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Genetic variation in serotonin function impacts on altruistic punishment in the ultimatum game: A longitudinal approach

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ABSTRACT

Growing evidence demonstrates that the serotonin system influences punishment behavior in social decision-making and that individual differences in the propensity to punish are, at least in part, due to genetic variation. However, the specific genes and their mechanisms by which they influence punishment behavior are not yet fully characterized. Here, we examined whether serotonin system-related gene variation impacts on altruistic punishment in the ultimatum game by using a longitudinal approach with three time points, covering a time frame up to four months in young adults ($N = 106$). Specifically, we investigated additive effects of *5-HTTLPR* and *TPH2* G-703T genotypes by using a composite score. This composite score was significantly associated with altruistic punishment, with individuals carrying both the S-allele and the G-allele demonstrating less punishment behavior. The results suggest that serotonin system-related gene variation contributes to individual differences in altruistic punishment. Furthermore, comparably high test-retest correlations suggest that punishment behavior in the ultimatum game represents a relatively stable, trait-like behavior.

1. Introduction

Civilized human life depends on cooperation and on limiting one's self-interests in order to comply with moral and social norms and values. There are several theories trying to explain the evolution of human cooperation, for example by kin selection and direct or indirect reciprocity (Axelrod & Hamilton, 1981; Hamilton, 1964; Nowak, Page, & Sigmund, 2000). However, these theories cannot fully account for the maintenance of cooperation even in large groups of genetically unrelated people or in (anonymous) one-shot interactions, where people will never meet again and thus reputation building is not possible. Here, the strong reciprocity account provides an explanation based on so-called altruistic punishment: that is, the punishment of norm-violations, even at personal cost and no chance that these costs will be repaid, but with potential benefit for other individuals (Bowles & Gintis, 2004; Boyd, Gintis, Bowles, & Richerson, 2003; Fehr & Fischbacher, 2003; Fehr & Gächter, 2002; for review, Strobel, 2016). However, the understanding of the decision-making process during altruistic punishment (sometimes termed costly punishment) is still limited and debates continue on the explanation of its underlying mechanisms (Kurzban, Burton-Chellew, & West, 2015).

In neuroeconomic research, altruistic punishment is typically investigated using experimental games such as the ultimatum game (Güth, Schmittberger, & Schwarze, 1982). In the ultimatum game, two players—a proposer and a responder—are shown a sum of money, for example 20 money units (MU). The proposer can make any offer to split the money between him and the responder. The latter in turn can either accept this offer, then the money is shared accordingly, or reject, then both players receive nothing. Critically, a responder confronted with a low offer faces a conflict between economic self-interest, encouraging him to accept even a low, but at least non-zero offer, and his fairness norms, driving him toward rejecting it. Evidence has shown that offers of less than 30% of the total amount (and around 20% of all offers) are often rejected (Camerer, 2011; Henrich, 2006). Moreover, rejection of an offer (and, thus, the punishment of the proposer) is wide-spread with up to 84% of players punishing at least once within ten rounds (Fehr & Gächter, 2002). Further, altruistic punishment can be observed in various cultures and even holds under third-party conditions, where the individual under investigation is not direct part of the interaction, but is observing an interaction of other players (Henrich, 2006; Herrmann,

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Thöni, & Gächter, 2008; Mothes, Enge, & Strobel, 2016). Interestingly, a twin study by Wallace, Cesarini, Lichtenstein, and Johannesson (2007) reported that additive genetic effects account for 42% of the observed variation in responder behavior, highlighting the role of genetic effects in altruistic punsihment. Given this substantial genetic influence, genetic factors alongside psychological and emotional factors should be taken into consideration in order to elucidate the driving forces of altruistic punishment.

In a seminal fMRI study by Sanfey (2003), greater activation when receiving unfair compared to fair offers was found in the right dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC) and the anterior insula, that is, regions regularly found to be involved in both cognitive and emotional processing. These activation differences were suggested by the authors to represent the conflict between accepting and rejecting unfair offers by the proposer. Interestingly, the insular activation was directly correlated with (a) the degree of unfairness of the offer, and (b) rejection rates of unfair offers, being interpreted as reflecting the responders negative emotional state, which points to the importance of emotions in altruistic punishment. In a similar vein, another study found that anger about the perceived unfairness was a better explanation of rejecting unfair offers than the perception of unfairness *per se* (Pillutla & Murnighan, 1996a). Accordingly, Fehr and Gächter (2002) state negative emotions towards defectors as a proximate mechanism for costly punishment behavior in humans. Similarly, animal studies show that even capuchin monkeys respond negative to unequal reward distribution (so-called inequality aversion; Brosnan & de Waal, 2003).

