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# A neurochemical approach to valuation sensitivity over gains and losses

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Prospect theory proposes the hypothesis that people have diminishing sensitivity in valuing increases in the size of monetary outcomes, for both gains and losses. For decision-making under risk, this implies a tendency to be risk-tolerant over losses while being generally risk averse over gains. We offer a neurochemistry-based model of the diminishing valuation sensitivity hypothesis. Specifically, we propose that dopamine tone modulates the sensitivity towards valuation of gains while serotonin tone modulates the sensitivity towards valuation of losses. Consequently, higher dopamine tone would yield a more concave valuation function over gains while higher serotonin tone would yield a more convex valuation function over losses. Using a neurogenetics strategy to test our neurochemical model, we find that subjects with the 9-repeat allele of DAT1 (lower DA tone) are more risk-tolerant over gains than subjects with the 10-repeat allele, and that subjects with the 10-repeat allele of STin2 (higher 5HT tone) are more risk-tolerant over losses than subjects with the 12-repeat allele. Overall, our results support the implications of our model and provide the first neurogenetics evidence that risk attitudes are partially hard-wired in differentiating between gain- and loss-oriented risks.

**Keywords:** risk attitude; prospect theory; genetics; neuroeconomics; experimental economics

## 1. INTRODUCTION

The propensity to take risk underpins a wide spectrum of decision-making behaviour, ranging from common ones such as picking the right queue and ordering food in a restaurant to more substantial economic decisions, for instance, choosing a savings plan or starting a new business. Recently, the heritability of economic risk-taking has been investigated using classical twin studies (Cesarini *et al.* 2009; Zhong *et al.* 2009). At the same time, the question about specific genes being associated with risk-taking has been investigated in two studies that were carried out independently of the present study (Dreber *et al.* 2009; Kuhnen & Chiao 2009).

Central to the study of decision-making under risk is the question of how people evaluate the utility of lotteries. In their pioneering works, von Neumann and Morgenstern (von Neumann & Morgenstern 1944) and Savage (Savage 1954) provided the axiomatic foundation for the most widely used approach of decision-making under risk, known as expected utility theory. Under this model, the utility of a lottery is given by averaging the utility of outcomes with the associated probabilities. For much of the economics literature, people are assumed to possess diminishing marginal utility for money. In the context of expected utility, this is equivalent to the

decision-maker being *risk averse*, i.e. always preferring to receive the expected value of a lottery for sure rather than receiving the lottery itself. The risk-aversion assumption has been widely imposed in most of the models in economics and finance. This implication has found general support in the behaviour of the financial and insurance markets whose functioning relies on the relative prevalence of risk aversion among market participants.

By contrast, in their seminal paper on prospect theory, Kahneman & Tversky (1979) observed that risk-tolerance may be more prevalent in two other domains of risks. People tend to pay more than the expected gain to have a small chance at receiving a large gain, e.g. in purchasing a lottery ticket. When facing moderate chances of significant losses, people tend not to go for insuring the liability even if it were actuarially fair, i.e. paying the expected loss for sure. To account for this observed pattern of risk attitudes, Kahneman & Tversky modified, in prospect theory, both the utility function for wealth and how probabilities are weighted in arriving at the overall utility of a lottery. Specifically, they proposed the notion that the carriers of utility are the changes in wealth rather than the final wealth. They gave an analogy with human perception and judgement. For example, the experience of hot or cold depends on a reference temperature to which one has adapted. They linked the Weber–Fechner law, where psychological response is a concave function of

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the magnitude of physical change in sensory and perceptual dimensions, to the utility for wealth. That is, the decision-maker would be adapted to her sense of the status quo and perceive wealth changes in terms of financial gains and losses relative to the status quo. This gives rise to an S-shaped utility function having the property of diminishing sensitivity of valuation as the magnitude of gain or loss increases, i.e. the utility function in prospect theory is concave over gains and convex over losses (figure 1). Consequently, people would tend to be risk-averse (risk-tolerant) towards gain-oriented (loss-oriented) risks involving moderate probabilities.

