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

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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

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(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; Brunnlieb *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

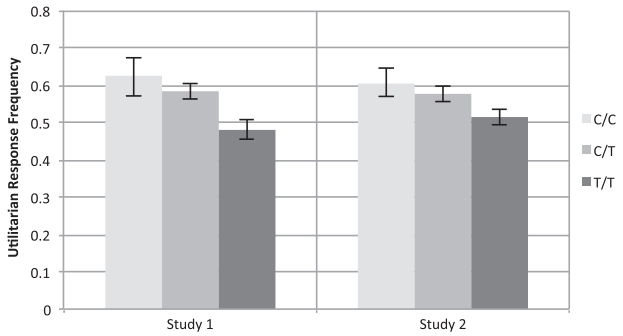

Fig. 1. Average frequency of utilitarian responses for Study 1 and Study 2 participants as a function of genotype. Shaded bars reflect the number of copies of the minor (T) allele of *OXTR* SNP rs237889. In Study 1, 91 participants (40.44%) had the C/C genotype, 109 (48.44%) were C/T, and 25 (11.11%) 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 (Gleichgerrcht *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 alexithymea (the inability to recognize and identify emotions) and autism. In fact, when measuring alexithymea 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.

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