LEARNING TO LOVE: *OXTR* AND *CD38* POLYMORPHISMS MODERATE THE DAILY POSITIVE EMOTION YIELD OF LOVING-KINDNESS TRAINING

Suzannah F. Isgett

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Approved by:

Barbara L. Fredrickson

Sara B. Algoe

Karen Grewen

ABSTRACT

SUZANNAH F. ISGETT: Learning to Love: *OXTR* and *CD38* Polymorphisms Moderate the Daily Positive Emotion Yield of Loving-kindness Training
(Under the direction of Barbara L. Fredrickson)

The oxytocin system, which is implicated in social cognition and behavior, is one potential biological pathway that influences an individual's capacity to extract positive emotions in social contexts. We tested whether several SNPs in two genes related to oxytocin reception (*OXTR*) and secretion (*CD38)* moderated positive emotion growth during a socially-focused intervention. For six weeks, a sample of mid-life adults participated in either loving-kindness or mindfulness training, and daily positive emotions were measured. DNA from blood was extracted to assess a set of SNPs within *OXTR* and *CD38*. Cumulative risk for *OXTR* and *CD38* genes moderated positive emotion change during loving-kindness training. Lower-risk individuals experienced gains in daily positive emotions from loving-kindness training, while higher-risk individuals did not with either form of training. These findings are some of the first to shed light on how genetic differences in oxytocin processing influence the capacity to experience positive emotions in social contexts.

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Introduction

Positive emotions are a key ingredient in broadening awareness and building resources (Fredrickson, 2013), important processes for psychological well-being and physical health. Because positive social connections are so tightly linked to positive emotionality (Kok et al., 2013), the ability to experience positive emotions through social connection with others appears crucial to achieving, sustaining, and increasing one's overall well-being. However, underlying individual differences in certain biological pathways, such as oxytocin signaling, may affect a person's capacity to enjoy social connection. In this study, we used a candidate gene and cumulative risk approach to explore to what extent polymorphisms in genes critical to oxytocin release and reception impact the positive emotions (PEs) extracted from socially-focused loving-kindness training.

While typically characterized as less salient and more diffuse than negative emotions (Baumeister, Bratslavsky, Finkenauer, & Vohs, 2001: Ellsworth & Smith, 1988), research suggests that positive emotions do not exist solely because they are ontologically pleasant. Studies over the past two decades have shown that positive affective states momentarily alter cognition by expanding the scope of attention (Wadlinger & Isaacowitz, 2006) and broadening thought-action repertoires (Fredrickson & Branigan, 2005). Importantly, these cognition-broadening effects extend into the social domain. For instance, positive emotional states also expand people's inclusive social categories (Dovidio, Gaertner, Isen, & Lowrance, 1995), increase feelings of social connection (Waugh & Fredrickson, 2006), improve perspective-taking

and compassion for dissimilar others (Nelson, 2009), and even reduce the effects of categories, such as race, that people typically use to divide social groups (Johnson & Fredrickson, 2005).

Beyond its psychosocial benefits, positive emotion experience has also been related to health outcomes. In fact, positive affect may be the critical ingredient whose absence was shown to predict mortality (Blazer & Hybels, 2004) and stroke (Ostir, Markides, Peek, & Goodwin, 2001) in the elderly, above and beyond greater levels of negative affect. While the mechanisms are not entirely understood, positive emotions may influence health at the cellular level by building up personal resources, such as social support and purpose in life (Fredrickson et al., 2008). Specifically, these particular markers of psychological wellness, also known as eudaimonic well-being, have been associated with lower levels of daily cortisol and pro-inflammatory cytokines (Ryff, Singer, & Love, 2004), as well as with gene expression profiles that suggest lower inflammation and stronger immune function (Fredrickson et al., 2013). Importantly, even positive emotions on a daily level have been associated with lower levels of cortisol and fibrinogen stress response – neuroendocrine and inflammatory markers of stress (Steptoe, Wardle, & Marmot, 2005).

Most everyday social interactions tend to be pleasant, and their rewarding nature may have an evolutionary basis (Brown & Brown, 2006), because living in groups was crucial to survival in early human history. Even today, people are still biologically wired for social interactions. Similar to positive affect, the lack of feeling socially connected (i.e. loneliness) broadly contributes to morbidity and mortality (Cacioppo, Hawkley, & Bernston, 2003; Cole, 2013). By examining leukocytes in individuals who reported feeling lonely, Cole and colleagues (2007) found that these cells exhibited an up-regulation of genes controlling inflammation and a down-regulation of antiviral and antibody synthesis genes. A meta-analysis found that social

relationships were a robust predictor of mortality, and this finding was consistent regardless of age, sex, or initial health status (Holt-Lundstad, Smith, & Layton, 2010). Positive social connections, like positive emotions, thus appear important to health. In fact, these two facets of well-being were found to be reciprocally connected in predicting changes in cardiac vagal tone, a proxy index of health (Kok & Fredrickson, 2010). When given the opportunity to reflect on their social connections each day, people who reported greater changes in PEs and social connectedness experienced greater increases in cardiac vagal tone. Additionally, those with higher initial levels of cardiac vagal tone had the largest boosts in PEs and social connection. Later work that used socially-focused loving-kindness training confirmed that, indeed, social connectedness mediated the increases in cardiac vagal tone as a result of gains in daily positive emotions (Kok et al., 2013). Because perceived social connection and positive emotions work together in an upward spiral dynamic, examining the biological systems related to social bonding may reveal insights into how individuals are able to achieve and sustain psychological well-being.

Oxytocin

One of the key neuroendocrine components implicated in sociality is the neuropeptide oxytocin (OT). Beyond its role in parturition and lactation, OT has been associated with a myriad of psychological and social functions. OT may regulate social behavior in the brain by strengthening connectivity between the hypothalamus and the amygdala, hippocampus, and anterior cingulate cortex (Carter, 2007), areas that have been broadly implicated in social cognition and emotional processing. Through dampening amygdala activity and HPA stress responses, OT has been proposed to facilitate approach behavior by inhibiting defensive or avoidant behavior (Carter, 1998; Carter et al., 2008). In humans and other mammals, OT

influences a variety of social psychological processes, such as pair bonding (Young & Wang, 2004; Donaldson & Young, 2008), parenting behaviors (Feldman et al., 2012), empathy (Domes et al., 2007; Bartz et al., 2010), and prosociality (Zak, Stanton, & Ahmadi, 2007), as well as disorders such as autism (Modahl et al., 1998; Hollander et al., 2007).

