



Variation in the oxytocin receptor gene (OXTR) is associated with differences in moral judgment

Regan M. Bernhard,¹ Jonathan Chaponis,² Richie Siburian,² Patience Gallagher,² Katherine Ransohoff,³ Daniel Wikler,⁴ Roy H. Perlis,^{2,5,*} and Joshua D. Greene^{1,*}

¹Department of Psychology, Harvard University, 02138, Cambridge, MA, USA, ²Psychiatric and Neurodevelopmental Genetics Unit, Center for Human Genetics Research, Massachusetts General Hospital, 02114, Boston MA, USA, ³Stanford University School of Medicine, 94305, Stanford, CA, USA, ⁴Department of Global Health and Population, Harvard School of Public Health, 02115, Boston, MA, USA, and ⁵Center for Experimental Drugs and Diagnostics, Massachusetts General Hospital and Harvard Medical School, 02114, Boston, MA, USA

*These authors contributed equally to this work.

Correspondence should be addressed to Regan Bernhard, Department of Psychology, Harvard University, 33 Kirkland Street, Cambridge, MA 02138, USA. E-mail: regan.bernhard@gmail.com.

Abstract

Moral judgments are produced through the coordinated interaction of multiple neural systems, each of which relies on a characteristic set of neurotransmitters. Genes that produce or regulate these neurotransmitters may have distinctive influences on moral judgment. Two studies examined potential genetic influences on moral judgment using dilemmas that reliably elicit competing automatic and controlled responses, generated by dissociable neural systems. Study 1 ($N = 228$) examined 49 common variants (SNPs) within 10 candidate genes and identified a nominal association between a polymorphism (rs237889) of the oxytocin receptor gene (OXTR) and variation in deontological vs utilitarian moral judgment (that is, judgments favoring individual rights vs the greater good). An association was likewise observed for rs1042615 of the arginine vasopressin receptor gene (AVPR1A). Study 2 ($N = 322$) aimed to replicate these findings using the aforementioned dilemmas as well as a new set of structurally similar medical dilemmas. Study 2 failed to replicate the association with AVPR1A, but replicated the OXTR finding using both the original and new dilemmas. Together, these findings suggest that moral judgment is influenced by variation in the oxytocin receptor gene and, more generally, that single genetic polymorphisms can have a detectable effect on complex decision processes.

Key words: morality; genetics; decision-making

Introduction

Moral judgments are produced through the coordinated interaction of multiple neural systems, none of which appear to be specifically dedicated to moral judgment (Young and Dungan, 2012; Greene, 2014a,b). Such systems represent value and motivate its pursuit (Schultz *et al.*, 1997; Rangel *et al.*, 2008; Shenhav and

Greene, 2010), enable cognitive control (Miller and Cohen, 2001; Greene *et al.*, 2004), form representations of complex distal events (Raichle *et al.*, 2001; Buckner *et al.*, 2008; Amit and Greene, 2012) and represent social information (Young *et al.*, 2007; Mitchell, 2009; Skuse and Gallagher, 2009; Meyer-Lindenberg *et al.*, 2011). These systems depend critically on specific neurotransmitters such as dopamine, in the case of the mesolimbic reward pathway

Received: 30 March 2016; Revised: 2 July 2016; Accepted: 21 July 2016

© The Author (2016). Published by Oxford University Press.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

(Schultz et al., 1997), and oxytocin, in the case of closely related pathways that enable social cognition (Skuse and Gallagher, 2009; Meyer-Lindenberg et al., 2011). These neurotransmitters, in turn, are influenced by genes such as *DRD2* and *OXTR* that regulate the production of proteins that act as their receptors (Grandy et al., 1989; Kimura et al., 1992). The foregoing suggests that common variations in genes with broad neuromodulatory functions may be expected to influence moral judgment phenotypes. Here we present two studies—one exploratory and one confirmatory—examining potential genetic influences on moral judgment. Study 1 examines common variants within 10 candidate genes related to neural systems that have been implicated in moral judgment (Greene, 2014a,b). Study 2 attempts to replicate the two nominal associations observed in Study 1.

Both studies employ a set of moral dilemmas that have been widely used in research examining the cognitive and neural bases of moral judgment (see below). In each of these dilemmas the reader is asked to decide whether or not to save the lives of several people by severely harming or killing one person (Foot, 1978; Thomson, 1985; Petrinovich et al., 1993; Greene et al., 2001). Study 2 employs an additional set of more realistic medical dilemmas that have a similar structure to those used in Study 1 (Ransohoff, 2011; Ransohoff et al., manuscript in preparation). Both sets of dilemmas reflect the ubiquitous social tradeoff between the rights of the individual and the greater good (Fischer and Ravizza, 1992; Paxton et al., 2013). While such dilemmas are not representative of everyday moral decision problems, their exaggerated features, analogous to those of high-contrast visual stimuli, make them exceptionally useful cognitive probes (Cushman and Greene, 2012). More specifically, these dilemmas reliably elicit competing automatic and controlled responses generated by dissociable cognitive systems (Greene et al., 2001; Greene et al., 2004; Greene et al., 2008; Moore et al., 2008; Suter and Hertwig, 2011; Paxton et al., 2012; Conway and Gawronski, 2013; Paxton et al., 2013; Shenhav and Greene, 2014).

On a neural level, characteristically deontological judgments against harming some individuals to help a larger number of others (and thus favoring individual rights over the greater good) are associated with increased amygdala response (Greene et al., 2004; Glenn et al., 2009; Shenhav and Greene, 2014). Consistent with this, the administration of citalopram, a selective serotonin reuptake inhibitor (SSRI) that in the short-term heightens affective responses in the amygdala, tends to increase deontological judgment (Crockett et al., 2010). In a parallel finding, the anti-anxiety drug lorazepam tends to decrease deontological judgment (Perkins et al., 2013). The amygdala is densely interconnected with the ventromedial prefrontal cortex (VMPFC), which plays a critical role in the integration of affective responses into decisions (Bechara et al., 1994; Rangel and Hare, 2010; Padoa-Schioppa and Cai, 2011). Consistent with this, patients with VMPFC damage make dramatically fewer deontological judgments than control subjects (Ciaramelli et al., 2007; Koenigs et al., 2007; Moretto et al., 2010; Thomas et al., 2011). Here, it appears that the amygdala generates an initial negative response to such harmful actions, while the VMPFC is responsible for integrating that response into an ‘all things considered’ judgment (Blair, 2007; Shenhav and Greene, 2014). Opposing judgments that are characteristically utilitarian (reflecting a cost-benefit analysis favoring the greater good over the rights of the individual) are associated most closely with activation in the dorsolateral prefrontal cortex (DLPFC) (Greene et al., 2004), consistent with broader behavioral evidence linking utilitarian judgment to controlled processing (Greene et al., 2008; Moore et al., 2008; Suter and Hertwig, 2011; Paxton et al., 2012; Paxton

et al., 2013). We note that the terms ‘deontological’ and ‘utilitarian’ characterize the *judgment itself* (whether it is naturally justified by appeal to individual rights vs impartial cost-benefit analysis) and carry no direct implication concerning the broader philosophical commitments of the individual making the judgment (Greene, 2007, 2014a, b).

The association between deontological moral judgment, on the one hand, and affective responses enabled by the amygdala and VMPFC (Decety and Porges, 2011), on the other, suggests a critical role for oxytocin in the shaping of automatic negative responses to harmful actions. The amygdala appears to be a major target for oxytocin, consistent with oxytocin’s influence on a range of associated social behaviors including social recognition, affiliation and response to threat (Skuse and Gallagher, 2009; Meyer-Lindenberg et al., 2011). Oxytocin binding sites are prevalent in both the rodent and human amygdala (Veinante and Freund-Mercier, 1997; Young, 1999; Bale et al., 2001; Huber et al., 2005; Boccia et al., 2013), and variation in the human oxytocin receptor gene (*OXTR*) is associated with increased amygdala volume (Inoue et al., 2010; Furman et al., 2011; Marusak et al., 2015). Likewise, intranasal administration of oxytocin has been shown to attenuate the amygdala’s response to faces (Domes et al., 2007; Gamer et al., 2010; Koch et al., 2015), fear inducing stimuli (Kirsch et al., 2005; Petrovic et al., 2008), and betrayals of trust (Baumgartner et al., 2008). Effects of oxytocin in the VMPFC appear to be more indirect than those in the amygdala (Petrovic et al., 2008; Meyer-Lindenberg et al., 2011), consistent with this region’s role in the top-down regulation of amygdala function (Phelps et al., 2004) and its more general role as a hub for integrating affective signals that bear on decision-making (Bechara et al., 1994; Rangel and Hare, 2010; Padoa-Schioppa and Cai, 2011). Consistent with the above, a recent study found that oxytocin administration shortly after experiencing trauma decreased amygdala-VMPFC functional connectivity during trauma related imagery when compared to placebo (Frijling et al., 2015).

