi.org/10.1016/S0899-3289(01)00084-0)
- Miller, W. R. (1998). Researching the spiritual dimensions of alcohol and other drug problems. *Addiction*, *93*, 979–990. <http://dx.doi.org/10.1046/j.1360-0443.1998.9379793.x>
- Moore, R. C., Eyler, L., Mills, P. J., O'Hara, R. M., Wachmann, K., & Lavretsky, H. (2015). Biology of positive psychiatry. In D. V. Jeste & B. W. Palmer (Eds.), *Positive psychiatry: A clinical handbook*. Washington, DCL American Psychiatric Publishing. <http://dx.doi.org/10.1176/appi.books.9781615370818.dj13>
- Munafò, M. R., Matheson, I. J., & Flint, J. (2007). Association of the DRD2 gene Taq1A polymor-

- phism and alcoholism: A meta-analysis of case-control studies and evidence of publication bias. *Molecular Psychiatry*, *12*, 454–461.
- Murrough, J. W., Henry, S., Hu, J., Gallezot, J. D., Planeta-Wilson, B., Neumaier, J. F., & Neumeister, A. (2011). Reduced ventral striatal/ventral pallidal serotonin1B receptor binding potential in major depressive disorder. *Psychopharmacology*, *213*, 547–553. <http://dx.doi.org/10.1007/s00213-010-1881-0>
- Nemoda, Z., Lyons-Ruth, K., Szekely, A., Bertha, E., Faludi, G., & Sasvari-Szekely, M. (2010). Association between dopaminergic polymorphisms and borderline personality traits among at-risk young adults and psychiatric inpatients. *Behavioral and Brain Functions*, *6*, 4. <http://dx.doi.org/10.1186/1744-9081-6-4>
- Nemoda, Z., Szekely, A., & Sasvari-Szekely, M. (2011). Psychopathological aspects of dopaminergic gene polymorphisms in adolescence and young adulthood. *Neuroscience and Biobehavioral Reviews*, *35*, 1665–1686. <http://dx.doi.org/10.1016/j.neubiorev.2011.04.002>
- Neville, M. J., Johnstone, E. C., & Walton, R. T. (2004). Identification and characterization of ANKK1: A novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. *Human Mutation*, *23*, 540–545. <http://dx.doi.org/10.1002/humu.20039>
- Newberg, A. B., & Iversen, J. (2003). The neural basis of the complex mental task of meditation: Neurotransmitter and neurochemical considerations. *Medical Hypotheses*, *61*, 282–291. [http://dx.doi.org/10.1016/S0306-9877\(03\)00175-0](http://dx.doi.org/10.1016/S0306-9877(03)00175-0)
- Nilsson, K. W., Damberg, M., Öhrvik, J., Leppert, J., Lindström, L., Anckarsäter, H., & Oreland, L. (2007). Genes encoding for AP-2β and the Serotonin Transporter are associated with the Personality Character Spiritual Acceptance. *Neuroscience Letters*, *411*, 233–237. <http://dx.doi.org/10.1016/j.neulet.2006.10.051>
- Noble, E. P. (2003). D2 dopamine receptor gene in psychiatric and neurologic disorders and its phenotypes. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *116B*, 103–125. <http://dx.doi.org/10.1002/ajmg.b.10005>
- Park, J. H., Gail, M. H., Weinberg, C. R., Carroll, R. J., Chung, C. C., Wang, Z., . . . Chatterjee, N. (2011). Distribution of allele frequencies and effect sizes and their interrelationships for common genetic susceptibility variants. *Proceedings of the National Academy of Sciences of the United States of America*, *108*, 18026–18031. <http://dx.doi.org/10.1073/pnas.1114759108>
- Parsons, M. J., D'Souza, U. M., Arranz, M. J., Kerwin, R. W., & Makoff, A. J. (2004). The –1438A/G polymorphism in the 5-hydroxytryptamine type 2A receptor gene affects promoter activity. *Biological Psychiatry*, *56*, 406–410. <http://dx.doi.org/10.1016/j.biopsych.2004.06.020>
- Peciña, M., Mickey, B. J., Love, T., Wang, H., Langenecker, S. A., Hodgkinson, C., . . . Zubieta, J. K. (2013). DRD2 polymorphisms modulate reward and emotion processing, dopamine neurotransmission and openness to experience. *Cortex*, *49*, 877–890. <http://dx.doi.org/10.1016/j.cortex.2012.01.010>
- Perroud, N. (2009). Religion/spirituality and neuropsychiatry. In P. Huguelet & H. G. Koenig (Eds.), *Religion and spirituality in psychiatry*. Cambridge, UK: Cambridge University Press.