OT has been used as a pharmacological experimental manipulation to test how exogenous OT affects cognition and behavior in humans. Administered intranasally, OT exhibits effects on social cognition (e.g. social memory, emotion recognition, emotion detection, self-reported affect) and prosociality (e.g. trust behavior, socioemotional responding, in-group favoritism, social motivation) (for a review, see Bartz, Zaki, Bolger, & Ochsner, 2011). Frequently, endogenous levels of OT in humans are measured through saliva, plasma or urine (MacDonald & MacDonald, 2010). Because OT ostensibly exerts its influence on behavior through the brain, the role of peripheral OT on behavior is not clear, although measures obtained from these peripheral bodily fluids have nonetheless been correlated with various aspects of social behavior, such as nonverbal displays of romantic love (Gonzaga et al., 2006), parent-to-infant touching (Feldman et al., 2012), and general positive affect (Schneiderman, Zagoory-Sharon, Leckman, & Feldman, 2012).

An alternative method to explore how endogenous levels of oxytocin influence behavior is to examine genes associated with oxytocin secretion and signal transduction. Slight variations in how proteins are coded within DNA can affect the protein's efficacy or function. For example, the *5-HTTLPR* is a polymorphic region of DNA within the *SLC6A4* gene, which encodes for a serotonin transporter protein. Variants in this region, which are traditionally studied as "short" and "long" alleles, have been widely studied as genetic predictors of depression. The actual polymorphism affects the degree to which the gene is expressed. Carriers of the "short" variant

have smaller amygdalar volume, which suggests that the differences in gene expression play a role in neurodevelopment (Kobiella et al., 2011). In the case of oxytocin, functional variants have not been as widely studied. Nevertheless, polymorphisms within genes related to oxytocin signaling may suggest differences in underlying neurology that ultimately affects cognition and behavior (but see Tansey et al., 2010). In the present study, single nucleotide polymorphisms (SNPs) within two different genes important to OT function (*OXTR* and *CD38)* were studied to test whether genetic differences in these genes are related to benefits gained from socially-focused loving-kindness training.

OXTR

The human oxytocin receptor gene, *OXTR*, is located on the short arm of chromosome 3 and codes for a receptor protein for the neuropeptide oxytocin. *OXTR* is expressed early in neurodevelopment (Shapiro & Insel, 1989), such that OXTR proteins are found most densely concentrated in brain areas involved in social behaviors. *OXTR* knock-out mice, relative to wild-type controls, exhibit social behavioral deficits, such as reduced vocalizations during social isolation and greater aggressive behavior (Takayanagi et al., 2005). Because of oxytocin's role in social bonding, human polymorphisms in *OXTR* have been linked to a variety of psychological traits and disorders, from autism and depression to social sensitivity, parenting styles, and empathy (for a review, see Kumsta & Heinrichs, 2013).

OXTR *SNPs*. One of the most widely studied Single Nucleotide Polymorphisms (SNPs) of *OXTR* is *rs53576*, located within the third intron of the gene. One genotype of this SNP, GG, has been associated with greater prosocial nonverbal displays, greater trust, more sensitive parenting, and increased functional coupling between the hypothalamus and amygdala during emotional cue processing (Kumsta and Heinrichs, 2013). The SNP has also been shown to

interact with the cultural environment, such that GG individuals are better at different emotional regulation strategies, depending on what is normative within their culture (Kim et al., 2011). However, because *rs53576* resides in an intronic region that is excised during post-transcriptional modification, its functionality is still unknown.

Other SNPs within *OXTR* have been linked to neurological and psychological differences. Several studies have shown that the SNP *rs2254298* is associated with amygdalar volume and stronger functional coupling among the amygdala, dACC, and hypothalamus during emotional face processing (see Kumsta and Heinrichs, 2013). The SNP *rs1042778* has been linked to plasma OT levels, with "risk" alleles being associated with lower plasma OT and less parent-to-child touch (Feldman et al., 2012). However, a recent meta-analysis on *OXTR* effects in humans examined the combined effect sizes across 82 samples (for *rs53576* and *rs2254298*) and failed to explain a significant part of human social behavior, personality, or psychological dysfunction (Bakermans-Kranenburg & van IJzendoorn, 2013). The authors note, however, that gene-by-environment interaction effects were not taken into account.

CD38

CD38 is a transmembrane protein involved in formation of Ca^{2+} signaling molecules, and has recently been discovered to be a key protein in the secretion of OT within hypothalamic neurons. A study with *CD38* knockout mice showed that these mice displayed deficits in plasma OT, as well as impairments in social behavior (Jin et al., 2007). Several SNPs within *CD38* have been linked with Autism Spectrum Disorder; risk alleles of these SNPs (including *CD38 rs3796863*) have been associated with lower plasma OT and less parental touch (Feldman et al., 2012). In a study by Algoe and Way (2014), risk alleles within *CD38* SNPs – *rs3796863* and *rs6449182* – were significantly associated with lower global relationship satisfaction and

decreased behavioral expressions of gratitude towards romantic partners. Thus, there is a small but growing body of evidence that *CD38* also plays a role in psychological processes involving social bonding.

Overview of Empirical Approach

Whether measured peripherally, determined genetically, or administered intranasally, a body of evidence demonstrates how differences in OT have effects on social cognition and behavior. However, even though the link between sociality and positive emotions is well-established, OT's downstream effects on emotions have received less empirical attention. The present study aims to fill this gap. The study utilized a randomized control trial of mid-life adults who received training in either of two types of meditation practice: loving-kindness meditation training or mindfulness meditation training. Unlike mindfulness training, loving-kindness training has been shown to increase positive emotions and perceived social connections (Fredrickson et al., 2008; Kok et al., 2013). While both types of meditation draw on ancient Buddhist practices and have been shown to improve well-being (Wallace & Shapiro, 2006), loving-kindness meditation specifically trains the individual to cultivate positive, compassionate emotions towards the self and others. As such, increases in positive emotions are generally expected for loving-kindness training but not for mindfulness training. However, due to the inherently social focus of loving-kindness training, we hypothesize that underlying neurological differences in OT secretion and reception would moderate its emotional benefits. As a proxy for these underlying neurological differences among individuals, we selected a set of SNPs from *OXTR* and *CD38* to test our hypothesis. Specifically, we hypothesize that allelic variants of these two genes that have been associated with lower OT and/or deficits in social cognition would predict little to no positive emotional gains from loving-kindness training relative to mindfulness

training. Because effect sizes in candidate gene studies are typically small, we did not have specific hypotheses for particular SNPs, but elected to treat all polymorphisms as potential moderators.