There has also been substantial research on the effect of exogenous oxytocin on pro-social behavior in humans (Ditzen et al., 2009; Heinrichs et al., 2009; Riem et al., 2013; Bartz et al., 2015; De Dreu and Kret, 2016). However, these findings may be gender and context specific (Bartz et al., 2011), and the mechanism by which intranasal oxytocin potentially affects behavior remains an open question (Leng and Ludwig, 2016). Of particular relevance to the present research is a study showing that intranasal administration of oxytocin makes males less willing to sacrifice in-group members in order to save the lives of a larger group (De Dreu et al., 2011).

Closely related to oxytocin in both structure and function is arginine vasopressin (AVP), which has been implicated in a range of relevant social behaviors including aggression, affiliation and pair-bonding (Ebstein et al., 2009; Meyer-Lindenberg et al., 2011). Higher endogenous levels of AVP are associated with increased aggression in individuals diagnosed with personality disorders (Coccaro et al., 1998) and increased amygdala activation during the processing of negative stimuli (Motoki et al., 2016). In men, intranasal administration of vasopressin is associated with increased reciprocal cooperation (Rilling et al., 2012), improved memory for both happy and angry faces (Guastella et al., 2010), and decreased perceptions of friendliness in unfamiliar faces (Thompson et al., 2006). Exogenous vasopressin also affects amygdala activation and functional connectivity between the amygdala and medial prefrontal cortex in response to emotional faces, scenes, or social interactions (Zink et al., 2010; Rilling et al., 2012; Brunnelieb et al., 2013).

The studies summarized above strongly suggest the importance of the aforementioned gene products in influencing moral judgment. The influence of the SSRI citalopram on moral judgment (Crockett et al., 2010) suggests a modulatory role for 5-HTTLPR, the promoter region of the serotonin transporter gene (SLC6A4), which is known to affect amygdala responses to aversive images (Heinz et al., 2004; Canli et al., 2005; Smolka et al., 2007) and fearful faces (Hariri et al., 2002). Likewise, the association between utilitarian judgment and controlled cognition (Greene et al., 2004; Greene et al., 2008; Moore et al., 2008; Suter and Hertwig, 2011; Paxton et al., 2012; Conway and Gawronski, 2013; Paxton et al., 2013) suggests a modulatory role for COMT and, more specifically, the val/met polymorphism, which is associated with variation in performance on attention-demanding tasks (Egan et al., 2001; Blasi et al., 2005; Winterer et al., 2006) (but see Barnett et al., 2008).

Finally, the foregoing suggests that moral judgment may be influenced by genes related to oxytocin and vasopressin. These include OXT (which encodes a pre-cursor protein necessary to produce oxytocin), OXTR (which encodes the oxytocin receptor protein) and AVPR1A (which encodes the type 1A AVP receptor protein). Several polymorphisms of OXTR have been associated with autism spectrum disorders and their associated deficits in social cognition (Lerer et al., 2008; Campbell et al., 2011; Harrison et al., 2015; LoParo and Waldman, 2015; Kranz et al., 2016) (but see Tansey et al., 2010). Variation in the rs53576 allele of the OXTR gene, more specifically, has been associated with sensitive parenting (Bakermans-Kranenburg and van IJzendoorn, 2008), empathy (Christ et al., 2015; Rodrigues et al., 2009; Uzefovsky et al., 2014), theory of mind ability (Wu and Su, 2014; Wade et al., 2015), pro-social temperament (Tost et al., 2010) and real-world pro-social behavior (Poulin et al., 2012). Further, OXTR variation has been linked to pro-social behavior in the dictator game (Israel et al., 2009), though a more recent study with a larger sample did not replicate this effect (Apicella et al., 2010). Variation in the RS3 promoter region of AVPR1A has also been associated with dictator-game behavior in adults (Knafo et al., 2008) and pre-schoolers (Avinun et al., 2011). Likewise, AVPR1A RS3 variation has been associated with pair-bonding (Walum et al., 2008) and maternal behavior (Avinun et al., 2012) in humans. Finally, differential activation in the amygdala is associated with variation in both the RS3 and RS1 regions of AVPR1A when viewing emotional faces (Meyer-Lindenberg et al., 2009).

Two studies have examined the relationships between specific genetic polymorphisms and moral judgment. Marsh et al. (2011) examined effects of variation in the promoter region of the serotonin transporter gene (5-HTTLPR) using dilemmas related to those employed in the present research. They found that L-allele carriers gave more utilitarian responses to dilemmas in which the harm is merely foreseen rather than intended. They found no effect of genotype on responses to dilemmas in which the utilitarian action requires an intentional harm. This pattern is surprising because it is dilemmas involving ('personal') intentional harm that are the most affectively salient (Greene et al., 2001; Ciaramelli et al., 2007; Koenigs et al., 2007; Moretto et al., 2010; Conway and Gawronski, 2013) and that have been directly linked to amygdala response (Glenn et al., 2009; Shenhav and Greene, 2014) and serotonin function (Crockett et al., 2010). More recently Walter et al. (2012) examined effects of an OXTR SNP (rs2268498) on judgments of blame in response to intentional, accidental and attempted harms. They found that C-allele carriers rated accidental harms as more blameworthy, with no differences for intended harms and failed attempts to harm.

While the results of these studies are both plausible and intriguing, they have several critical limitations. Most notably, the sample sizes are very small ($N=64$ for Marsh et al. and $N=154$ for Walter et al.). It is also not clear whether these studies included unreported tests of other genetic variants, raising concerns about multiple comparisons (Benjamini et al., 2001; Weller et al., 1998). Neither study includes a replication sample, nor has either been replicated in subsequent research. Finally, neither study addressed the problem of population stratification (Cardon and Bell, 2001; Freedman et al., 2004) another major contributor to type I error. A burgeoning literature illustrates the challenge of type I error in translational and clinical research (Ioannidis, 2005).

The present research takes a more systematic approach to the discovery of genetic influences on moral judgment. As noted above, there is now a substantial literature associating specific responses to moral dilemmas with the operations of dissociable neural systems. Based on this literature, along with research on the genetics of human social behavior (see above), we identified 10 candidate genes potentially related to variation in moral judgment. Likewise, we identified and ultimately analyzed 49 candidate polymorphisms within these genes based on the extant literature and, in the case of OXTR, a statistical analysis aimed at maximizing coverage of the total variation within the gene (see Supplementary Table 1 for a full list of candidate genes). Our key behavioral measure is the extent of utilitarian (*vs* deontological) judgment in response to a widely used set of moral dilemmas, focusing specifically on 'high-conflict' (Koenigs et al., 2007), 'personal' (Greene et al., 2001) dilemmas. Study 1 examines the relationship between the 49 selected SNPs and utilitarian/deontological moral judgment. Study 2 aims to replicate the two above-threshold effects observed in Study 1.

Study 1

Materials and methods

Participants. Participants were recruited through the study pool operated by the Department of Psychology, Harvard University; through advertisements posted publicly in Cambridge, MA, USA; and through advertisements on Craig's List. Potential participants were screened for psychiatric or neurological illness and a history of substance abuse. Only Caucasian participants were selected for participation to reduce population stratification artifacts (Cardon and Bell, 2001) although formal control for population admixture was incorporated as described below. Participants were paid \$10 for participation and \$5 for travel if necessary.