This paper seeks a deeper understanding of attitude towards economic risk-taking, including the loss-gain differentiation in risk attitude, beyond revealed choice to the neurogenetics level. We propose a neurochemical model of prospect theory's diminishing valuation sensitivity hypothesis by conjecturing that the two evolutionarily ancient neurotransmitters, dopamine (DA) and serotonin (5HT) are linked, respectively, to the valuations of gains and losses. Tonic DA (5HT) levels represent the constant low-level background DA (5HT) neuron-firing in a slow, irregular single spike mode. Presumably, polymorphic genes coding for elements of DA (5HT) neurotransmission partially regulate DA (5HT) tone by modulating the available amount of neurotransmitter and receptor number that contribute to background DA (5HT) neuron-firing. Synaptic or phasic levels of DA (5HT) are mediated primarily by bursting events at the level of the cell body and are believed to lead to a much larger dopamine release than when these neurons fire in their background 'tonic' state. It is also likely that polymorphic DA (5HT) also contribute to phasic DA (5HT) release. Altogether, the concept of DA (5HT) tone includes both tonic and phasic DA (5HT) levels. Our conjecture on the role of DA is based on pervasive evidence demonstrating that midbrain dopaminergic neurons encode reward prediction errors (Schultz *et al.* 1997; Schultz 2002). DA tone is associated with prefrontal and striatal activation in response to reward sensitivity (Yacubian *et al.* 2007). At both the behavioural and the neural levels, the administration of DA drugs affects risky decision-making under gains but not under losses (Pessiglione *et al.* 2006). In the presence of both gains and losses, it was reported (D'Ardenne *et al.* 2008) that the neural activation in ventral tegmental area reflects positive reward prediction errors modulated by the probability of winning, but there is no significant correlation with loss-oriented events. As argued in Berns *et al.* (2007), the natural biological bound on 5HT tone offers an explanation for the concavity of the utility function over gains.

We further conjecture that 5HT tone modulates the sensitivity towards valuations of losses. Our conjecture draws on the work of Daw *et al.* (2002) showing that, due to their low spontaneous firing rate, the inhibitory response of dopaminergic neurons to prediction of no reward (or its omission) is weak. They then proposed 5HT to be in 'opponent partnership' with DA and further hypothesized it to mediate aversion-specific responses. It follows that the biological bound on 5HT tone offers an explanation of the convexity of the utility function over losses.

In sum, the boundedness of DA and 5HT tones gives rise to diminishing valuation sensitivity in responding to

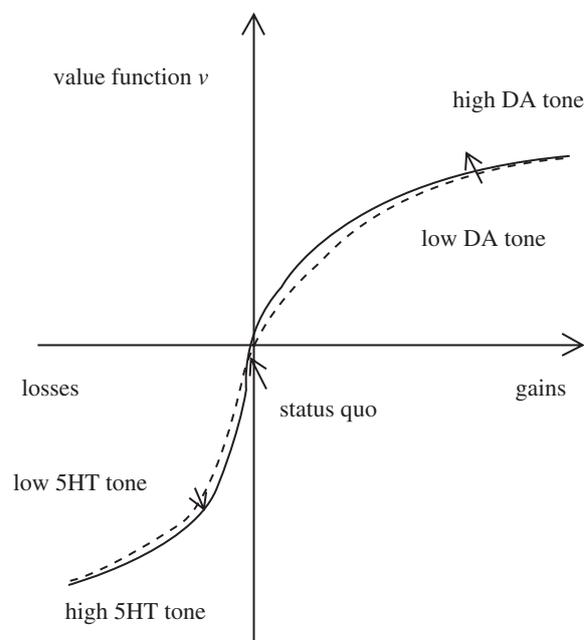


Figure 1. Loss-gain differentiation. Prospect theory assumes a loss-averse value function that is concave over gains, convex over losses and vanishes at the status quo, represented by 0. Our hypothesis is that: DA (5HT) tone modulates sensitivity towards incremental gain (loss) and the higher the DA (5HT) tone, the lower (higher) the sensitivity towards incremental gain (loss).

increases in the magnitude of both gains and losses. Consequently, as illustrated in figure 1, the higher the DA (5HT) tone, the more concave (convex) is the utility function over gains (losses). Our model is tested by investigating the association between subjects' risk attitudes over gains and losses, assessed using standard experimental economics method, and candidate genes that are selected based on advances in the neurogenetics of psychiatry and personality.