Method

Participants

A total of 124 healthy mid-life adults (73% female; *M* age = 49 years, *SD* = 9) were recruited from the counties surrounding Chapel Hill and Durham, North Carolina[1] . Seventy-nine percent of participants self-identified as Caucasian, 13% as African-American, 7% as Asian, and 1% as another race. 6 participants self-identified as being Hispanic or Latino. Flyers were posted and email advertisements were sent to people within the community, with a subject line asking for people interested in learning how to meditate, explaining that "science has shown that meditation improves people's health and well-being." Everybody received up to $244 in compensation for completing various aspects of the study, which included three 60-minute lab sessions to provide urine and blood samples, participation in a six-week meditation workshop, and completion of daily questionnaires before, during, and after the meditation workshop. All potential participants were first screened with a phone call to assess if they were eligible: within the age range or 35 to 64 years old, able to write and speak English, the absence of chronic illness or disability, and not currently engaged in regular meditation practice. Then, those who met the initial selection criteria were formally enrolled in the study.

Study Design

The study implemented a randomized longitudinal design, and the current analyses examine 7 out of 12 weeks of the study. After the initial lab session, participants completed two

[1] The original sample (*N* = 174) included people who were assigned to a waitlist control group. Because

weeks of daily questionnaires before being randomly assigned to one of two different workshops: Loving-kindness Training (LKT) (n = 62) or Mindfulness Training (MT) (n = 62). Throughout the training period, they continued to complete daily questionnaires. The training workshops were both taught by experienced meditation instructors. For Loving-kindness Training (LKT), loving-kindness meditation was used, which draws from ancient Buddhist techniques of meditation. Throughout the workshop, participants were taught how to develop positive mental states, including friendliness and compassion. Mindfulness meditation was used for Mindfulness Training (MT), which also draws from Buddhist contemplative techniques. Both meditative practices instructed participants to sit quietly, usually with eyes closed and an initial focus on the breath. During mindfulness meditation, people are trained to pay attention to the present moment in a nonjudgmental, open-minded way. In contrast, loving-kindness meditation trains people to direct attention toward their emotions, particularly warm feelings about the self and others. First, individuals are trained to focus on the heart and contemplate a person for whom they currently have warm and tender feelings (e.g. a child or spouse). Then, they are trained to gradually extend these warm feelings to others, in an ever-increasing circle of social connections. Using these techniques, we were able to train people to cultivate heightened levels of other-focus, while utilizing mindfulness meditation as an active control to account for other potential effects of a training intervention.

Measures

mDES (daily). The modified Differential Emotions Scale (mDES) is a 20-item measure that assesses the degree to which people experience different emotions (Fredrickson, 2013). Ten negative emotions (anger, shame, fear, disgust, embarrassment, repentance, hate, sadness, scorn, and stress) and ten positive emotions (amusement, awe, gladness, gratitude, hope, inspiration,

love, pride, and serenity) are measured. People were asked to rate the greatest degree that they experienced a particular emotion in the past 24 hours on a 5-point Likert-type scale (0 = Not at all, 4 = Extremely). Participants completed this measure daily. Average positive emotion and negative emotion scores were calculated for each day.

Genomic DNA. Blood samples from each participant were obtained via venipuncture during the initial lab session. DNA extracted from peripheral-blood leukocytes was assayed for genotypes using a commercial TaqMan Genotyping Assay (Applied Biosystems, Foster City, CA) and iCycler real-time polymerase chain reaction instrument (BioRad, Hercules, CA) following protocols provided by the manufacturer described previously (Bower et al., 2013). The specific genotypes included five different SNPs: *OXTR rs53576, OXTR rs1042778, OXTR rs2254298, CD38 rs3796863,* and *CD38 rs6449182*.

Procedure

Once informed consent was obtained, participants first completed a laboratory session, in which several biological measures were taken, including a blood draw (see "Genomic DNA" above). Then, for the following two weeks, they completed daily questionnaires online from home. Other than measuring emotions, participants completed numerous other measures that are beyond the scope of the study (see Fredrickson et al., 2008 for similar measures). Next, participants who were randomly assigned to either loving-kindness training or mindfulness training met weekly, in small groups, with an instructor experienced with that particular meditative technique. Throughout these six weeks of class instruction, participants continued to complete daily questionnaires.

Analytic Strategy

A conditional longitudinal growth model was used to assess how training type and genotype differentially predicted positive emotions, using restricted maximum likelihood (REML) for parameter estimates. To adjust for how the day in week affects positive emotions (i.e. weekend reports generally higher), we used Week-in-Study as a continuous measure of time, with the intercept coded as the week before training began. Because the initial measurement of daily emotions may have an effect on self-report behavior, the first week of daily PEs was excluded from all analyses. Participant gender was used as a covariate in the full model, because estrogen has been shown to up-regulate OT processing (Lim & Young, 2006). When testing individual SNPs, genotypes were coded into two categories: carriers of the minor allele (homozygous or heterozygous), and homozygous carriers of the major allele. Then, depending on the existing empirical literature, these two categories were individually classified as indicative of "risk" or "non-risk" status; that is, the genotypes described in past research to be associated with lower plasma OT, autism, or social deficits were considered to indicate "risk." We note, however, that for *OXTR rs1042778*, the TT homozygous genotype has been considered "risk" (Feldman et al., 2012; Israel et al., 2009), whereas G carriers are considered "non-risk." Yet with T being the minor allele (q = .40), only 18 homozygous individuals were present in the sample, and these individuals were further randomly subdivided into LKT or MT conditions. Because of the allele's unknown functionality and the size of our sample, we retained our coding scheme for this SNP as major allele homozygotes (GG; "non-risk") and minor allele carriers (TT or TG; "risk").