Materials. The moral judgment task employed a modified set of 36 standard scenarios (Greene et al., 2001; Greene et al., 2004; Greene et al., 2008) falling into three categories (see Supplementary Materials for dilemmas). In the 12 critical 'high-conflict' (Koenigs et al., 2007) dilemmas (e.g. the *footbridge* dilemma) one can save several lives by harming or killing one individual in a 'personal' manner (Greene et al., 2001, 2009). Here, the utilitarian option is to approve of the harmful action because it produces a greater good. The 'impersonal' dilemmas also include a utilitarian option where the harm is produced in a less 'personal' manner and (typically) occurs as a side-effect. In the low-conflict 'dilemmas' one can harm an individual in a 'personal' manner, but in a way that does not promote the greater good. Consistent with previous methods (Greene et al.,

2008; Paxton et al., 2012; Shenhav and Greene, 2014) only data from high-conflict dilemmas were analyzed. The 'impersonal' and 'low-conflict' dilemmas were included in an attempt to reduce rote responding by making the dilemmas more variable.

Participants completed the moral judgment task on a computer. The task consists of 36 scenarios written in the second person. Each scenario is presented in three screens. Screen 1 describes a situation. In the critical high-conflict scenarios/dilemmas, the situation involves an imminent harm. Screen 2 describes an active and passive response to the situation and the expected consequences of those responses. Screen 3 prompts participants for a yes/no response to the question, 'Is it morally acceptable for you to [perform action described in Screen 2]?'

After finishing the moral judgment task, participants completed a battery of the following personality measures: the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988; Thompson, 2007), Need for Cognition Scale (Cacioppo et al., 1984), the Disgust Scale (Haidt et al., 1994), the neuroticism subscale of the Five Factor Inventory (Costa and MacCrae, 1992), Behavioral Inhibition System/Behavioral Activation System Scales (Carver and White, 1994), Barratt Impulsiveness Scale (Patton et al., 1995), Cognitive Reflection Task (Frederick, 2005), Faith in Intuition Scale (Epstein et al., 1996), the Ten Item Personality Inventory (Gosling et al., 2003) and a temporal discounting task. Participants were asked to describe their general political orientations with respect to social and economic issues, as well as their views on several specific moral controversies. Finally, they reported on their recent experiences (if any) with depression/anhedonia.

SNP selection and genotyping. Because one of our primary hypotheses concerned OXTR, a sample of 25 SNPs from OXTR was selected to capture common variation in that gene. SNPs in the remaining genes were selected based on the extant literature associating candidate genes with relevant cognitive processes and social behaviors (see above). SNP genotyping was performed at the Massachusetts General Hospital Center for Human Genetic Research using the Sequenom iPLEX Gold® chemistry and the MassARRAY® system (see Supplementary Materials for detailed genotyping procedures).

Genotyping quality control. In Study 1, 102 markers were genotyped in 274 samples (including 3 duplicates). 62 of these markers spanned 10 candidate genes and the other 40 markers were part of a standard laboratory ancestry informative marker set (AIMs) used to visualize sample clustering by race/ethnicity. Summary statistics were performed using PLINK (Purcell et al., 2007) to determine sample and genotyping quality and to remove poor SNPs and/or samples if needed (see Supplementary Materials for detailed quality control procedures). Following quality control checks, 83 markers (34 of which were ancestry markers) and 267 samples remained.

Genetic ancestry analysis. Multi-dimensional scaling (MDS) analysis was performed in PLINK combining the HapMap Phase 3 (HapMap3) data set with our data set on the AIMs panel to visualize how the samples would cluster in a two-dimensional scatter plot and help assist in measuring genetic distance. The AIMs panel contains a set of markers that best differentiate and cluster individuals in a data set into continental populations. This helps identify population structure to allow for control of population stratification. In MDS analysis, PLINK assigns an Identity by State (IBS) score for each sample pair at each marker. We created a scatter plot using the first two dimensions or axes of variation to determine where the samples fall relative to the

HapMap3 samples (Supplementary Figures 1 and 2 for MDS plots). Of the 267 samples that passed QC, 228 (225 for OXTR SNP rs237889) were included in the association analysis because they fell within the HapMap3 European/Caucasian cluster and included complete phenotype data. We also used the first four MDS components as covariates in all regression models to enhance adjustment for ancestry.

Association analysis. Our single-marker analysis used linear regression to test our quantitative traits for SNP association while controlling for ancestral diversity as described above. The linear regression model is SNP additive; depending on the direction of the beta coefficient, each additional minor allele represents an increase or decrease in the phenotype of interest. Our primary analysis examined the relationship between our selected SNPs and the frequency of utilitarian responses to the high-conflict moral dilemmas. Permutation testing was run (10 000 permutations) to evaluate the significance of each SNP while controlling for multiple comparisons.

Results

In Study 1, 274 participants (aged 18–64, average 24.2 years old, 58% female, 14.9 mean years of education) completed a moral judgment task and underwent genotyping. Of these, 228 participants' genetic data passed initial quality control, had complete behavioral data and met genetic ancestry criteria (see Materials and Methods for details). The data from only these participants were included in our analyses.

In the moral judgment task, participants were asked to decide whether or not the action described in the dilemma was morally acceptable. A 'yes' response was always the utilitarian decision. The proportion of utilitarian responses was then calculated for each participant. A single SNP association used linear regression to evaluate the relationship between the number of copies of the minor allele of 49 high quality markers and the percentage of utilitarian responses to the high-conflict moral dilemmas. In order to control for population stratification, we conducted MDS genetic ancestry analysis. We then used the first four MDS components as covariates in our regression model (see Materials and Methods and Supplementary Materials for more details).

Two SNPs reached significance at an uncorrected threshold of $P < 0.05$. For the SNP rs237889, found on chromosome 3 in an intron of the OXTR gene, there was a significant negative association between the number of copies of the minor allele, T, and the frequency of utilitarian responses ($\beta = -0.156$, $P = 0.019$). In other words, participants homozygous for the C allele gave the most utilitarian responses, and participants homozygous for the T allele gave the fewest (Figure 1, left). This effect persisted when including sex ($\beta = -0.152$, $P = 0.024$), age ($\beta = -0.166$, $P = 0.015$), or mood ($\beta = -0.161$, $P = 0.016$) as covariates. In addition to this effect, the synonymously coding SNP rs1042615 found in AVPR1A on chromosome 12, was also significantly negatively associated with the frequency of utilitarian responses to moral dilemmas ($\beta = -0.168$, $P = 0.011$). This effect also persisted while including sex ($\beta = -0.17$, $P = 0.01$), age ($\beta = -0.17$, $P = 0.015$), or mood ($\beta = -0.17$, $P = 0.011$) as covariates. On average, individuals homozygous for the minor T allele gave the fewest utilitarian responses while individuals homozygous for the C allele gave the most. Neither of these effects reached study-wide significance after correction for multiple comparisons using a permutation test.

Additionally, we found nominally significant associations between several supplementary self-report measures and

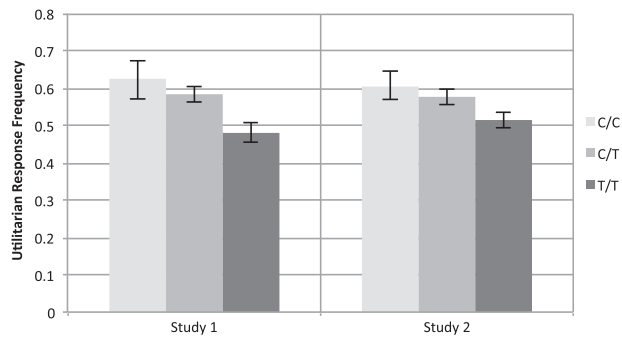


Fig. 1. Average frequency of utilitarian responses for Study 1 and Study 2 participants as a function of genotype. Shaded bars reflect the number of copies of the minor (T) allele of OXTR SNP rs237889. In Study 1, 91 participants (40.44%) had the C/C genotype, 109 (48.44%) were C/T, and 25 (11.11%) were T/T. In Study 2, 118 (36.65%) participants were C/C, 156 (48.45%) were C/T, and 48 (14.91%) were T/T.