- Perroud, N., Bondolfi, G., Uher, R., Gex-Fabry, M., Aubry, J. M., Bertschy, G., . . . Kosel, M. (2011). Clinical and genetic correlates of suicidal ideation during antidepressant treatment in a depressed outpatient sample. *Pharmacogenomics*, *12*, 365–377. <http://dx.doi.org/10.2217/pgs.10.189>
- Pilowsky, D. J., Wickramaratne, P., Nomura, Y., & Weissman, M. M. (2006). Family discord, parental depression, and psychopathology in offspring: 20-year follow-up. *Journal of the American Academy of Child & Adolescent Psychiatry*, *45*, 452–460. <http://dx.doi.org/10.1097/01.chi.0000198592.23078.8d>
- Rew, L., & Wong, Y. J. (2006). A systematic review of associations among religiosity/spirituality and adolescent health attitudes and behaviors. *Journal of Adolescent Health*, *38*, 433–442. <http://dx.doi.org/10.1016/j.jadohealth.2005.02.004>
- Richards, P., & Bergin, A. E. (2014). *Handbook of psychotherapy and religious diversity*. Washington, DC: American Psychological Association. <http://dx.doi.org/10.1037/14371-000>
- Rodrigues, S. M., Saslow, L. R., Garcia, N., John, O. P., & Keltner, D. (2009). Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *106*, 21437–21441. <http://dx.doi.org/10.1073/pnas.0909579106>
- Roetker, N. S., Yonker, J. A., Lee, C., Chang, V., Basson, J. J., Roan, C. L., . . . Atwood, C. S. (2012). Multigene interactions and the prediction of depression in the Wisconsin Longitudinal Study. *British Medical Journal Open Access*, *2*. <http://dx.doi.org/10.1136/bmjopen-2012-000944>
- Ropers, H. H. (2010). Single gene disorders come into focus—Again. *Dialogues in Clinical Neuroscience*, *12*, 95–102.
- Saiz, P. A., Garcia-Portilla, M. P., Herrero, R., Arango, C., Corcoran, P., Morales, B., . . . Bobes, J. (2010). Interactions between functional serotonergic polymorphisms and demographic factors influence personality traits in healthy Spanish Caucasians. *Psychiatric Genetics*, *20*, 171–178. <http://dx.doi.org/10.1097/YPG.0b013e32833a20b9>

- Saiz, P. A., García-Portilla, M. P., Paredes, B., Arango, C., Morales, B., Alvarez, V., . . . Bobes, J. (2008). Association between the A-1438G polymorphism of the serotonin 2A receptor gene and nonimpulsive suicide attempts. *Psychiatric Genetics, 18*, 213–218. <http://dx.doi.org/10.1097/YPG.0b013e3283050ada>
- Saroglou, V. (2002). Religion and the five factors of personality: A meta-analytic review. *Personality and Individual Differences, 32*, 15–25. [http://dx.doi.org/10.1016/S0191-8869\(00\)00233-6](http://dx.doi.org/10.1016/S0191-8869(00)00233-6)
- Sasaki, J. Y., Kim, H. S., & Xu, J. (2011). Religion and well-being: The moderating role of culture and the oxytocin receptor gene (OXTR). *Journal of Cross-Cultural Psychology, 42*, 1394–1405. <http://dx.doi.org/10.1177/0022022111412526>
- Sasaki, J. Y., Mojaverian, T., & Kim, H. S. (2015). Religion priming and an oxytocin receptor gene (OXTR) polymorphism interact to affect self-control in a social context. *Development and Psychopathology, 27*, 97–109. <http://dx.doi.org/10.1017/S0954579414001321>
- Schwab, S. G., Franke, P. E., Hoefgen, B., Guttenthaler, V., Lichtermann, D., Trixler, M., . . . Wildenauer, D. B. (2005). Association of DNA polymorphisms in the synaptic vesicular amine transporter gene (SLC18A2) with alcohol and nicotine dependence. *Neuropsychopharmacology, 30*, 2263–2268. <http://dx.doi.org/10.1038/sj.npp.1300809>
- Shoval, G., Bar-Shira, O., Zalsman, G., John Mann, J., & Chechik, G. (2014). Transitions in the transcriptome of the serotonergic and dopaminergic systems in the human brain during adolescence. *European Neuropsychopharmacology, 24*, 1123–1132. <http://dx.doi.org/10.1016/j.euroneuro.2014.02.009>