Additionally, we calculated a Cumulative Genetic Risk score for each participant for a continuous measure of oxytocin functionality. Drawing from past procedures (Schneiderman,

Kabat-Maymon, Ebstein & Feldman, 2013), a cumulative score for genetic predisposition for social and communication deficits was determined for each participant. This was calculated by summing up the number of risk alleles for each SNP, which included *OXTR rs53576* A allele (Saphire-Berstein et al., 2011), *OXTR rs1042778* T allele (Israel et al., 2009), *OXTR rs2254298* G allele (Lerer et al., 2008), *CD38 rs3796863* C allele (Munesue et al., 2010), and *CD38 rs6449182* G allele (Algoe & Way, 2014). Thus, for each SNP, a person could have zero, one, or two copies of the risk allele. Taken together, this resulted in a risk score that ranged from 0 (no risk alleles) to 10 (risk allele homozygote for all SNPs under investigation). SPSS statistical software (IBM Corp., version 22) was used to run all models. Our specific predictions for the model were as follows:

i) There will be a significant cross-level interaction of *week* and *training condition*, such that people would show greater boosts in Positive Emotions (PEs) over time in the LKT condition relative to the MT condition.

ii) There will *not* be significant main effects of *genotype* or interaction between *week* and *genotype*, since we do not expect variation in OT-relevant genes to affect positive emotions generally.

iii) There will be a significant three-way interaction between *week*, *genotype*, and *training condition*, such that people with genotypes associated with social deficits will not gain the same boosts in PEs from LKT as people with non-risk genotypes.

Results

Preliminary Analyses

Out of 124 participants, all genotypes were successfully assayed, so no participants were excluded from subsequent analyses. Comparing the Loving-kindness Training (LKT) group to the Mindfulness Training (MT) group, a series of difference tests were conducted to determine if the two subsets significantly differed in demographic characteristics or baseline positive emotions (Table 1). LKT and MT groups did not differ significantly by age, sex make-up, percent Hispanic ethnicity, or percent identified as White. Importantly, the two conditions did not differ significantly in baseline levels of positive emotions (assessed before random assignment), although we note that people in LKT trended toward having a higher baseline than those in MT.

Five Single Nucleotide Polymorphisms (SNPs), three within *OXTR* (*rs53576, rs1042778, rs2254298*) and two within *CD38 (rs3796863, rs6449182)* were assayed for all individuals. All SNPs were found to be in Hardy-Weinberg Equilibrium (Table 2). All SNP genotypes were evenly distributed between genders. Descriptive statistics for this cumulative risk score indicate that the sample ranged from scores of 1 risk allele to 8 risk alleles, and the distribution was approximately normal, with indices of skewness (.11; *SE* = .22) and kurtosis (-.04; *SE* = .43) not exceeding twice their standard errors.

To initially fit the model, a Random-Effects ANOVA was used to assess the degree of nesting within the data, using the MIXED procedure in SPSS. Indeed, we found that the Intraclass Correlation (ICC) was .669, indicating that most of the variation in positive emotions

(PEs) can be explained by between-person differences, and that people's PEs are highly correlated over time. Next, we plotted person-averaged means of PEs by condition across weeks to observe if a linear model would fit best. Indeed, the weekly means showed a linear trend (Figure 1). Therefore, we conducted a Likelihood Ratio Test to compare the original RE-ANOVA with an unconditional linear growth model with Week-in-Study as the time component. Indeed, the second model led to a significant increase in model fit ($p < .0001$). Building from this, several time-invariant covariates were added for the full model: gender, condition (LKT vs. MT) and genotype (lower-risk vs. higher-risk); interactions between Condition*Genotype, the cross-level interactions of Week*Condition and Week*Genotype; and the three-way cross-level interaction of Week*Condition*Genotype. Although adding condition (LKT vs. MT) and genotype did not lead to a better fitting model, we retained this full model to test our hypotheses. We compared the null model and the full model to compute the variance explained (R^2). This model was run for each of the five SNPs and cumulative risk (Table 3). In 5 out of 6 of these models, gender was a significant predictor of PEs, such that men had significantly lower levels of PEs at baseline; the exception was *OXTR 1042778*, for which gender was not significant ($p = .054$). In alternative models, gender did not significantly interact with condition or genotype, and so is not discussed further.

To test whether negative emotions were also being influenced by condition and/or genotype, all final models were also run using data on daily negative emotions. Neither the cumulative risk model nor the individual SNP models revealed any significant predictors for daily negative emotions.

Hypothesis Testing

Hypothesis I: Loving-kindness training increases positive emotions over time. Regarding our first prediction (i), the expected *week* by *condition* interaction was significant in three of the six models (Table 3). Specifically, being in the LKT condition lead to significantly greater increases in positive emotions per week in the Cumulative Risk model ($B = .13$; $p < .001$). Among the single SNP models, this same significant interaction emerged for models that tested *OXTR rs1042778* ($B = .09$; $p < .001$) and *CD38 rs3796863* (B = .05; $p = .004$).

Hypothesis II: Effect of genotype is conditional. Because OT genes are not presumed to directly influence global positive emotions, we predicted that the only effects of genotype would be conditional on which type of training the participant received. In other words, we predicted (ii) no main effects of *genotype* or interaction of *genotype* by *week*. This hypothesis was also supported.

Hypothesis III: Change in positive emotions depends on condition and genotype. Because LKT is socially oriented, we predicted that people at a genetically higher risk for social deficits would gain the positive emotions boost associated with loving-kindness training. Therefore, we predicted a three-way interaction between condition, genotype, and time, such that people in the LKT condition with risk genotypes would experience little to no growth in PEs, relative to those with non-risk genotypes. Because MT does not have a social focus, we did not predict that genotype would have an effect on emotion in this condition. In the Cumulative Risk model, this hypothesis was supported ($B = -.04$; $p = .002$). To illustrate the model, we plotted the model-implied values for low-risk, medium-risk, and high-risk individuals within MT and LKT, respectively (Figure 2). For people in the MT condition, there is no significant change in PEs, regardless of cumulative risk. By contrast, within the LKT condition, people with low (1 SD

below mean) or medium (mean) cumulative risk appear to increase in PEs over time. High cumulative risk individuals show no changes in PEs during loving-kindness training. Within the single SNP models, for two of the five SNPs this same predicted three-way interaction was also significant: *OXTR rs1042778* (B = -.10; p = .001) and *CD38 rs3796863* (B = -.07; p = .013).