The re-uptake mechanisms of the dopamine transporter (*SLC6A3*) (Berger *et al.* 2004; Thapar *et al.* 2005; Bertolino *et al.* 2008) and the serotonin transporter (*SLC6A4*) (Canli & Lesch 2007) in regulating DA and 5HT tones have important implications for normal as well as abnormal behaviours. Both transporters are characterized by functional variable number tandem repeats (VNTRs) that have been extensively investigated (Haddley *et al.* 2008). The DAT (*SLC6A3*) VNTR (Vandenberg *et al.* 1992) is located in intron 3 (DAT1) that modulates transcription (VanNess *et al.* 2005), mid-brain activation (Schott *et al.* 2006) and *in vivo* transporter availability (van Dyck *et al.* 2005), with the 10-repeat allele having stronger enhancer-like properties resulting in higher DA tone than the 9-repeat allele (van Dyck *et al.* 2005). The serotonin transporter gene (*SLC6A4*) is characterized by a 44 bp insertion/deletion (5-HTTLPR) in the promoter region (Lesch *et al.* 1996; Canli & Lesch 2007) and a second intronic (STin2) 17 bp variable number of tandem repeat (Lesch *et al.* 1994). 5-HTTLPR with the short allele is transcriptionally less effective than that with the long allele and is associated with anxiety-related personality traits and depression (Lesch *et al.* 1996). In addition, the reuptake inhibitor drugs that increase serotonin

synaptic levels are known to be effective (Ansorge *et al.* 2004), suggesting that the short allele results in low 5HT tone. It has been suggested that the VNTR region may act as a transcriptional regulator of *SLC6A4* with the 12-repeat allele having stronger enhancer-like properties, hence lower 5HT tone, than the 10-repeat allele (Hranilovic *et al.* 2004). Notably, the STin2 VNTR has been associated with schizophrenia in a recent meta-analysis (Fan & Sklar 2005).

Besides DAT, STin2 and 5-HTTLPR, the dopamine D4 receptor exon 3 polymorphism (*DRD4*) would ordinarily make a good candidate. *DRD4* exon 3 is characterized by a highly polymorphic VNTR containing a 48 bp repeat (Van Tol *et al.* 1992). Its 7-repeat allele is known for contributing to individual differences in traits including novelty seeking (Ebstein *et al.* 1996), attention-deficit hyperactivity disorder (Faraone *et al.* 2001) and recently economic risk-taking (Dreber *et al.* 2009; Kuhn & Chiao 2009). However, there is extensive evidence showing the low incidence of the *DRD4* 48 bp VNTR 7-repeat allele among Asians, especially Han Chinese (Ding *et al.* 2002). For our sample, the allele frequency of the 7-repeat allele is 0.8 per cent. Consequently, *DRD4* was not included as a candidate in the present study.

## 2. MATERIAL AND METHODS

We recruited a cohort of 350 Chinese subjects in Beijing through Internet advertisement, posters and word of mouth to assess their risk attitude and genotype the three polymorphisms. The first group was recruited in July 2007; the second group was recruited in February 2008. Demographics of the subjects are summarized as follows: mean age  $28.2 \pm 10.8$ ; 162 males, 188 females; 123 non-student subjects, 227 student subjects; 67 subjects with high school education, 194 subjects with college education, 89 subjects with postgraduate education; 325 Han Chinese, 25 non-Han Chinese. Only the 325 Han Chinese are included in our analysis in order to enhance our control on the characteristics of the population. Subjects first filled in the informed consent form, approved by the Internal Review Board at Hong Kong University of Science and Technology. We adhered to the practice in experimental economics of applying monetary incentive to motivate decision-making without using deception. After the experiment, subjects each donated  $10 \text{ cm}^3$  of blood for genotyping.

To assess risk-attitudes, we used a simple experimental elicitation procedure, known as the multiple price list design (see, e.g. Harrison & Rutstrom 2008 for a survey), which entails giving the subject in an ordered array of binary choices. While Miller *et al.* (1969) exemplifies an early usage of this design, Holt & Laury (2002) represents a recent development of the method. Relative to other experiment-based studies of risk aversion, one advantage of this design is that the task is simple and relatively context free. Moreover, Anderson *et al.* (2008) offer suggestive evidence of stability of risk preference assessed using this design over 17 months. The multiple price list design was also shown to predict risky behaviours including cigarette smoking, heavy drinking, being overweight or obese, seat belt non-use and acceptance of risky food (Lusk & Coble 2005; Anderson & Mellor 2008).