AVPR1A rs1042615 or OXTR rs237889 (see Supplementary Table 2 for the full results). Using linear regression, controlling for population stratification as described above, we found marginally significant associations between the OXTR SNP and the motor impulsiveness subscale of the Barratt Impulsiveness Scale ($\beta = 0.16$, $P = 0.037$), the Behavioral Inhibition System Scale ($\beta = 0.164$, $P = 0.013$), two facets of the neuroticism domain of the Five Factor Inventory (NEO-FFI) (impulsiveness: $\beta = 0.143$, $P = 0.029$; self-consciousness: $\beta = 0.128$, $P = 0.046$), as well as total neuroticism score ($\beta = 0.159$, $P = 0.014$). Further, we found marginally significant associations between the AVPR1A SNP and total score on the Faith in Intuition Scale ($\beta = 0.176$, $P = 0.008$), the hostility facet of the neuroticism domain on the NEO-FFI ($\beta = -0.156$, $P = 0.017$), total score on the Need for Cognition Scale ($\beta = 0.172$, $P = 0.009$), the positive affect subscale of the PANAS ($\beta = 0.141$, $P = 0.033$), and the openness subscale of the Ten Item Personality Inventory (TIPI) ($\beta = 0.163$, $P = 0.015$). None of these results survived correction for multiple comparisons. There was no significant association between either of these SNPs and any of the demographic information we collected, including age, education, and social or economic conservatism.

Because none of our results reached study wide significance after correcting for multiple comparisons, we attempted to replicate these findings in a second, independent sample. In Study 2, we measured only the relationship between our two marginally significant SNPs from Study 1 and the behavioral measures with which they were associated. All other SNPs and measures were not included in Study 2 analyses.

Study 2

Materials and methods

In Study 2, 370 participants (aged 18–65, average 26.31 years old, 57% female, 15.46 mean years of education) completed a moral judgment task identical to that of Study 1, but with three modifications. First, in an attempt to increase the sensitivity of our key measure, we replaced Study 1's dichotomous yes/no response with a seven-point rating scale anchored by the phrases 'completely unacceptable' to 'completely acceptable.' Second, we eliminated the impersonal and low-conflict dilemmas, which were not analyzed in Study 1 (see Materials and Methods). Finally, for Study 2 we also included an additional set of five medical dilemmas (Ransohoff, 2011; Ransohoff et al., manuscript in preparation). These dilemmas retain the

essential structure of the standard 'high-conflict' dilemmas (pitting individual rights against the greater good) and are more realistic, with particular relevance to the field of bioethics. Participants also completed the same battery of supplementary behavioral measures used in Study 1. Of the 370 individuals who participated in Study 2, 322 had complete behavioral data and had genetic data that passed quality control and ancestry criteria (see Study 1 Materials and Methods). Only these participants were included in further analyses.

Results

In Study 2, we examined the effects of our critical SNPs (rs1042615 of AVPR1A and rs237889 of OXTR) on participants' mean rating scale responses to our moral dilemmas. As in Study 1, we included the first four MDS components as covariates in our regression model. Supporting the findings of Study 1, we found a consistent negative linear relationship between the number of copies of the minor allele of rs237889 and moral judgments ($\beta = -0.151$, $P = 0.007$) across all 17 dilemmas (original high-conflict and new medical dilemmas). As in Study 1, participants homozygous for the minor allele, T, gave the least utilitarian responses, while participants homozygous for the C allele gave the most, with the heterozygotes in between. This effect was also present when restricted to the original set of high-conflict dilemmas ($\beta = -0.14$, $P = 0.013$) and within the new set of medical dilemmas ($\beta = -0.135$, $P = 0.015$). As expected, responses to the medical dilemmas correlated positively with responses to the original dilemmas ($R = 0.62$, $P < 0.001$). Further, reliability analysis found the full set of 17 dilemmas to be highly reliable with a Cronbach's alpha of 0.88. The effect of genotype on subjects' average response to the full set of dilemmas survived correction for multiple comparisons (Bonferroni corrected $P = 0.014$). This effect also persisted after including mood ($\beta = -0.139$, $P = 0.014$) or age ($\beta = -0.134$, $P = 0.019$) as covariates. However, unlike in Study 1, the association between participants' average response to the full set of moral dilemmas and the OXTR SNP was somewhat attenuated by sex ($\beta = -0.114$, $P = 0.042$). Focusing on the direct relationship between gender and moral judgment, we found that males' responses were significantly more utilitarian than females' (males: $M = 4.66$, s.d. = 0.94; females: $M = 4.2$, s.d. = 0.95; $t(310) = 4.225$, $P < 0.01$).

In contrast to Study 1, variation in AVPR1A SNP rs1042615 exhibited no significant relationship with utilitarian moral judgment ($\beta = -0.043$, $P = 0.45$). Further, none of the other behavioral measures that were nominally significantly associated with either the AVPR1A or OXTR SNPs in Study 1 maintained their significant relationship in Study 2 (see Supplementary Table 3 for full results).

Because Study 2's objective was to replicate Study 1's results, we also recoded Study 2's continuous responses to form a dichotomous variable, enabling a more direct comparison between the studies. Each response greater than 4 (the scale midpoint) was recoded as a utilitarian response, and each response less than 4 was recoded as deontological. This produced a utilitarian score (percentage of utilitarian responses) for each participant in Study 2, equivalent to our phenotype variable of interest in Study 1 (this did not result in dropping any subjects because each subject gave at least one response smaller or larger than 4). We then conducted our primary analysis exactly as in Study 1, examining the effects of our critical SNPs on the percentage of utilitarian responses to the original set of high-conflict dilemmas. Consistent with the findings using our

continuous measure, we found a significant association between the number of copies of the minor allele of the OXTR SNP rs237889 and the percentage of utilitarian responses ($\beta = -0.119$, $P = 0.034$) (Figure 1, right). Likewise, consistent with our finding using the continuous measure, SNP rs1042615 of AVPR1A failed to reach nominal significance using our dichotomized measure.

Thus, while Study 2 failed to confirm the original AVPR1A finding, it successfully reproduced the previously observed relationship between OXTR rs237889 and utilitarian/deontological judgment in response to high-conflict moral dilemmas. It also extended this result to a new set of more realistic medical dilemmas. An analysis employing all 17 Study 2 dilemmas (original + medical), yielded an effect size almost identical to that of the original OXTR result observed in Study 1 (Study 2: $\beta = -0.151$, $P = 0.007$ vs Study 1: $\beta = -0.156$, $P = 0.019$). Combining the results of Studies 1 and 2 using Study 2's dichotomous measure (standardized within study) we find a robust association between OXTR rs237889 variation and moral judgment ($\beta = -0.135$, $P = 0.002$).

Discussion

The present results provide evidence for a link between variation in OXTR and moral judgment, employing a sample of more than 500 individuals responding to set of widely studied moral dilemmas. In Study 1 ($N = 228$), we observed a correlation between variation in SNP rs237889 and the frequency of utilitarian judgment ($P = 0.019$, uncorrected), with a linear trend observed across T/T, C/T and C/C genotypes (Figure 1, left). Study 2 replicated this finding using a larger sample ($N = 322$), revealing significant effects using the same testing materials ($P = 0.013$) and a new set of medical dilemmas ($P = 0.015$) (Figure 1, right). Once again, the effect observed in Study 2's replication sample was nearly identical to that observed in Study 1. Thus, these data provide the strongest evidence to date linking variation in a specific gene to variation in moral judgment.