Interaction Probing

For the cumulative risk model and models of single SNPs that revealed significant three-way interactions, the three-way interaction was probed to compare the slopes within groups. In the cumulative risk model, low-risk individuals in the LKT condition showed significant increases in PEs over time (p = .0036), while neither low-risk individuals in MT nor high-risk individuals showed any significant changes in their PE growth trajectories.

For *OXTR rs1042778*, non-risk individuals in the LKT condition showed significant increases in PEs, and a contrast revealed that this trajectory was significantly different from non-risk individuals in the MT condition (p = .0003), who did not show increases in PEs (Figure 3a). The pattern is consistent with the overall finding that has emerged in past research, that people who learn loving-kindness training show greater boosts in PEs (Kok et al., 2013). However, people with the risk genotype of *OXTR rs1042778* did not exhibit this same pattern. Interestingly, while model trajectories for risk individuals in LKT did not change, there was a small but significant increase in PEs for risk individuals in the MT condition (p = .045) (Figure 3b). A similar analysis was conducted for risk and non-risk individuals for the *CD38 rs3796863* SNP. Non-risk individuals in LKT show a significant increase in PEs, and a contrast revealed that this trajectory is significantly greater than that of their non-risk non-risk counterparts in MT (p = .008; Figure 3c). Conversely, risk individuals did not show PE increases in the LKT condition, and their model-implied trajectories did not differ significantly from the MT condition

(p = .358; Figure 3d). For risk individuals in the MT condition, there was a slight *increase* in PEs over time, although this slope shows only a trend (p = .062), and is not significant.

Discussion

In the present study, we aimed to test the association of genetic variability in the OT pathway with the emotional effectiveness of a socially-oriented intervention. Variability in genes essential to OT signaling may indicate underlying neurobiological differences in the brain, such as amygdalar and anterior cingulate cortex (ACC) volume (Furman et al., 2011; Inoue et al., 2010; Tost et al., 2011). These genetic variants, which naturally occur in human populations, may help to explain the link between the OT system and individual differences in positive affectivity in social contexts, perhaps via morphological and connectivity differences in the extended amygdala network. While we replicated the overall effects of loving-kindness training on daily positive emotions (Fredrickson, 2008; Kok et al., 2013), we were able to genetically differentiate individuals who extracted more positive emotions from the intervention. Relative to those who learned mindfulness meditation (MT), people in the loving-kindness training (LKT) condition showed gradual increases in positive emotions. This effect was qualified, however, by OT gene polymorphisms. Specifically, individuals with certain non-risk variants of *OXTR* and *CD38*, as well as individuals with low cumulative risk, displayed the predicted pattern: those in the LKT condition gained more positive emotions than those in the MT condition. However, training condition did not have an impact on positive emotions for carriers of the corresponding risk variants. These results are consistent with other research suggesting that human sociality is, in part, influenced by the oxytocinergic system, and that this pathway includes OXTR, the primary receptor for OT, and CD38, a protein essential to the neuropeptide's secretion in the brain.

Previous studies have found associations between these genetic variants and differences in adeptness at social processes such as emotion recognition (Lucht et al., 2012; Rodrigues et al., 2009), emotional face processing (Sauer et al., 2012), empathy (Wu, Li, & Su, 2012), sensitive parenting (Feldman et al., 2012), and emotional expression within romantic relationships (Algoe & Way, 2014). Because of oxytocin's role in human social processes, we sought to extend our investigation into how a genetic predisposition for social and communicative deficits could hinder the ability to experience emotional benefits during a socially-focused intervention. We assessed the role of genetic variation in 5 SNPs within *CD38* and *OXTR*, two genes necessary for OT signaling, which have been associated with deficits in social emotional processing. While gender was a significant covariate in our models, with women reporting more positive emotions at baseline, it did not significantly interact with genotype. Our hypotheses that risk alleles of *CD38* and *OXTR* would be negatively associated with increases in positive emotion during Loving-kindness Training (but not Mindfulness Training) were confirmed. In addition, because LKT is known to influence positive but not negative emotions, we did not expect genotype to influence negative emotions, and our model supported that prediction. However, we unexpectedly found that, for risk carriers of *OXTR rs1042778*, MT actually led to an increase in PEs. Overall, the current findings suggest that underlying differences in the OT system may influence the positive emotion yield from a socially-focused intervention.

Currently, cumulative risk assessment is considered to be a useful framework when studying the heritable etiology of psychiatric disorders (Belsky et al., 2009). Because our study contained a modest sample size for a genetic study, we decided not to use other methods that more finely assess genetic risk, such as a principle components analysis (Gauderman et al., 2007). When tested individually, although four of five SNPs had non-significant three-way

interactions in the predicted direction, only two SNPs were significantly associated with changes over time in positive emotions. The cumulative risk approach may therefore reveal the smaller contributions of each SNP that were not detectable individually. Alternatively, it is possible that the cumulative risk score added more statistical variance to the model, relative to testing individual SNPs. Yet noting that the hypothesized three-way interaction also emerged for the measure of cumulative risk, this suggests that our findings, at least for *OXTR rs1042778* and *CD38 rs3796863* may be particularly robust.

These findings provide evidence for one of the biological systems that underpins positive affectivity in sociality. Because oxytocin has been shown to regulate the release of dopamine in the mesocorticolimbic dopamine system in rodents during instances of maternal bonding (Shahrokh et al., 2010), our findings also support the idea that oxytocin plays a role in the inherently rewarding nature of social interaction. While oxytocin, either administered intranasally or measured peripherally, has been implicated in social processes that involve positive affect, such as attentional bias towards positively-valenced faces (Domes et al., 2012) and positive behaviors during conflict discussion (Ditzen et al., 2009). The present study, however, is one of the first studies to tie the OT system to positive emotions after experimentally inducing a heightened other-focus. Thus, oxytocin most likely does not affect global positive emotionality, but rather the positive emotional benefit from being other-focused.