In this paper, we use a simplified version of this procedure to assess subjects' risk attitudes. In assessing risk attitude

over gains, subjects chose between an even-chance lottery between receiving Y60 and receiving zero, versus receiving the expected outcome of Y30 for sure. Subjects were incentivized for their choice in this comparison. For those subjects choosing the lottery, they were further asked to choose between the lottery and a higher certain amount of Y35; for those subjects choosing to receive the expected outcome for sure, they were further asked to choose between the lottery and a lower certain amount of Y25. Subjects are not incentivized for either of these two follow-up comparisons. Based on their decisions, subjects' valuation of the gamble is categorized as follows: less than Y25, if certainty is chosen twice; less than Y30 and not less than Y25, if certainty is chosen followed by lottery; less than Y35 and not less than Y30, if lottery is chosen followed by certainty; not less than Y35, if lottery was chosen in both cases.

Correspondingly, in assessing risk attitude over losses, subjects began by choosing between a lottery which involves losing Y10 and losing zero with equal probability versus losing Y5 for sure. Subjects were incentivized, i.e. losses were deducted from subjects' show-up fees. Subjects choosing the lottery were further asked to choose between that lottery and losing Y4 for sure; subjects choosing the sure loss were asked to choose between the lottery and losing Y6 for sure. This elicitation procedure gives rise to the following categories of valuation: less than  $-Y6$ ; less than  $-Y5$  and not less than  $-Y6$ ; less than  $-Y4$  and not less than  $-Y5$ ; not less than  $-Y4$ .

Under this design, we manage to have a four-level measure of risk aversion in both the gain domain and the loss domain. We further generate a measure of the subject's overall risk attitude across gains and losses by aggregating the levels of the subject's risk aversion over gains and over losses.

To characterize the polymorphisms for the *SLC6A4* (44bp deletion/insertion (5-HTTLPR) in the promoter region and the intron2 17 bp VNTR), the DAT-1 VNTR and the *DRD4* exon3, we used the PCR amplification procedure with the following primers: (1) *SLC6A4*-5-HTTLPR: F5'-GGCGTTGCCGCTCTGAATTGC-3', R5'-GAGGGACTGAGTGGACAACC-3'; (2) *SLC6A4* intron2 VNTR: F5'-GTCAGTATCACAGGCTGCGAG-3', R5'-TGTTCCCTA GTCTTACGCCAGT-3'; (3) DAT-1: F5'-TGTGGTGTA GGAACGGCCTG-3', R5'-CTTCCTGGAGGTCAC GGCTCA-3'; (4) *DRD4*: F5'-CTT CCT ACC CTG CCC GCT CAT GCT GCT GCT CTA CTGG-3' and R5'-ACC ACC ACC GGC AGG ACC CTC ATG GCC TTG CGC TC-3'. PCR reactions were performed using 5  $\mu\text{l}$  Master Mix (Thermo scientific), 2  $\mu\text{l}$  primers (0.5  $\mu\text{M}$ ), 0.6  $\mu\text{l}$  Mg Cl<sub>2</sub> (2.5 mM), 0.4  $\mu\text{l}$  DMSO 5% and 1  $\mu\text{l}$  of water to total of 9  $\mu\text{l}$  total volume and an additional 1  $\mu\text{l}$  of genomic DNA was added to the mixture. All PCR reactions were carried out on a Biometra T1 Thermocycler (Biometra, Göttingen, Germany). PCR reaction conditions were as follows: *SLC6A4* 5-HTTLPR and DAT1: preheating step at 94.0°C for 5 min, 34 cycles of denaturation at 94.0°C for 30 s, reannealing at 55°C for 30 s and extension at 72°C for 90 s. The reaction proceeded to a hold at 72°C for 5 min. All reaction mixtures were electrophoresed on a 3% agarose gel (AMRESCO) with ethidium bromide to screen for genotype. *SLC6A4* intron2 VNTR: preheating step at 94.0°C for 5 min, 34 cycles of denaturation at 94.0°C for 30 s, reannealing at 61°C for 30 s and extension at 72°C for 30 s. The reaction proceeded to a hold at 72°C for 10 min. The mixtures were electrophoresed on a 4% agarose gel (AMRESCO) with ethidium

bromide to screen for genotype; *DRD4*: preheating step at 94.0°C for 5 min, 34 cycles of denaturation at 94.0°C for 30 s, reannealing at 55°C for 30 s, and extension at 72°C for 90 s. The reaction proceeded to a hold at 72°C for 5 min. The reaction mixture was then electrophoresed on a 3% agarose gel (AMRESCO) with ethidium bromide to screen for genotypes.