As noted above, OXTR was selected as a candidate gene for the present study because of oxytocin's observed influence on moral judgment (De Dreu et al., 2011) and social cognition more generally (Heinrichs et al., 2009; Skuse and Gallagher, 2009; Meyer-Lindenberg et al., 2011), along with its role in modulating activation in brain regions known to play a critical role in moral judgment (Kirsch et al., 2005; Domes et al., 2007; Baumgartner et al., 2008; Petrovic et al., 2008; Gamer et al., 2010; Koch et al., 2015). Likewise, OXTR polymorphisms have been associated with variation in relevant social-behavioral phenotypes such as proneness to empathy (Rodrigues et al., 2009) and pro-social temperament (Tost et al., 2010). However, the SNP implicated here (rs237889) was not selected because of previously observed relationships with relevant phenotypes. Instead, it was selected using an algorithm designed to maximize coverage of the variation within OXTR as a whole. As it happens, rs237889 appears in a non-coding region (intron) of OXTR. Nevertheless, one study assessing the effects of OXTR SNPs on RNA expression levels in 365 samples found that variation in rs237889 is significantly linearly associated with OXTR expression (Myers et al., 2014). However, the direction of this association was not reported.

Several studies implicate rs237889 in increased risk for autism spectrum disorders (Lerer et al., 2008; Campbell et al., 2011; Harrison et al., 2015; Kranz et al., 2016). Specifically, individuals with ASD are more likely to have copies of the minor T allele than the general population. Further, those with more copies of this allele score significantly higher on the Autism Diagnostic Interview (Kranz et al., 2016). In the present research, carriers of

the T allele were also more likely to give more deontological responses to moral dilemmas. While historically research suggests that ASD is associated with utilitarian moral judgment (Gleichgerricht et al., 2013), a more recent study finds that the high levels of utilitarian responding, often observed in individuals on the autism spectrum, may in fact be due to the high co-occurrence of alexithymia (the inability to recognize and identify emotions) and autism. In fact, when measuring alexithymia and autistic traits separately in individuals with ASD, autistic traits are significantly negatively associated with utilitarian responses to moral dilemmas (Patil et al., 2016).

Our OXTR SNP of interest has also been associated with traits known to increase the risk of psychopathy. Dadds et al. (2014) found that 6- to 16-year-old children with diagnosable conduct disorders scored higher on measures of callous-unemotional traits if they carry more copies of the C allele of rs237889 (as part of a four haplotype block). As described above, C allele carriers gave significantly more utilitarian responses in the present research. In fact, past work on moral judgment and psychopathy has found a strong relationship between low-anxiety psychopathy and increased utilitarian responses to personal high-conflict moral dilemmas (Koenigs et al., 2012).

The neural mechanisms responsible for the correlation observed here remain largely unknown. However, past research suggests that variation in OXTR is most likely to influence moral judgment by modulating the influence of oxytocin within neural pathways that have previously been identified as preferentially supporting deontological moral judgment. More specifically, it is possible that OXTR variation influences the effects of oxytocin in the amygdala (Greene et al., 2004; Blair, 2007; Glenn et al., 2009; Decety and Porges, 2011; Shenhav and Greene, 2014), which in turn influences moral judgment by modulating the representation of decision weights in the VMPFC (Blair, 2007; Ciaramelli et al., 2007; Koenigs et al., 2007; Shenhav and Greene, 2010; Decety and Porges, 2011; Shenhav and Greene, 2014). This hypothesis may be tested using a combination of genotyping, intranasal administration of oxytocin, functional imaging and non-invasive brain stimulation such tDCS or TMS. Likewise, it may be possible to test components of this hypothesis using animal models that afford greater experimental control (Bartal et al., 2011).

The observed relationship with OXTR is notable because it connects individual differences at the molecular level to differences in complex social and, more specifically, moral judgment. One might assume, for example, that human maternal behavior depends critically on oxytocin and related genetic influences, as it does in non-human animals (Pedersen and Prange, 1979; Pedersen et al., 1982; Fahrbach et al., 1985; Insel et al., 1994; Pedersen et al., 1994; Young et al., 1997; Young et al., 2001). However, only humans can contemplate moral dilemmas pitting the rights of the individual against the greater good. The present results indicate that our divergent answers to these complex philosophical questions can be explained, at least in part, by identifiable genetic differences.

Supplementary data

Supplementary data are available at SCAN online.

Funding

This work was supported by the National Science Foundation [grant number SES-0952129] to J.D.G and R.H.P

and by the National Institutes of Health [grant number S10OD020039] to the Harvard Center for Brain Science.

Conflict of interest. None declared.

References

- Amit, E., Greene, J.D. (2012). You see, the ends don't justify the means visual imagery and moral judgment. *Psychological Science*, **23**(8), 861–8.
- Apicella, C.L., Cesarini, D., Johannesson, M., et al. (2010). No association between oxytocin receptor (OXTR) gene polymorphisms and experimentally elicited social preferences. *PLoS One*, **5**(6), e11153.
- Avinun, R., Ebstein, R.P., Knafo, A. (2012). Human maternal behaviour is associated with arginine vasopressin receptor 1A gene. *Biology Letters*, **8**(5), 894–6.
- Avinun, R., Israel, S., Shalev, I., et al. (2011). AVPR1A variant associated with preschoolers' lower altruistic behavior. *PLoS One*, **6**(9), e25274.
- 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**(2), 128–34.
- Bale, T.L., Davis, A.M., Auger, A.P., Dorsa, D.M., McCarthy, M.M. (2001). CNS region-specific oxytocin receptor expression: importance in regulation of anxiety and sex behavior. *The Journal of Neuroscience*, **21**(7), 2546–52.
- Barnett, J., Scoriels, L., Munafò, M. (2008). Meta-analysis of the cognitive effects of the catechol-O-methyltransferase gene Val158/108Met polymorphism. *Biological Psychiatry*, **64**(2), 137–44.
- Bartal, I.B.A., Decety, J., Mason, P. (2011). Empathy and pro-social behavior in rats. *Science* **334**(6061), 1427–30.
- Bartz, J.A., Lydon, J.E., Kolevzon, A., et al. (2015). Differential effects of oxytocin on agency and communion for anxiously and avoidantly attached individuals. *Psychological Science*, **26**(8), 1177–86.
- Bartz, J.A., Zaki, J., Bolger, N., Ochsner, K.N. (2011). Social effects of oxytocin in humans: context and person matter. *Trends in Cognitive Sciences*, **15**(7), 301–9.
- Baumgartner, T., Heinrichs, M., Vonlanthen, A., Fischbacher, U., Fehr, E. (2008). Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. *Neuron*, **58**(4), 639–50.
- Bechara, A., Damasio, A.R., Damasio, H., Anderson, S.W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition*, **50**(1), 7–15.
- Benjamini, Y., Drai, D., Elmer, G., Kafkafi, N., Golani, I. (2001). Controlling the false discovery rate in behavior genetics research. *Behavioural Brain Research*, **125**(1), 279–84.
- Blair, R. (2007). The amygdala and ventromedial prefrontal cortex in morality and psychopathy. *Trends in Cognitive Sciences*, **11**(9), 387–92.
- Blasi, G., Mattay, V.S., Bertolino, A., et al. (2005). Effect of catechol-O-methyltransferase val158met genotype on attentional control. *The Journal of Neuroscience*, **25**(20), 5038–45.
- Boccia, M., Petrusz, P., Suzuki, K., Marson, L., Pedersen, C.A. (2013). Immunohistochemical localization of oxytocin receptors in human brain. *Neuroscience*, **253**, 155–64.
- Brunnlieb, C., Münte, T.F., Tempelmann, C., Heldmann, M. (2013). Vasopressin modulates neural responses related to emotional stimuli in the right amygdala. *Brain Research*, **1499**, 29–42.
- Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L. (2008). The brain's default network. *Annals of the New York Academy of Sciences*, **1124**, 1–38.
- Cacioppo, J.T., Petty, R.E., Feng Kao, C. (1984). The efficient assessment of need for cognition. *Journal of Personality Assessment* **48**(3), 306–7.
- Campbell, D.B., Datta, D., Jones, S.T., et al. (2011). Association of oxytocin receptor (OXTR) gene variants with multiple phenotype domains of autism spectrum disorder. *Journal of Neurodevelopmental Disorders*, **3**(2), 101–12.
- Canli, T., Congdon, E., Gutknecht, L., Constable, R., Lesch, K. (2005). Amygdala responsiveness is modulated by tryptophan hydroxylase-2 gene variation. *Journal of Neural Transmission*, **112**(11), 1479–85.
- Cardon, L.R., Bell, J.I. (2001). Association study designs for complex diseases. *Nature Reviews Genetics*, **2**(2), 91–9.
- Carver, C.S., White, T.L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS scales. *Journal of Personality and Social Psychology*, **67**(2), 319.
- Christ, C.C., Carlo, G., Stoltenberg, S.F. (2016). Oxytocin receptor (OXTR) single nucleotide polymorphisms indirectly predict prosocial behavior through perspective taking and empathic concern. *Journal of Personality*, **84**(2), 204–13.
- Ciaramelli, E., Muccioli, M., Ladavas, E., di Pellegrino, G. (2007). Selective deficit in personal moral judgment following damage to ventromedial prefrontal cortex. *Social Cognitive and Affective Neuroscience*, **2**(2), 84–92.
- Coccaro, E.F., Kavoussi, R.J., Hauger, R.L., Cooper, T.B., Ferris, C.F. (1998). Cerebrospinal fluid vasopressin levels: correlates with aggression and serotonin function in personality-disordered subjects. *Archives of General Psychiatry*, **55**(8), 708–14.
- Conway, P., Gawronski, B. (2013). Deontological and utilitarian inclinations in moral decision making: a process dissociation approach. *Journal of Personality and Social Psychology*, **104**(2), 216.
- Costa, P.T., MacCrae, R.R. (1992). *Revised NEO Personality Inventory (NEO PI-R) and NEO Five-Factor Inventory (NEO FFI): Professional Manual*. Odessa, FL: Psychological Assessment Resources.
- Crockett, M.J., Clark, L., Hauser, M.D., Robbins, T.W. (2010). Serotonin selectively influences moral judgment and behavior through effects on harm aversion. *Proceedings of the National Academy of Sciences of the United States of America*, **107**(40), 17433–8.
- Cushman, F., Greene, J.D. (2012). Finding faults: how moral dilemmas illuminate cognitive structure. *Social Neuroscience*, **7**(3), 269–79.
- Dadds, M.R., Moul, D., Cauchi, A., et al. (2014). Polymorphisms in the oxytocin receptor gene are associated with the development of psychopathy. *Development and Psychopathology*, **26**(1), 21–31.
- De Dreu, C.K., Greer, L.L., Van Kleef, G.A., Shalvi, S., Handgraaf, M.J. (2011). Oxytocin promotes human ethnocentrism. *Proceedings of the National Academy of Sciences of the United States of America*, **108**(4), 1262–6.
- De Dreu, C.K., Kret, M.E. (2016). Oxytocin conditions intergroup relations through upregulated in-group empathy, cooperation, conformity, and defense. *Biological Psychiatry*, **79**(3), 165–73.
- Decety, J., Porges, E.C. (2011). Imagining being the agent of actions that carry different moral consequences: an fMRI study. *Neuropsychologia*, **49**(11), 2994–3001.
- Ditzen, B., Schaer, M., Gabriel, B., Bodenmann, G., Ehlert, U., Heinrichs, M. (2009). Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. *Biological Psychiatry*, **65**(9), 728–31.