The broaden-and-build theory of positive emotions suggests that positive emotions momentarily broaden aspects of cognition (including social cognition), and that this broaden effect can help people build psychological and interpersonal resources. Teaching people ways to increase their positive emotions through loving-kindness training can serve as a springboard that helps them have increased feelings of social connection (Kok et al., 2013). Specifically, social

capital is an important resource for its buffering effects against stress (Cohen & Wills, 1985), mental illness (DeSilva, McKenzie, Harpham, & Huttly, 2005), physical illness (Cohen, Gottlieb, & Underwood, 2000), and even mortality (Holt-Lunstad, Smith, & Layton, 2010). In this way, feelings of social connection are bolstered by positive emotions, and in turn positive emotions cultivate greater feelings of social connection – a reciprocal relationship that can help foster greater well-being (Fredrickson, 2013). However, like many types of interventions, loving-kindness training is not as effective for some people as for others. In particular, the results of this study point to potential biological mechanisms that may underlie individuals' abilities to extract the emotional benefit from this socially-oriented intervention. Expanding on this, it follows that individuals with genotypes associated with social cognitive deficits may not be as adept at learning loving-kindness training and would subsequently not reap the emotional benefits from this training. In fact, our unexpected finding in which risk carriers of *OXTR rs1042778* showed PE increases during mindfulness training suggests that non-social interventions may actually be more effective in eliciting positive emotions for individuals who are not as adept at social processing.

This research has potential implications for understanding and tailoring interventions for fostering optimal mental health. Because insofar as perceived social connection increases positive emotions, it is important to understand how cultivating feelings of compassion may be more difficult for certain individuals. Our study implies that the oxytocinergic system may be one of the underlying mechanisms that helps or hinders this process and may direct future interventions and triaging strategies, or pinpoint potential pharmaceutical targets.

This study has inherent limitations that we would like to acknowledge. Whereas the randomization of participants to training conditions allows us to draw causal inferences about the

effects of loving-kindness training on positive emotions, we note that the genetic data are correlational, so causal inferences cannot be made as to how underlying genetic variation affects positive emotions in this context. Specifically, genetic variation might be responsible for an unmeasured variable that in turn might account for the patterns of emotionality that emerged here. Additionally, the sample size is modest by genetic standards, and we encourage replication of these data in future studies. A critical next step will be to investigate whether these genetic variants are also associated with lower circulating levels of OT, which has not yet been determined in our sample. Although risk variants of *CD38 rs3796863* have been associated with lower circulating levels of plasma OT in humans (Feldman et al., 2012; Munesue et al., 2010), replicating this finding is key to determining whether, indeed, the genotypes targeted here also have observable endocrinological phenotypes. Additionally, individuals who were randomly assigned to the Loving-kindness Training condition happened to start out with higher levels of positive emotions than their Mindfulness Training counterparts. Although the difference was not statistically significant, these baseline differences may have influenced later positive emotion growth. Nevertheless, this study represents an important advance in understanding the underlying biological mechanisms that tie sociality to positive affect.

The current study has clinical implications and may lend clues to targeted behavioral interventions that aim to prevent affective disorders such as depression. Previous research has demonstrated that loving-kindness training, through methods such as loving-kindness meditation, can increase people's daily positive emotions, raise parasympathetic activity (as indexed through HF-HRV, or high-frequency heart rate variability; Kok et al., 2013), and decrease minor illness symptomatology (Fredrickson et al., 2008). However, this study demonstrates that portions of the population may not benefit from this type of behavioral training due to underlying genetic

variation. For these individuals, other targeted interventions should be explored. Potentially, a person's cumulative risk for OT-related social deficits could be used to implement a more personalized approach to selecting behavioral training to improve health and well-being. While participants in this study were not diagnosed with Autism Spectrum Disorder (ASD), this finding may help shed light on developing more targeted therapies and interventions that improve the well-being of individuals with Autism Spectrum Disorder, some of whom show abnormal levels of endogenous OT (Green et al., 2001).

Genetic variation in the CD38-OXTR-OT axis remains poorly understood, especially as to how it influences socioemotional processes. Future research should aim to uncover how natural variants in these genes actually alter gene expression and/or the molecular function of proteins critical to OT signaling, which is a critical step in explaining behavioral outcomes related to these polymorphisms. Additionally, more research is necessary to determine the psychological mechanisms within individuals with risk variants of these two OT genes that impedes their growth in positive emotions when given the opportunity to receive loving-kindness training or other socially-focused practices. In light of the current findings that suggest oxytocin is one of the molecular substrates involved, intranasal OT administration during loving-kindness training may be one avenue to pharmacologically manipulate biological support for social orientation and possible subsequent changes in positive emotions. Finally, the complexity of human sociality suggests that there are likely biological pathways at multiple levels that influence the emotional benefits of social interaction, and these other measures should also be investigated to gain a deeper understanding of the biological basis of sociality.

In sum, we endeavored to investigate how underlying neurobiological differences in OT reception and secretion influences positive affectivity in response to a socially-focused

intervention. Existing genetic variability in our sample was used to test how a biological predisposition for deficits in social cognition may be a factor that impedes the ability to extract positive emotions from sociality. Indices of genetic risk within *OXTR* and *CD38* were associated with no growth in positive emotions during loving-kindness training. Our findings suggest that oxytocin is involved in positive emotionality within social contexts. This goes beyond previous literature that implicates OT in emotional perception and processing, and may actually point to its involvement in the experiential facets of positive emotion in some contexts. Understanding the biology that underpin an individual's capacity to feel positive emotions in social contexts may lead to better triaging strategies and more targeted interventions that allow a broader range of people to increase their well-being and ultimately their health.

Table 1. *Participant Characteristics*

Measure	LKT (n = 62)			MT (n = 62)					
	M	*SD*	%	*M*	*SD*	%	Test statistic	df	*p*
Age (years)	48.68	8.46		48.68	9.34		$t < .01$	122	> .99
Sex (female)			69			76	$\chi^2 = .65$	1	.55
Race									
White			76			81	$\chi^2 = .78$	1	.38
Black			19			6			
Asian			5			10			
Pacific Islander			0			2			
Hispanic Ethnicity			3			6	$\chi^2 = .70$	1	.68
Baseline PEs	1.71	.64		1.50	.78		$t = 1.62$	122	.11

Note: Chi-square test for Race was based on White vs. non-White individuals.