For DAT1, we have 12.2 per cent of 9/10 genotype and 81.2 per cent of 10/10 genotype. For 5-HTTLPR, we have 51.7 per cent of s/s genotype, 36.2 per cent of s/l genotype and 12.1 per cent of l/l genotype. For STin2, we have 1.6 per cent of 10/10 genotype, 16.5 per cent of 10/12 genotype and 82.0 of 12/12 genotype. For *DRD4*, we have 2.5 per cent of 2/2 genotype, 32.1 per cent of 2/4 genotype, 56.1 per cent of 4/4 genotype, 1.6 per cent of 4/7 genotype. The allele frequencies are consistent with the previous studies of DAT1 (Li *et al.* 2006), 5-HTTLPR (Li *et al.* 2007), STin2 (Li *et al.* 2007) and *DRD4* (Ding *et al.* 2002) with Chinese sample. The observed unbalanced frequencies suggest that they result from random sampling. In the association studies, sampling imbalance has been a perennial problem. All the polymorphisms are in Hardy–Weinberg equilibrium.

As discussed in the recent study of Jakobsdottir *et al.* (2009), there are two basic statistical approaches for evaluating markers. The risk-based approach models the risk as a function of marker(s), often with adjustment for covariates, and is commonly applied in genetic studies. In case–control studies, this is done with logistic regression, and the markers with the strongest effect on disease risk are those associated with the smallest *p*-values and most extreme odds ratios. In the current investigation we used this method which is most commonly employed in genetic association studies. To test the effect of genotypes on our ordered four-category of risk attitude over gains/losses, we used ordered logit regression with robust s.e. for both genotype and allele association analysis with STATA 8.0. Age, sex and student status were included as independent variables. For the allele model, given that there is one data point for each allele giving rise to two data points for each subject, we used subject ID as a cluster variable for robust s.e. For the genotype model, we report on the additive model that assumes the absence of dominant genetic effects of any particular allele. Five subjects did not complete their decisions in the gain domain and four subjects did not complete their decisions in loss domain. These decisions were treated as missing data in our analysis.

### 3. RESULTS

We observe that 72 per cent of the subjects are risk-tolerant in the loss domain. Consistent with the implications of prospect theory and empirical evidence reported elsewhere (e.g. Schmidt & Traub 2002), this proportion is significantly more than that for the gain domain where 48 per cent of the subjects are risk-tolerant (*t*-test, *p* = 0.001).

We assess the subject's overall risk attitude across gains and losses by aggregating the levels of the subject's risk aversion over gains and over losses, and test its association with DAT1, STin2 and 5-HTTLPR. We find that both DAT1 and STin2 are significantly associated with the subjects' overall risk attitude (DAT1: genotype model, *p* = 0.018; allele model, *p* = 0.027; STin2: genotype model, *p* = 0.027; allele model, *p* = 0.023). We do not

find significant association with 5-HTTLPR (genotype model, *p* = 0.099; allele model, *p* = 0.076). These findings are summarized in table 1.