- Domes, G., Heinrichs, M., Gläscher, J., Büchel, C., Braus, D.F., Herpertz, S.C. (2007). Oxytocin attenuates amygdala responses to emotional faces regardless of valence. *Biological Psychiatry*, *62*(10), 1187–90.
- Ebstein, R.P., Israel, S., Lerer, E., et al. (2009). Arginine vasopressin and oxytocin modulate human social behavior. *Annals of the New York Academy of Sciences*, *1167*(1), 87–102.
- Egan, M.F., Goldberg, T.E., Kolachana, B.S., et al. (2001). Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(12), 6917–22.
- Epstein, S., Pacini, R., Denes-Raj, V., Heier, H. (1996). Individual differences in intuitive–experiential and analytical–rational thinking styles. *Journal of Personality and Social Psychology*, *71*(2), 390.
- Fahrback, S., Morrell, J., Pfaff, D. (1985). Possible role for endogenous oxytocin in estrogen-facilitated maternal behavior in rats. *Neuroendocrinology*, *40*(6), 526–32.
- Fischer, J.M., Ravizza, M. (1992). When the will is free. *Philosophical Perspectives*, *6*, 423–51.
- Foot, P. (1978). *Virtues and Vices and Others Essays in Moral Philosophy*. Berkeley: University of California Press.
- Frederick, S. (2005). Cognitive reflection and decision making. *Journal of Economic Perspectives*, *19*(4), 25–42.
- Freedman, M., Reich, D., Penney, K., et al. (2004). Assessing the impact of population stratification on genetic association studies. *Nature Genetics*, *36*(4), 388–93.
- Frijling, J.L., van Zuiden, M., Koch, S.B., Nawijn, L., Veltman, D.J., Olff, M. (2015). Intranasal oxytocin affects amygdala functional connectivity after trauma script-driven imagery in distressed recently trauma-exposed individuals. *Neuropsychopharmacology*, *41*(5), 1286–96.
- Furman, D.J., Chen, M.C., Gotlib, I.H. (2011). Variant in oxytocin receptor gene is associated with amygdala volume. *Psychoneuroendocrinology* *36*(6), 891–7.
- Gamer, M., Zurowski, B., Büchel, C. (2010). Different amygdala subregions mediate valence-related and attentional effects of oxytocin in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(20), 9400–5.
- Gleichgerricht, E., Torralva, T., Rattazzi, A., Marengo, V., Roca, M., Manes, F. (2013). Selective impairment of cognitive empathy for moral judgment in adults with high functioning autism. *Social Cognitive and Affective Neuroscience*, *8*(7), 780–8.
- Glenn, A.L., Raine, A., Schug, R.A. (2009). The neural correlates of moral decision-making in psychopathy. *Molecular Psychiatry*, *14*, 5–6.
- Gosling, S.D., Rentfrow, P.J., Swann, W.B. (2003). A very brief measure of the big-five personality domains. *Journal of Research in Personality*, *37*(6), 504–28.
- Grandy, D.K., Litt, M., Allen, L., et al. (1989). The human dopamine D2 receptor gene is located on chromosome 11 at q22-q23 and identifies a TaqI RFLP. *American Journal of Human Genetics*, *45*(5), 778.
- Greene, J.D. (2007). The secret joke of Kant’s soul. In Nadelhoffer, T., Eddy, N., Nichols, S., editors. *Moral Psychology: Historical and Contemporary Readings*, Malden, MA: Wiley-Blackwell, 359–72.
- Greene, J.D. (2014a). The cognitive neuroscience of moral judgment and decision-making. In Gazzaniga, M., editor. *The Cognitive Neurosciences Vol. 5*, Cambridge, MA: MIT Press; pp. 1013023.
- Greene, J.D. (2014b). Beyond point-and-shoot morality: why cognitive (neuro) science matters for ethics*. *Ethics*, *124*(4), 695–726.
- Greene, J.D., Cushman, F.A., Stewart, L.E., Lowenberg, K., Nystrom, L.E., Cohen, J.D. (2009). Pushing moral buttons: the interaction between personal force and intention in moral judgment. *Cognition*, *111*(3), 364–71.
- Greene, J.D., Morelli, S.A., Lowenberg, K., Nystrom, L.E., Cohen, J.D. (2008). Cognitive load selectively interferes with utilitarian moral judgment. *Cognition*, *107*(3), 1144–54.
- Greene, J.D., Nystrom, L.E., Engell, A.D., Darley, J.M., Cohen, J.D. (2004). The neural bases of cognitive conflict and control in moral judgment. *Neuron*, *44*(2), 389–400.
- Greene, J.D., Sommerville, R.B., Nystrom, L.E., Darley, J.M., Cohen, J.D. (2001). An fMRI investigation of emotional engagement in moral judgment. *Science*, *293*(5537), 2105–8.
- Guastella, A.J., Kenyon, A.R., Alvares, G.A., Carson, D.S., Hickie, I.B. (2010). Intranasal arginine vasopressin enhances the encoding of happy and angry faces in humans. *Biological Psychiatry*, *67*(12), 1220–2.
- Haidt, J., McCauley, C., Rozin, P. (1994). Individual differences in sensitivity to disgust: A scale sampling seven domains of disgust elicitors. *Personality and Individual Differences*, *16*(5), 701–13.
- Hariri, A.R., Mattay, V.S., Tessitore, A., et al. (2002). Serotonin transporter genetic variation and the response of the human amygdala. *Science*, *297*(5580), 400–3.
- Harrison, A.J., Gamsiz, E.D., Berkowitz, I.C., Nagpal, S., Jerskey, B.A. (2015). Genetic variation in the oxytocin receptor gene is associated with a social phenotype in autism spectrum disorders. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *168*(8), 720–9.
- Heinrichs, M., von Dawans, B., Domes, G. (2009). Oxytocin, vasopressin, and human social behavior. *Frontiers in Neuroendocrinology*, *30*(4), 548–57.
- Heinz, A., Braus, D.F., Smolka, M.N., et al. (2004). Amygdala-pre-frontal coupling depends on a genetic variation of the serotonin transporter. *Nature Neuroscience*, *8*(1), 20–1.
- Huber, D., Veinante, P., Stoop, R. (2005). Vasopressin and oxytocin excite distinct neuronal populations in the central amygdala. *Science* *308*(5719), 245–8.
- Inoue, H., Yamasue, H., Tochigi, M., et al. (2010). Association between the oxytocin receptor gene and amygdalar volume in healthy adults. *Biological Psychiatry*, *68*(11), 1066–72.
- Insel, T., Winslow, J., Wang, Z., Young, L., Hulihan, T. (1994). Oxytocin and the molecular basis of monogamy. *Advances in Experimental Medicine and Biology*, *395*, 227–34.
- Ioannidis, J. (2005). Why most published research findings are false. *PLoS Med*, *2*(8), e124.
- Israel, S., Lerer, E., Shalev, I., et al. (2009). The oxytocin receptor (OXTR) contributes to prosocial fund allocations in the dictator game and the social value orientations task. *PLoS One*, *4*(5), e5535.
- Kimura, T., Tanizawa, O., Mori, K., Brownstein, M.J., Okayama, H. (1992). Structure and expression of a human oxytocin receptor. *Nature*, *356*(6369), 526–9.
- Kirsch, P., Esslinger, C., Chen, Q., et al. (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. *The Journal of Neuroscience*, *25*(49), 11489–93.
- Knafo, A., Israel, S., Darvasi, A., et al. (2008). Individual differences in allocation of funds in the dictator game associated with length of the arginine vasopressin 1a receptor RS3 promoter region and correlation between RS3 length and hippocampal mRNA. *Genes, Brain and Behavior*, *7*(3), 266–75.
- Koch, S.B., van Zuiden, M., Nawijn, L., Frijling, J.L., Veltman, D.J., Olff, M. (2015). Intranasal oxytocin administration dampens amygdala reactivity towards emotional faces in male and female PTSD patients. *Neuropsychopharmacology*, *41*, 1495–504.