Table 2. *Genotype Frequencies and test for Hardy-Weinberg Equilibrium*

Single Nucleotide Polymorphism	Observed *n*	Expected *n*	χ^2 (*p*)
OXTR rs53576			.29 (.86)
GG	57	58.2	
GA	56	53.5	
AA	11	12.3	
OXTR rs1042778			.65 (.72)
GG	42	44.2	
GT	64	59.7	
TT	18	20.2	
OXTR rs2254298			1.14 (.57)
GG	83	84.7	
GA	39	35.5	
AA	2	84.7	
CD38 rs3796863			
GG	49	50.1	.425 (.81)
GT	61	57.1	
TT	14	16.0	
CD38 rs6449182			.004 (.99)
CC	84	83.9	
CG	36	36.2	
GG	4	3.9	

Table 3. *Fixed Effects Estimates for Models of the Predictors of Daily Positive Emotion*

Parameter	Genotype					
	Cumulative Risk	*OXTR rs53576*	*OXTR rs1042778*	*OXTR rs2254298*	*CD38 rs3796863*	*CD38 rs6449182*
			Fixed Effects *B (95% CI)*			
Intercept	***1.309 (.691—1.927)	***1.507 (1.264—1.750)	***1.643 (1.376—1.910)	***1.550 (1.255—1.845)	***1.437 (1.212—1.663)	***1.556 (1.344—1.769)
Week	-.032 (-.104—.039)	.021 (-.007—.049)	-.018 (-.049—.012)	-.006 (-.040—.028)	-.008 (-.034—.018)	.010 (-.015—.035)
LKT	.191 (-.670—1.051)	.266 (-.079—.612)	.025 (-.381—.431)	.121 (-.295—.537)	*.374 (.073—.676)	*.304 (.015—.592)
[Genotype]	.054 (-.073—.182)	.116 (-.221—.452)	-.138 (-.478—.201)	.020 (-.332—.372)	.308 (-.030—.645)	.020 (-.341—.381)
Week x LKT	**.153 (.055—.254)	.015 (-.027—.056)	***.091 (.045—.138)	.048 (-.001—.098)	**.051 (.016—.086)	.027 (-.007—.062)
[Genotype] x LKT	.014 (-.162—.190)	-.030 (-.509—.450)	.355 (-.146—.857)	.199 (-.309—.707)	-.251 (-.745—.243)	-.141 (-.657—.374)
Week x [Genotype]	.009 (-.006—.023)	-.029 (-.069—.012)	*.044 (.005—.084)	.021 (-.021—.063)	.037 (-.003—.077)	-.008 (-.051—.036)
Week x [Genotype] x LKT	**-.028 (-.048— -.007)	.022 (-.035—.079)	***-.102 (-.160— -.045)	-.036 (-.097—.024)	*-.074 (-.131— -.016)	-.010 (-.071—.051)

Note: * $p < .05$; ** $p < .01$; *** $p \leq .001$. Genotype was coded to positively indicate risk allele status. Gender was a covariate in all models and a significant predictor ($p < .05$) in models for cumulative risk, *rs53576*, *rs2254298*, *rs3796863*, and *rs6449182*.

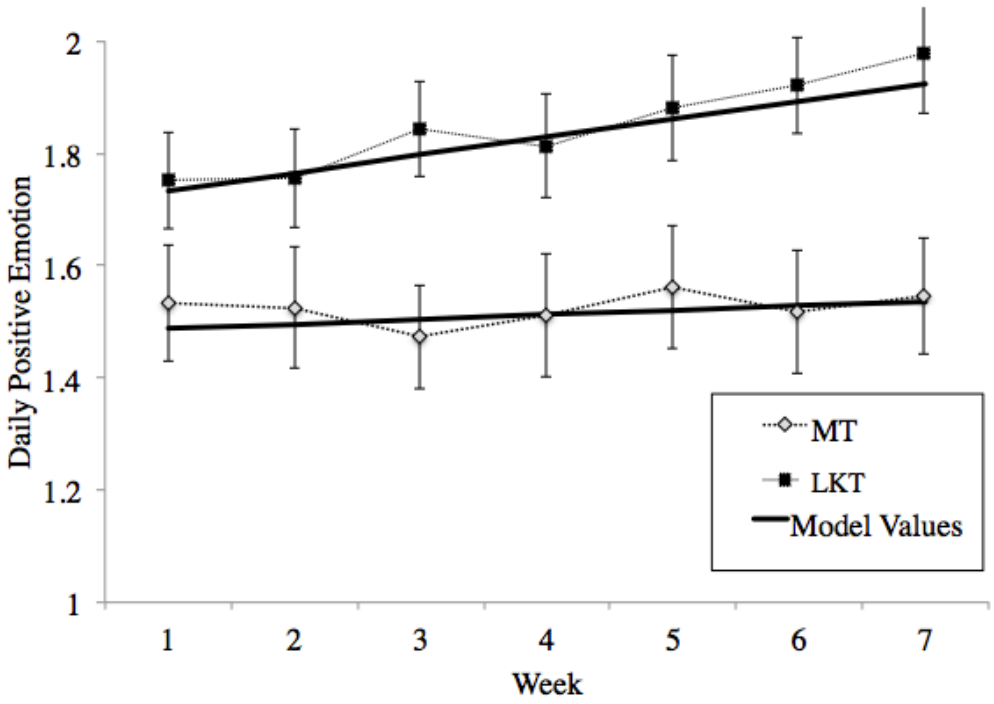

Figure 1. Mean daily positive emotions over the course of the study. Actual means are plotted over a linear model. MT = Mindfulness Training; LKT = Loving-kindness Training. Week 1 indicates baseline emotions, before training was assigned.