We further investigate the loss–gain differentiation in risk attitude and study its association with each polymorphism separately. We find that DAT1 is significantly associated with risk attitude over gains (allele model, *p* = 0.035; genotype model, *p* = 0.026), and not over losses (allele model, *p* = 0.118; genotype model, *p* = 0.109). Subjects with the 9-repeat allele of DAT1 (low DA tone) are more risk-tolerant over gains than subjects with the 10-repeat allele (figure 2). STin2 is found to be significantly associated with risk attitude over losses (allele model, *p* = 0.029; genotype model, *p* = 0.027), and not for risk attitude over gains (allele model, *p* = 0.104; genotype model, *p* = 0.103). Subjects with the 10-repeat allele of STin2 (high 5HT tone) are more risk-tolerant over losses than subjects with the 12-repeat allele (figure 2). This notwithstanding, the regression analysis did not reveal significant association between 5-HTTLPR and risk attitude over gains (allele model, *p* = 0.264; genotype model, *p* = 0.266). While 5-HTTLPR is not significantly associated with risk attitude over losses (allele model, *p* = 0.075; genotype model, *p* = 0.075), subjects with the long allele (high 5HT tone) are nominally more risk-tolerant over losses than subjects with the short allele (figure 2). The statistics of the association results are summarized in table 1.

### 4. DISCUSSION

Overall, our results support the implication of our neurochemical model of the diminishing valuation sensitivity hypothesis that lower DA tone (e.g. 9-repeat allele of DAT1) yields more risk tolerance in the gain domain while lower 5HT tone (e.g. 12-repeat allele of STin2) yields greater risk aversion in the loss domain (figure 1). Our approach follows Knafo *et al.* (2008) in extending the scope of the experimental economics methodology (Smith 1982; Plott & Smith 2005) to the neurogenetics level. This complements the recent twin studies (Cesarini *et al.* 2009; Zhong *et al.* 2009) and imaging studies of attitude towards economic risk (Gehring & Willoughby 2002; Huettel *et al.* 2005; Kuhnen & Knutson 2005; Preuschoff *et al.* 2006; Yacubian *et al.* 2006; Seymour *et al.* 2007; Tom *et al.* 2007; Preuschoff *et al.* 2008). Our research is accomplished independently of two recent neurogenetics studies of financial risk-taking (Dreber *et al.* 2009; Kuhnen & Chiao 2009) using sample sizes of 98 and 65, respectively. They show that subjects with the 7-repeat allele in the dopamine receptor D4 gene (*DRD4*) exon 3, hence low DA tone (Van Craenenbroeck *et al.* 2005) is more risk-tolerant than subjects without the 7-repeat allele. Both results, being in the same direction as the current report, corroborate our conjecture that DA tone modulates sensitivity of valuation over gains.

However, given the low incidence of the *DRD4* 48 bp VNTR 7-repeat allele among Asians, especially Han Chinese (Ding *et al.* 2002), *DRD4* would not make a good candidate gene for our subject pool. The *DRD4* 48 bp VNTR has been the subject of much speculation about its evolution and role in human behaviour across cultures. The systematic and strong association between migration