Therefore, altruistic punishment—if it can obviously be triggered by anger and frustration to perceived unfairness—may to some extent represent an emotional-driven, impulsive response to perceived provocation resulting from uncooperative behavior, or interpersonal frustration because of a perceived norm violation. Note that some authors argue that precisely the upcoming of these negative emotions may lead to costly punishment behavior, an act to foster mutual reciprocity, fairness and equity at the group level (Fehr & Gächter, 2002; Koenigs & Tranel, 2007; Pillutla & Murnighan, 1996b; Singer et al., 2006; Tabibnia, Satpute, & Lieberman, 2008). In this context, other authors stress that retributive motives may be sufficient to motivate rejecting even moderately unfair offers, "which satisfies not only a motive to express negative affect but also these individuals' elevated sensitivity to compliance with cooperative norms" (Brethel-Haurwitz, Stoycos, Cardinale, Huebner, & Marsh, 2016). In line with this, Crockett and colleagues provided compelling evidence for impulses driving altruistic punishment by showing that temporarily lowering serotonin (5-HT) via tryptophan depletion increases both impulsive choice and altruistic punishment in the ultimatum game (Crockett, Clark, Lieberman, Tabibnia, & Robbins, 2010). Further work by Crockett et al. (2013) demonstrated that reducing 5-HT signaling during the ultimatum game increases the likelihood of punishing unfair offers by modulating striatal activations, suggesting that 5-HT may set the sensitivity threshold for fairness- and punishment-related processing. Therefore, the authors suggest that impairing 5-HT function enhances the drive for retaliation, while simultaneously reducing fairness preferences. Further support for the role of 5-HT in punishment behavior comes from Wood, Rilling, Sanfey, Bhagwagar, and Rogers (2006) who found that tryptophan depletion reduced cooperative responses of individuals while playing a prisoner's dilemma game with a strict tit-for-that strategy (this is even more intriguing as tit-for-tat strategies are highly effective in eliciting cooperative behaviors; Axelrod and Hamilton, 1981). As opposed to this, enhancing 5-HT signaling via tryptophan supplementation increased agreeable behaviors and perceptions of agreeableness in everyday social interactions (aan het Rot, Moskowitz, Pinard, & Young, 2006), suggesting that an increase in 5-HT function results in facilitation of positive behaviors in response to social stimuli.

Based on the findings on 5-HT influences on prosocial behaviors like altruistic punishment, genetic variation that affects 5-HT availability may contribute to individual differences in this behavior. Two promising candidate genes are the serotonin transporter (5-HTT) polymorphism (serotonin transporter gene-linked polymorphic region; *5-HTTLPR;* SLC6A4) and a polymorphism in the gene encoding tryptophan hydroxylase-2 (*TPH2* G-703T), an enzyme that catabolizes serotonin from its precursor tryptophan. The *5-HTTLPR* comprises either long (L) or short (S) alleles. In homozygotic carriers of the L-allele, the expression of the 5-HTT is higher and the reuptake of 5-HT is almost 2-fold as compared to heterozygous or homozygous carriers of the S-allele (Heils et al., 1996). While L-carriers show higher reuptake of 5-HT, S-carriers have lower brain 5-HT function (Canli & Lesch, 2007) and demonstrate higher levels of negative emotionality and trait anxiety such as neuroticism (Lesch et al., 1996; Sen, Burmeister, & Ghosh, 2004) as well as increased sensitivity towards environmental influences (Belsky et al., 2009). At the functional level, *5-HTTLPR* has been associated with stronger amygdala activation in response to emotional—especially fearful—faces (Hariri, 2002; Heinz et al., 2005). Furthermore, there is an A/G single nucleotide polymorphism (SNP) in the L-allele of the *5-HTTLPR*, leading to the distinction between L_A and L_G variants, with the L_G variant being functionally similar to the S-allele (Hu et al., 2006). Hence, the L_G variant is also referred as the S-allele. Interestingly, in a study by Stoltenberg, Christ, and Carlo (2013), the triallelic *5-HTTLPR* genotype was significantly associated with prosocial behavior: individuals carrying the S-allele reported lower rates of helping others. Besides, approximately 33% of this effect was mediated by social anxiety. A more recent study on electrophysiological and behavioral correlates of altruistic punishment by Enge, Mothes, Fleischhauer, Reif, and Strobel (2017) even found that individuals carrying the S-allele punished unfair offers in the dictator game less strongly than L/L homozygotes. In a similar vein, other studies showed that individuals carrying the S/S genotype were significantly less risky (Ernst et al., 2014; Kuhnen & Chiao, 2009) and exhibited higher loss aversion relative to L-allele carriers who in turn seemed to be more inclined to show impulsive behavioral tendencies (Glenn, 2011; He et al., 2010).

Another key player in the regulation of 5-HT neurotransmission in the brain is the rate limiting enzyme in the biosynthesis of neuronal 5-HT, the tryptophan hydroxylase-2 (TPH2; Zhang, Beaulieu, Sotnikova, Gainetdinov, & Caron, 2004). In the transcriptional control region of the *TPH2* gene, a potentially functional G-703T single-nucleotide polymorphism (SNP; rs4570625) has been described (Canli, Congdon, Gutknecht, Constable, & Lesch, 2005; Chen, Vallender, & Miller, 2008; Lin et al., 2007). While the functional role of this variant remains to be resolved (Chen et al., 2008; Lim, Pinsonneault, Sadee, & Saffen, 2006; Lin et al., 2007; Scheuch et al., 2007), *TPH2* G-703T has repeatedly been associated with amygdala reactivity to emotional stimuli (Brown et al., 2005; Canli et al., 2005). These findings are in line with behavioral studies showing that carriers of the G-allele demonstrate higher levels of trait anxiety such as harm avoidance and neuroticism (Gutknecht et al., 2007; Reuter, Kuepper, & Hennig, 2007; Strobel et al., 2007). Moreover, in a recent meta-analysis, the G-allele was associated with major depressive disorder (Gao et al., 2012). Finally, *TPH2* variants were found to be associated with cognitive control, suggesting an impact on prefrontal cortex function (Enge, Fleischhauer, Lesch, Reif, & Strobel, 2014; Strobel et al., 2007). Regarding both *5-HTTLPR* and *TPH2* G-703T, two separate studies investigated their influence on emotion appraisal and found that S-allele carriers and G/G homozygotes, respectively, judged that fear and sadness in autobiographical memories had a greater impact on their goals and that they were less able to cope with these negative emotions compared to L/L homozygotes, and T-allele carriers, respectively (Szily, Bowen, Unoka, Simon, & Kéri, 2008; Szily & Kéri, 2012), pointing to possible additive effects of both genes.

Because 5-HTT and TPH2 are two key proteins for the regulation of serotonin levels, and because serotonergic functioning promotes emotion-related prosocial and punishment behavior, we investigated