- Simons, R. L., Lei, M. K., Beach, S. R., Brody, G. H., Philibert, R. A., & Gibbons, F. X. (2011). Social environment, genes, and aggression evidence supporting the differential susceptibility perspective. *American Sociological Review, 76*, 883–912. <http://dx.doi.org/10.1177/0003122411427580>
- Smith, L., Watson, M., Gates, S., Ball, D., & Foxcroft, D. (2008). Meta-analysis of the association of the Taq1A polymorphism with the risk of alcohol dependency: A HuGE gene-disease association review. *American Journal of Epidemiology, 167*, 125–138. <http://dx.doi.org/10.1093/aje/kwm281>
- Smith, R. M., Papp, A. C., Webb, A., Ruble, C. L., Munsie, L. M., Nisenbaum, L. K., . . . Sadee, W. (2013). Multiple regulatory variants modulate expression of 5-hydroxytryptamine 2A receptors in human cortex. *Biological Psychiatry, 73*, 546–554. <http://dx.doi.org/10.1016/j.biopsych.2012.09.028>
- Smith, T. B., McCullough, M. E., & Poll, J. (2003). Religiousness and depression: Evidence for a main effect and the moderating influence of stressful life events. *Psychological Bulletin, 129*, 614–636. <http://dx.doi.org/10.1037/0033-2909.129.4.614>
- Solovieff, N., Roberts, A. L., Ratanatharathorn, A., Haloosim, M., De Vivo, I., King, A. P., . . . Koenen, K. C. (2014). Genetic association analysis of 300 genes identifies a risk haplotype in SLC18A2 for post-traumatic stress disorder in two independent samples. *Neuropsychopharmacology, 39*, 1872–1879. <http://dx.doi.org/10.1038/npp.2014.34>
- Soyka, M., Preuss, U. W., Koller, G., Zill, P., & Bondy, B. (2004). Association of 5-HT1B receptor gene and antisocial behavior in alcoholism. *Journal of Neural Transmission, 111*, 101–109. <http://dx.doi.org/10.1007/s00702-003-0064-0>
- Sperry, L. E., & Shafranske, E. P. (2005). *Spiritually oriented psychotherapy*. Washington, DC: American Psychological Association. <http://dx.doi.org/10.1037/10886-000>
- Stoltenberg, S. F., Christ, C. C., & Highland, K. B. (2012). Serotonin system gene polymorphisms are associated with impulsivity in a context dependent manner. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 39*, 182–191. <http://dx.doi.org/10.1016/j.pnpbp.2012.06.012>
- Thompson, R. J., Parker, K. J., Hallmayer, J. F., Waugh, C. E., & Gotlib, I. H. (2011). Oxytocin receptor gene polymorphism (rs2254298) interacts with familial risk for psychopathology to predict symptoms of depression and anxiety in adolescent girls. *Psychoneuroendocrinology, 36*, 144–147. <http://dx.doi.org/10.1016/j.psyneuen.2010.07.003>
- Trull, T. J., & Sher, K. J. (1994). Relationship between the five-factor model of personality and Axis I disorders in a nonclinical sample. *Journal of Abnormal Psychology, 103*, 350–360. <http://dx.doi.org/10.1037/0021-843X.103.2.350>
- Unschuld, P. G., Ising, M., Erhardt, A., Lucae, S., Kloiber, S., Kohli, M., . . . Keck, M. E. (2007). Polymorphisms in the serotonin receptor gene HTR2A are associated with quantitative traits in panic disorder. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics, 144B*, 424–429. <http://dx.doi.org/10.1002/ajmg.b.30412>
- Vaht, M., Kiive, E., Veidebaum, T., & Harro, J. (2016). A functional vesicular monoamine transporter 1 (VMAT1) gene variant is associated with affect and the prevalence of anxiety, affective and alcohol use disorders in a longitudinal population-representative birth cohort study. *International Journal of Neuropsychopharmacology, 19*, pyw013. <http://dx.doi.org/10.1093/ijnp/pyw013>
- Van Capellen, P., Way, B. W., Isgett, S. F., & Fredrickson, B. L. (2016). Effects of oxytocin administration on spirituality and emotional responses to meditation. *Social Cognitive and Affective Neuroscience, 11*, 1579–1587.