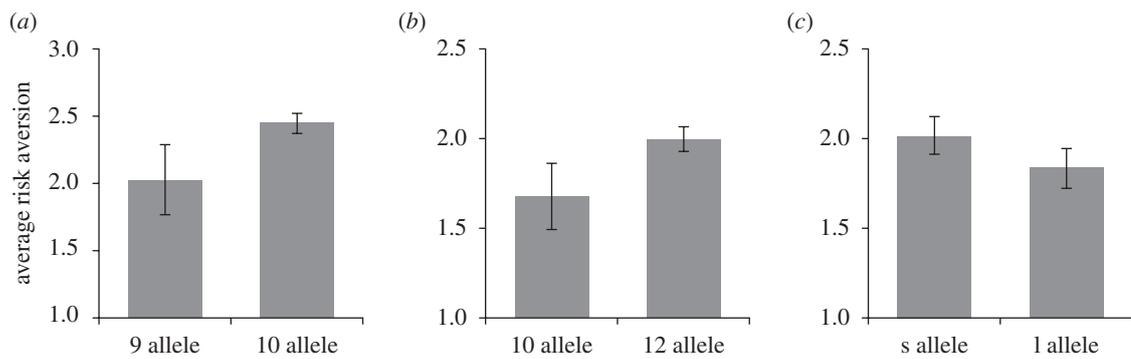


Figure 2. (a) Risk attitude over gains and DAT1. We elicited four levels of risk aversion, coded from 1 (most risk-tolerant) to 4 (most risk-averse). The columns represent the means of risk attitude over gains of the different allele. Error bars represent s.e.m. Subjects with the 9-repeat allele (low DA tone) are more risk-tolerant than subjects with the 10-repeat allele (high DA tone). (b) Risk attitude over losses and STin2. We elicited four levels of risk aversion, coded from 1 (most risk-tolerant) to 4 (most risk-averse). The columns represent the means of risk attitude over losses of the different allele. Error bars represent s.e.m. Subjects with the 10-repeat allele (high 5HT tone) are more risk-tolerant than subjects with the 12-repeat allele (low 5HT tone). (c) Risk attitude over losses and 5-HTTLPR. We elicited four levels of risk aversion, coded from 1 (most risk-tolerant) to 4 (most risk-averse). The columns represent the means of risk attitude over losses of the different allele. Error bars represent s.e.m. Subjects with the long allele (high 5HT tone) are nominally more risk-tolerant than subjects with the short allele (low 5HT tone), though this relation is not statistically significant.

Table 1. Association between risk attitudes over gains and losses with DAT1, STin2 and 5-HTTLPR.

phenotype	gene	allele model				genotype model					
		OR	CI	<i>z</i> -value	<i>p</i> -value	OR	CI	<i>z</i> -value	<i>p</i> -value		
overall	DAT1	1.91	1.09	3.31	2.28	0.022 <sup>a</sup>	2.13	1.14	3.98	2.38	0.017 <sup>a</sup>
	STin2	1.32	1.03	1.7	2.17	0.03 <sup>a</sup>	1.7	1.07	2.71	2.23	0.026 <sup>a</sup>
	5-HTTLPR	1.32	0.95	1.82	1.66	0.098	1.27	0.95	1.69	1.66	0.096
gains	DAT1	1.77	1.04	3.04	2.07	0.035 <sup>a</sup>	2.00	1.09	3.68	2.23	0.026 <sup>a</sup>
	STin2	1.22	0.96	1.54	1.63	0.104	1.43	0.93	2.21	1.63	0.103
	5-HTTLPR	1.21	0.86	1.68	1.12	0.264	1.18	0.88	1.58	1.11	0.266
losses	DAT1	1.63	0.88	2.99	1.56	0.118	1.73	0.88	3.41	1.60	0.109
	STin2	1.36	1.03	1.79	2.18	0.029 <sup>a</sup>	1.82	1.07	3.09	2.21	0.027 <sup>a</sup>
	5-HTTLPR	1.36	0.97	1.90	1.78	0.075	1.31	0.97	1.76	1.78	0.075

<sup>a</sup>Statistically significant at 5 per cent using a two-sided *t*-test.

and the allele frequencies of the *DRD4* gene has ruled out that the frequency of the 7-repeat allele is due to either a single spontaneous mutation or genetic drift (Chang *et al.* 1996). Interestingly, Chen and colleagues (1999) observed that populations who migrated farther in the past 30 000 to 1000 years ago had a higher frequency of 7-repeat allele. They also showed that nomadic populations (include Biaka, Mbuti, San, Cheyenne, Muskoke, Pima, Guahibo, Karitiana, R. Surui, Ticuna and Yakut) had higher frequencies of 7-repeat allele than sedentary ones. More recently it has been observed that the health status of nomadic Ariaal men was higher if they had 7-repeat allele. However, in recently sedentary (non-nomadic) Ariaal those with 7-repeat allele seemed to have slightly deteriorated health.

Despite a sample four times greater, the present study did not replicate the association between financial risk-taking and 5-HTTLPR reported in Kuhnen & Chiao (2009) in terms of statistical significance, although the direction of association partially corroborates our results, suggesting that the precise role of 5-HTTLPR in risk-taking over losses merits further investigation. This lack of statistical significance may be due to differences in

the sample population, specifically the known difference in allele frequencies between Caucasians and Han Chinese—the short allele is present in 42 per cent of Caucasians, but in 71 per cent of Han Chinese (Li *et al.* 2007). Another possibility has to do with differences in experimental design. Kuhnen & Chiao assessed attitude towards financial risk-taking using a portfolio choice framework (subjects decide on the relative holding of a risky asset versus that of a riskless asset), which concurrently encompasses gain and loss considerations. This contrasts with our design where we assess risk attitudes over gains and over losses separately and based directly on binary choice between a lottery and a sure payoff.