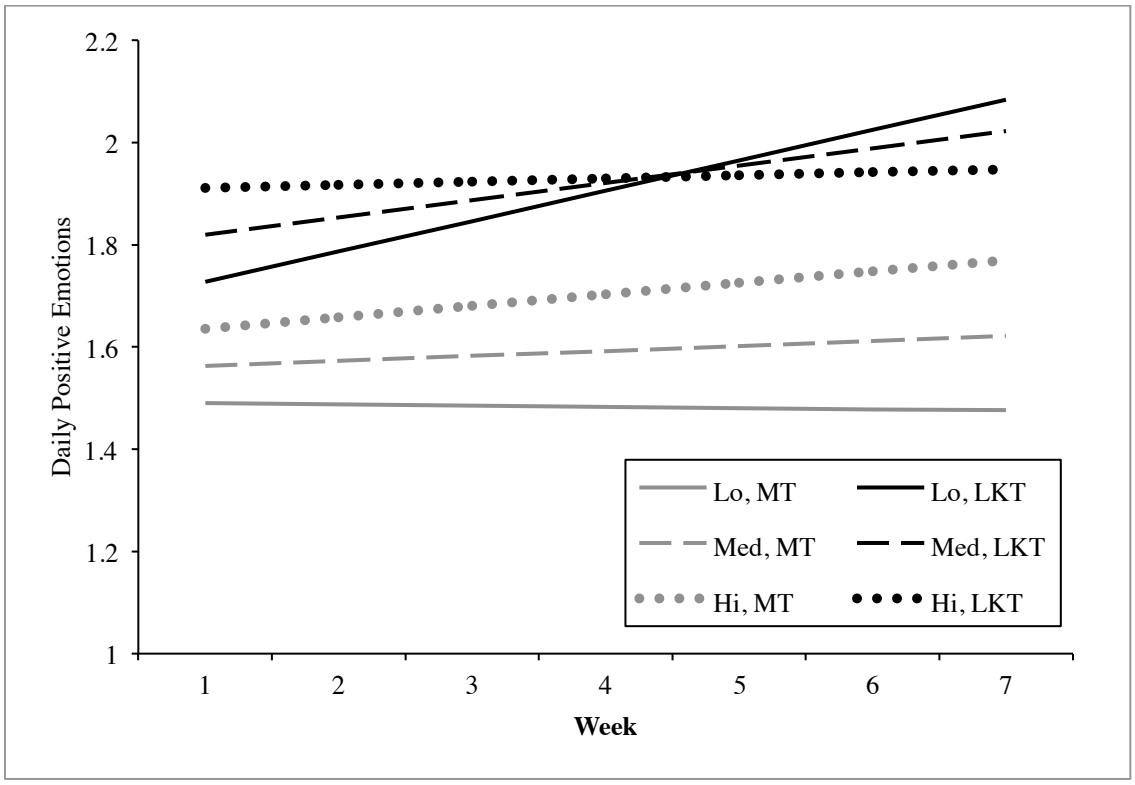

Figure 2. Daily positive emotion change by condition and cumulative risk score. MT = Mindfulness Training; LKT = Loving-kindness Training. Lo = low cumulative risk (1 SD below mean); Med = medium cumulative risk (mean); Hi = high cumulative risk (1 SD above mean).

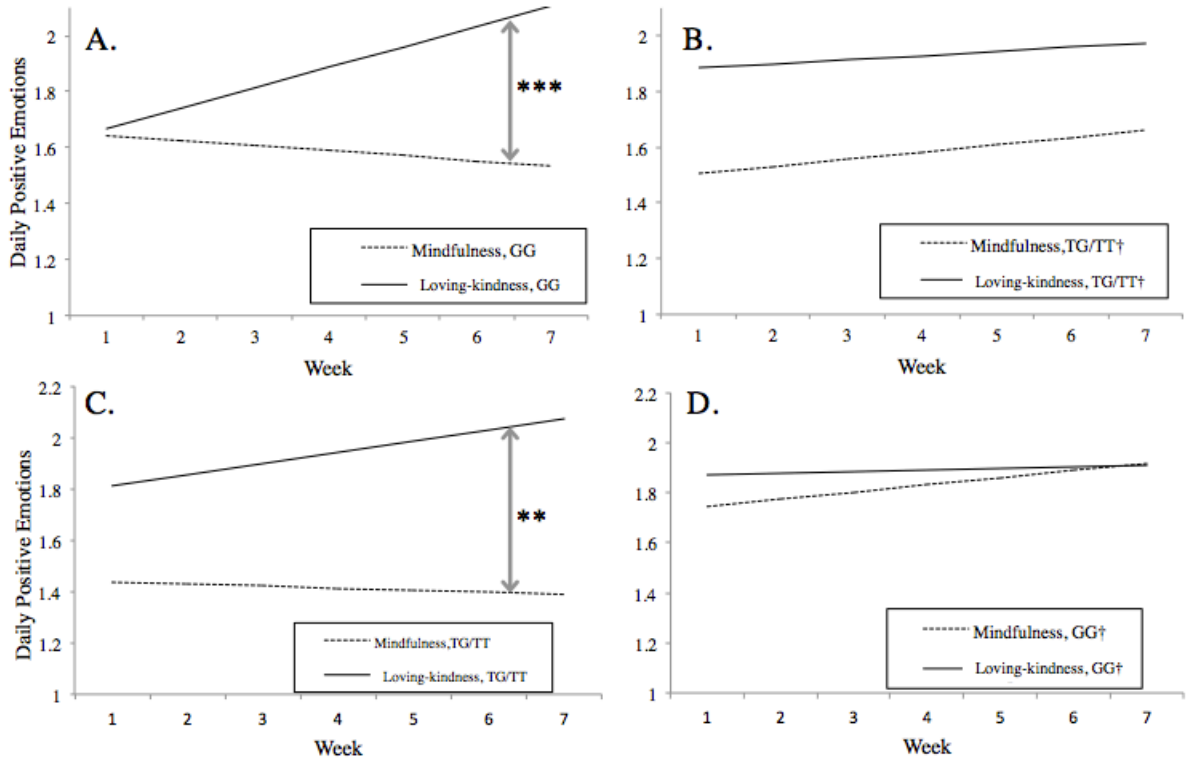

Figure 3. Daily positive emotion change by condition and genotype. ** $p < .01$; *** $p < .001$. † indicates "risk" genotypes. A. *OXTR rs1042778* non-risk genotype by condition. B. *OXTR rs1042778* risk genotypes by condition. C. *CD38 rs3796863* non-risk genotypes by condition. D. *CD38 rs3796863* risk genotype by condition.

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