- Koenigs, M., Kruepke, M., Zeier, J., Newman, J.P. (2012). Utilitarian moral judgment in psychopathy. *Social Cognitive and Affective Neuroscience*, 7(6), 708–14.
- Koenigs, M., Young, L., Adolphs, R., et al. (2007). Damage to the prefrontal cortex increases utilitarian moral judgements. *Nature*, 446(7138), 908–11.
- Kranz, T.M., Kopp, M., Waltes, R., et al. (2016). Meta-analysis and association of two common polymorphisms of the human oxytocin receptor gene in autism spectrum disorder. *Autism Research*, doi: 10.1002/aur.1597.
- Leng, G., Ludwig, M. (2016). Intranasal oxytocin: myths and delusions. *Biological Psychiatry*, 79(3), 243–50.
- Lerer, E., Levi, S., Salomon, S., Darvasi, A., Yirmiya, N., Ebstein, R. (2008). Association between the oxytocin receptor (OXTR) gene and autism: relationship to Vineland Adaptive Behavior Scales and cognition. *Molecular Psychiatry*, 13(10), 980–8.
- LoParo, D., Waldman, I.D. (2015). The oxytocin receptor gene (OXTR) is associated with autism spectrum disorder: a meta-analysis. *Molecular Psychiatry*, 20(5), 640–6.
- Marsh, A.A., Crowe, S.L., Henry, H.Y., Gorodetsky, E.K., Goldman, D., Blair, R. (2011). Serotonin transporter genotype (5-HTTLPR) predicts utilitarian moral judgments. *PLoS One*, 6(10), e25148.
- Marusak, H.A., Furman, D.J., Kuruvadi, N., et al. (2015). Amygdala responses to salient social cues vary with oxytocin receptor genotype in youth. *Neuropsychologia*, 79, 1–9.
- Meyer-Lindenberg, A., Domes, G., Kirsch, P., Heinrichs, M. (2011). Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nature Reviews Neuroscience*, 12(9), 524–38.
- Meyer-Lindenberg, A., Kolachana, B., Gold, B., et al. (2009). Genetic variants in AVPR1A linked to autism predict amygdala activation and personality traits in healthy humans. *Molecular Psychiatry*, 14(10), 968–75.
- Miller, E.K., Cohen, J.D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, 24(1), 167–202.
- Mitchell, J.P. (2009). Inferences about mental states. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 364(1521), 1309–16.
- Moore, A.B., Clark, B.A., Kane, M.J. (2008). Who shalt not kill? Individual differences in working memory capacity, executive control, and moral judgment. *Psychological Science*, 19(6), 549–57.
- Moretto, G., Làdavas, E., Mattioli, F., Di Pellegrino, G. (2010). A psychophysiological investigation of moral judgment after ventromedial prefrontal damage. *Journal of Cognitive Neuroscience*, 22(8), 1888–99.
- Motoki, K., Sugiura, M., Takeuchi, H., et al. (2016). Are plasma oxytocin and vasopressin levels reflective of amygdala activation during the processing of negative emotions? A preliminary study. *Frontiers in Psychology*, 7.
- Myers, A.J., Williams, L., Gatt, J.M., et al. (2014). Variation in the oxytocin receptor gene is associated with increased risk for anxiety, stress and depression in individuals with a history of exposure to early life stress. *Journal of Psychiatric Research*, 59, 93–100.
- Padoa-Schioppa, C., Cai, X. (2011). The orbitofrontal cortex and the computation of subjective value: consolidated concepts and new perspectives. *Annals of the New York Academy of Sciences*, 1239(1), 130–7.
- Patil, I., Melsbach, J., Hennig-Fast, K., Silani, G. (2016). Divergent roles of autistic and alexithymic traits in utilitarian moral judgments in adults with autism. *Scientific Reports*, 6.
- Patton, J.H., Stanford, M.S., Barratt, E.S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology*, 51, 768–74.
- Paxton, J.M., Bruni T., Greene, J.D. (2013). Are “counter-intuitive” deontological judgments really counter-intuitive?: An empirical reply to Kahane et al. (2012). *Social Cognitive and Affective Neuroscience*, 9(9), 1368–72.
- Paxton, J.M., Ungar, L., Greene, J.D. (2012). Reflection and reasoning in moral judgment. *Cognitive Science*, 36(1), 163–77.
- Pedersen, C.A., Ascher, J.A., Monroe, Y.L., Prange, A.J. (1982). Oxytocin induces maternal behavior in virgin female rats. *Science*, 216(4546), 648–50.
- Pedersen, C.A., Caldwell, J.D., Walker, C., Ayers, G., Mason, G.A. (1994). Oxytocin activates the postpartum onset of rat maternal behavior in the ventral tegmental and medial preoptic areas. *Behavioral Neuroscience*, 108(6), 1163.
- Pedersen, C.A., Prange, A.J. (1979). Induction of maternal behavior in virgin rats after intracerebroventricular administration of oxytocin. *Proceedings of the National Academy of Sciences of United States of America*, 76(12), 6661–5.
- Perkins, A.M., Leonard, A.M., Weaver, K., et al. (2013). A dose of ruthlessness: interpersonal moral judgment is hardened by the anti-anxiety drug lorazepam. *Journal of Experimental Psychology: General*, 142(3), 612.
- Petrinovich, L., O’Neill, P., Jorgensen, M. (1993). An empirical study of moral intuitions: toward an evolutionary ethics. *Journal of Personality and Social Psychology*, 64(3), 467.
- Petrovic, P., Kalisch, R., Singer, T., Dolan, R.J. (2008). Oxytocin attenuates affective evaluations of conditioned faces and amygdala activity. *The Journal of Neuroscience*, 28(26), 6607–15.
- Phelps, E.A., Delgado, M.R., Nearing, K.I., LeDoux, J.E. (2004). Extinction learning in humans: role of the amygdala and vmPFC. *Neuron*, 43(6), 897–905.
- Poulin, M., Holman, E., Buffone, A. (2012). The neurogenetics of nice: receptor genes for oxytocin and vasopressin interact with threat to predict prosocial behavior. *Psychological Science*, 23(5), 446–52.
- Purcell, S., Neale, B., Todd-Brown, K., et al. (2007). PLINK: a tool set for whole-genome association and population-based linkage analyses. *The American Journal of Human Genetics*, 81(3), 559–75.
- Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America*, 98(2), 676–82.
- Rangel, A., Camerer, C., Montague, P.R. (2008). A framework for studying the neurobiology of value-based decision making. *Nature Reviews Neuroscience*, 9(7), 545–56.
- Rangel, A., Hare, T. (2010). Neural computations associated with goal-directed choice. *Current Opinion in Neurobiology*, 20(2), 262–70.