Our findings complement recent functional magnetic resonance imaging studies involving both gains and losses (Gehring & Willoughby 2002; De Martino *et al.* 2006; Yacubian *et al.* 2006; Seymour *et al.* 2007; Tom *et al.* 2007; Roiser *et al.* 2009). These studies generally highlight the involvement of prefrontal cortex, striatum and amygdala in differentiating between risks involving gains and risks involving losses. Among them, De Martino *et al.* (2006), Tom *et al.* (2007) and Roiser

*et al.* (2009) are more oriented towards experimental economics, where subjects' decisions were incentivized, and data were analysed based on economic models.

Two imaging studies have direct bearing on the current findings. De Martino *et al.* (2006) showed that loss–gain framing of risks is associated with prefrontal–amygdala interaction. In their design, somewhat different from our own, subjects were informed regarding the initial amount of money they are to play and it was explained that they could retain the whole amount but needed to choose between a sure bet and a gamble option. The sure option was presented in gain frame trials as the amount of money retained from the starting amount and in loss frame trials as the total amount of money lost from the starting amount. The gamble option was identical for both frames. Most recently, Roiser *et al.* (2009) demonstrated the role of 5-HTTLPR in mediating amygdala activation in the loss–gain framing decision task. Indeed, considerable imaging data underscores the importance of serotonin in amygdala activation (Hariri *et al.* 2006 for survey). Importantly, the study of De Martino *et al.* (2006) and Roiser *et al.* (2009) both support our hypothesis of serotonin's role in gain–loss differentiation in decision under risk.

Tom *et al.*'s (2007) study on prospect theory's loss aversion used mixed lotteries involving both gains and losses. Loss aversion refers to evidence of the differential impact of loss and gain in decision-making under risk, specifically that loss looms larger than gain. This study showed that the striatum apparently encodes both gains and losses leading Tom *et al.* to the conclusion that potential losses are represented by decreasing activity in regions that seem to code for subjective value rather than by increasing activity in regions associated with negative emotions. However, some pharmacological evidence suggests otherwise. Notably, Pessiglione *et al.* (2006) showed that the administration of DA drugs affects decision-making over gains but not over losses at both the behavioural and the neural levels. Thus, the pharmacological evidence suggests the probable involvement of additional neurotransmitters in the loss domain, especially serotonin, which may have a role in predicting short- and long-term rewards in the ventral and dorsal striatum (Tanaka *et al.* 2007; Doya 2008). Further imaging genetics studies using same behavioural tasks would greatly enhance our understanding about the role of neurotransmitters and brain regions in modulating decision-making under risk over gains and losses.

The neurogenetics evidence presented here suggests that normal brain mechanisms underlying risk evaluation reflects a utility model (Rangel *et al.* 2008). Moreover, individual differences in their valuation functions are partially hard-wired traits with important implications for normal and abnormal psychology (Cloninger 1987). With our neurogenetics-based validation of our neurochemical model of the diminishing valuation sensitivity hypothesis, the stage is set for neurogenetics analysis to be added to the toolbox of neuroeconomics towards identifying specific neurotransmitters contributing to attitude towards economic risk.

Because our primary analyses were based on *a priori* hypotheses supported by previous research, no adjustment was made for multiple comparisons (Rothman 1990). For the exploratory analyses, we did not use the overly

conservative Bonferroni correction owing to the increased risk of making type 2 errors (Perneger 1998). In addition, the range of odds ratio in our study from 1.45 to 2 is similar to the effect sizes for other complex traits (Jakobsdottir *et al.* 2009). The validation of our findings awaits replication in an independent sample, particularly in other ethnic groups. While the finding of the current report should be considered provisional, it has achieved an important goal of proof of principle that a neurogenetic strategy can contribute to a deeper understanding of the neurobiological mechanisms of loss–gain differentiation in decision-making under risk. Since the aim of this study is to propose a neurochemical approach rather than a comprehensive examination of all serotonergic and dopaminergic genes, we focused on two genes that are characterized by functional polymorphisms that regulate DA/5HT and, moreover, have been widely investigated in previous studies of normal and abnormal behaviour. As valuation sensitivity is a complex phenotype, it is expected that additional genes would contribute to its neurochemical underpinnings. The present finding prepares the ground for exploring other polymorphisms that code for elements of DA and 5HT neurotransmission, and it can lead to further testing of our neurochemical hypothesis using different population samples.

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