- Van Ness, P. H., & Larson, D. B. (2002). Religion, senescence, and mental health: The end of life is not the end of hope. *The American Journal of Geriatric Psychiatry, 10*, 386–397. <http://dx.doi.org/10.1097/00019442-200207000-00005>
- Varga, G., Szekely, A., Antal, P., Sarkozy, P., Nemoda, Z., Demetrovics, Z., & Sasvari-Szekely, M. (2012). Additive effects of serotonergic and dopaminergic polymorphisms on trait impulsivity. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics, 159B*, 281–288. <http://dx.doi.org/10.1002/ajmg.b.32025>
- Verdeli, H., Ferro, T., Wickramaratne, P., Greenwald, S., Blanco, C., & Weissman, M. M. (2004). Treatment of depressed mothers of depressed children: Pilot study of feasibility. *Depression and Anxiety, 19*, 51–58. <http://dx.doi.org/10.1002/da.10139>
- Villafuerte, S. M., Vallabhaneni, K., Śliwerska, E., McMahon, F. J., Young, E. A., & Burmeister, M. (2009). SSRI response in depression may be influenced by SNPs in HTR1B and HTR1A. *Psychiatric Genetics, 19*, 281–291. <http://dx.doi.org/10.1097/YPG.0b013e32832a506e>
- Voisey, J., Swagell, C. D., Hughes, I. P., Morris, C. P., van Daal, A., Noble, E. P., . . . Lawford, B. R. (2009). The DRD2 gene 957C>T polymorphism is associated with posttraumatic stress disorder in war veterans. *Depression and Anxiety, 26*, 28–33. <http://dx.doi.org/10.1002/da.20517>
- Walitza, S., Bové, D. S., Romanos, M., Renner, T., Held, L., Simons, M., . . . Grünblatt, E. (2012). Pilot study on HTR2A promoter polymorphism, –1438G/A (rs6311) and a nearby copy number variation showed association with onset and severity in early onset obsessive-compulsive disorder. *Journal of Neural Transmission, 119*, 507–515. <http://dx.doi.org/10.1007/s00702-011-0699-1>
- Wang, S., Zhang, K., Xu, Y., Sun, N., Shen, Y., & Xu, Q. (2009). An association study of the serotonin transporter and receptor genes with the suicidal ideation of major depression in a Chinese Han population. *Psychiatry Research, 170*, 204–207. <http://dx.doi.org/10.1016/j.psychres.2008.12.006>
- Weissman, M. M., Berry, O. O., Warner, V., Gameroff, M. J., Skipper, J., Talati, A., . . . Wickramaratne, P. (2016). A 30-Year Study of 3 Generations at High Risk and Low Risk for Depression. *Journal of the American Medical Association Psychiatry, 73*, 970–977. <http://dx.doi.org/10.1001/jamapsychiatry.2016.1586>
- Weissman, M. M., Wickramaratne, P., Gameroff, M. J., Warner, V., Pilowsky, D., Kohad, R. G., . . . Talati, A. (2016). Offspring of depressed parents: 30 years later. *American Journal of Psychiatry, 173*, 1024–1032. <http://dx.doi.org/10.1176/appi.ajp.2016.15101327>
- Weissman, M. M., Wickramaratne, P., Nomura, Y., Warner, V., Pilowsky, D., & Verdelli, H. (2006). Offspring of depressed parents: 20 years later. *The American Journal of Psychiatry, 163*, 1001–1008. <http://dx.doi.org/10.1176/ajp.2006.163.6.1001>
- Whitmer, A. J., & Gotlib, I. H. (2012). Depressive rumination and the C957T polymorphism of the DRD2 gene. *Cognitive, Affective & Behavioral Neuroscience, 12*, 741–747. <http://dx.doi.org/10.3758/s13415-012-0112-z>
- Wolfstein, M., & Trull, T. J. (1997). Depression and openness to experience. *Journal of Personality Assessment, 69*, 614–632. [http://dx.doi.org/10.1207/s15327752jpa6903\\_14](http://dx.doi.org/10.1207/s15327752jpa6903_14)
- Xu, Z., Zhang, Z., Shi, Y., Pu, M., Yuan, Y., Zhang, X., . . . Reynolds, G. P. (2012). Influence and interaction of genetic polymorphisms in the serotonin system and life stress on antidepressant drug response. *Journal of Psychopharmacology, 26*, 349–359. <http://dx.doi.org/10.1177/0269881114144452>
- Yao, J., Pan, Y.-q., Ding, M., Pang, H., & Wang, B.-j. (2014). Association between DRD2 (rs1799732 and rs1801028) and ANKK1 (rs1800497) polymorphisms and schizophrenia: A meta-analysis. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics, 168B*, 1–13.
- Zhang, L., Hu, L., Li, X., Zhang, J., & Chen, B. (2014). The DRD2 rs1800497 polymorphism increase the risk of mood disorder: Evidence from an update meta-analysis. *Journal of Affective Disorders, 158*, 71–77. <http://dx.doi.org/10.1016/j.jad.2014.01.015>
- Zhao, X., Sun, L., Sun, Y. H., Ren, C., Chen, J., Wu, Z. Q., . . . Lv, X. L. (2014). Association of HTR2A T102C and A-1438G polymorphisms with susceptibility to major depressive disorder: A meta-analysis. *Neurological Sciences, 35*, 1857–1866. <http://dx.doi.org/10.1007/s10072-014-1970-7>
- Zouk, H., McGirr, A., Lebel, V., Benkelfat, C., Rouleau, G., & Turecki, G. (2007). The effect of genetic variation of the serotonin 1B receptor gene on impulsive aggressive behavior and suicide. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics, 144B*, 996–1002. <http://dx.doi.org/10.1002/ajmg.b.30521>

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