- Ransohoff, K. (2011). Patients on the trolley track. (Undergraduate Thesis), Harvard University, Cambridge, MA.
- Ransohoff, K., Wikler, D., Greene, J.D. Manuscript in preparation.
- Riem, M.M., Bakermans-Kranenburg, M.J., Huffmeijer, R., van IJzendoorn, M.H. (2013). Does intranasal oxytocin promote prosocial behavior to an excluded fellow player? A randomized-controlled trial with Cyberball. *Psychoneuroendocrinology*, 38(8), 1418–25.
- Rilling, J.K., DeMarco, A.C., Hackett, P.D., et al. (2012). Effects of intranasal oxytocin and vasopressin on cooperative behavior and associated brain activity in men. *Psychoneuroendocrinology*, 37(4), 447–61.
- 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**(50), 21437–41.
- Schultz, W., Dayan, P., Montague, P.R. (1997). A neural substrate of prediction and reward. *Science*, **275**(5306), 1593–9.
- Shenhav, A., Greene, J.D. (2014). Integrative moral judgment: dissociating the roles of the amygdala and ventromedial prefrontal cortex. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, **34**(13), 4741–9.
- Shenhav, A., Greene, J.D. (2010). Moral judgments recruit domain-general valuation mechanisms to integrate representations of probability and magnitude. *Neuron*, **67**(4), 667–77.
- Skuse, D.H., Gallagher, L. (2009). Dopaminergic–neuropeptide interactions in the social brain. *Trends in Cognitive Sciences*, **13**(1), 27–35.
- Smolka, M., Bühler, M., Schumann, G., et al. (2007). Gene–gene effects on central processing of aversive stimuli. *Molecular Psychiatry*, **12**(3), 307–17.
- Suter, R.S., Hertwig, R. (2011). Time and moral judgment. *Cognition*, **119**(3), 454–8.
- Tansey, K.E., Brookes, K.J., Hill, M.J., et al. (2010). Oxytocin receptor (OXTR) does not play a major role in the aetiology of autism: genetic and molecular studies. *Neuroscience Letters*, **474**(3), 163–7.
- Thomas, B.C., Croft, K.E., Tranel, D. (2011). Harming kin to save strangers: further evidence for abnormally utilitarian moral judgments after ventromedial prefrontal damage. *Journal of Cognitive Neuroscience*, **23**(9), 2186–96.
- Thompson, E.R. (2007). Development and validation of an internationally reliable short-form of the positive and negative affect schedule (PANAS). *Journal of Cross-Cultural Psychology*, **38**(2), 227–42.
- Thompson, R., George, K., Walton, J., Orr, S., Benson, J. (2006). Sex-specific influences of vasopressin on human social communication. *Proceedings of the National Academy of Sciences of the United States of America*, **103**(20), 7889–94.
- Thomson, J.J. (1985). Double effect, triple effect and the trolley problem: squaring the circle in looping cases. *Yale Law Journal*, **94**(6), 1395–415.
- Tost, H., Kolachana, B., Hakimi, S., et al. (2010). A common allele in the oxytocin receptor gene (OXTR) impacts prosocial temperament and human hypothalamic-limbic structure and function. *Proceedings of the National Academy of Sciences of the United States of America*, **107**(31), 13936–41.
- Uzefovsky, F., Shalev, I., Israel, S., et al. (2014). Oxytocin receptor and vasopressin receptor 1a genes are respectively associated with emotional and cognitive empathy. *Hormones and Behavior*, **67**, 60.
- Veinante, P., Freund-Mercier, M.J. (1997). Distribution of oxytocin- and vasopressin-binding sites in the rat extended amygdala: a histoautoradiographic study. *Journal of Comparative Neurology*, **383**(3), 305–25.
- Wade, M., Hoffmann, T.J., Jenkins, J.M. (2015). Gene–environment interaction between the oxytocin receptor (OXTR) gene and parenting behaviour on children’s theory of mind. *Social Cognitive and Affective Neuroscience*, **10**(12), 1749–57.
- Walter, N.T., Montag, C., Markett, S., Felten, A., Voigt, G., Reuter, M. (2012). Ignorance is no excuse: moral judgments are influenced by a genetic variation on the oxytocin receptor gene. *Brain and Cognition*, **78**(3), 268–73.
- Walum, H., Westberg, L., Henningsson, S., et al. (2008). Genetic variation in the vasopressin receptor 1a gene (AVPR1A) associates with pair-bonding behavior in humans. *Proceedings of the National Academy of Sciences of the United States of America*, **105**(37), 14153–6.
- Watson, D., Clark, L.A., Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of Personality and Social Psychology*, **54**(6), 1063.
- Weller, J., Song, J., Heyen, D., Lewin, H., Ron, M. (1998). A new approach to the problem of multiple comparisons in the genetic dissection of complex traits. *Genetics*, **150**(4), 1699–706.
- Winterer, G., Musso, F., Vucurevic, G., et al. (2006). COMT genotype predicts BOLD signal and noise characteristics in prefrontal circuits. *Neuroimage*, **32**(4), 1722–32.
- Wu, N., Su, Y. (2014). Oxytocin receptor gene relates to theory of mind and prosocial behavior in children. *Journal of Cognition and Development*, **16**(2), 302–13.
- Young, L., Cushman, F., Hauser, M., Saxe, R. (2007). The neural basis of the interaction between theory of mind and moral judgment. *Proceedings of the National Academy of Sciences of the United States of America*, **104**(20), 8235–40.
- Young, L., Dungan, J. (2012). Where in the brain is morality? Everywhere and maybe nowhere. *Social Neuroscience*, **7**(1), 1–10.
- Young, L.J. (1999). Oxytocin and vasopressin receptors and species-typical social behaviors. *Hormones and Behavior*, **36**(3), 212–21.
- Young, L.J., Lim, M.M., Gingrich, B., Insel, T.R. (2001). Cellular mechanisms of social attachment. *Hormones and Behavior*, **40**(2), 133–8.
- Young, L.J., Winslow, J.T., Wang, Z., et al. (1997). Gene targeting approaches to neuroendocrinology: oxytocin, maternal behavior, and affiliation. *Hormones and Behavior*, **31**(3), 221–31.
- Zink, C.F., Stein, J.L., Kempf, L., Hakimi, S., Meyer-Lindenberg, A. (2010). Vasopressin modulates medial prefrontal cortex–amygdala circuitry during emotion processing in humans. *The Journal of Neuroscience*, **30**(20), 7017–22.