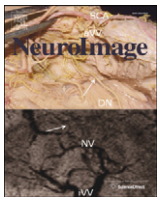
NeuroImage 59 (2012) 540–546

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg



Imaging genetics for utility of risks over gains and losses

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ARTICLE INFO

Article history:
Received 20 May 2011
Revised 2 July 2011
Accepted 11 July 2011
Available online 23 July 2011

Keywords:
Striatum
Amygdala
Dopamine
Serotonin
Decision making under risk
Imaging genetics

ABSTRACT

One tenet of behavioral economics is the asymmetry in how decision makers evaluate risks involving gains versus risks involving losses. Correspondingly, an increasingly important question is what neuroanatomical and neurochemical correlates underpin valuation over gains and losses. By employing an imaging genetics strategy, this paper aims at identifying the specific neurotransmitter pathways underlying these decision making processes. We find enhanced striatal activation responding to increases in the magnitude of utility for risks over gains and to increases in the magnitude of disutility for risks over losses, while increased amygdala activation correlates only with the disutility for risks over losses. Stratifying brain activation by genotype, we find that a well-characterized polymorphism in the dopamine transporter (*DAT1*) contributes to individual differences in striatal response for gain-oriented risks, whereas a polymorphism in the serotonin transporter (*STin2*) partially accounts for individual differences in amygdala responses for loss-oriented risks. Together, our results suggest the role of the amygdala and corresponding serotonergic pathway in evaluating losses. This further corroborates the hypothesis of serotonin being linked to dopamine in an "opponent partnership".

Introduction

One tenet of behavioral economics is the fundamental asymmetry in how decision makers evaluate gain versus loss proposed in prospect theory (Kahneman and Tversky, 1979; Tversky and Kahneman, 1992), widely considered the most influential behavioral model of decision making under risk. Prospect theory challenges the classical thinking in economics that people generally exhibit diminishing marginal utility of final wealth. It posits the notion of status quo, relative to which gains and losses are defined. It further suggests that the Weber–Fechner law of diminishing sensitivity to changes in sensory and perceptual dimensions would apply to the utility for both gains and losses, as their magnitudes increase. This gives rise to a utility function that is concave over gains and convex over losses. It follows that people would tend to be risk averse for gain-oriented risks, known as *prospects*, and to be risk tolerant for loss-oriented risks, called *hazards*, when these risks involve moderate probabilities. Correspondingly, an increasingly important question concerns the specific neuroanatomical and the neurochemical correlates of valuation over gains and losses.

Mesolimbic dopaminergic neurons (*DA*) have been implicated in reward computation and reward prediction errors in the reinforcement learning model (Schultz, 2002; Schultz et al., 1997). Yet whether *DA* neurons also encode punishment or negative prediction error remains to be resolved, as the literature reports both positive findings (Matsumoto and Hikosaka, 2009; Seymour et al., 2007) and negative findings (Bayer and Glimcher, 2005; Pessiglione et al., 2006; Tobler et al., 2003). At the same time, serotonin (*5-HT*) neurons have been linked to harm avoidance and aversive behavior in studies of personality genetics (Cloninger, 1987), which resonates with loss. Cumulative findings have given rise to the hypothesis of *5-HT* being linked to *DA* in an "opponent partnership" (Daw et al., 2002; Dayan and Huys, 2009). This hypothesis is also supported in an association study of decision making under risk (Zhong et al., 2009b).

At the neuroanatomical level, a number of studies have suggested the role of the striatum, a brain region known to receive afferent input from midbrain dopaminergic neurons, for valuation towards gains as well as losses (Carter et al., 2009; Knutson et al., 2001; Tom et al., 2007). Other studies show that the amygdala, a brain region characterized by processing of fear and threat, encodes expected loss as well as reward prediction error over losses (Kahn et al., 2002; Yacubian et al., 2006). With previous imaging genetics studies

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1053-8119/$ – see front matter
doi:10.1016/j.neuroimage.2011.07.031

supporting the link between *DA* and striatum activation (van Dyck et al., 2005; Volkow et al., 2009), as well as between *5-HT* and amygdala activation (Hariri et al., 2002; Hariri and Weinberger, 2003; Roiser et al., 2009), we are well positioned to test the respective role of *DA* and *5-HT* in mediating striatal and amygdala responses in processing gain and loss oriented risks.

The candidate dopamine genes of interest include the dopamine transporter (*SLC6A3*) gene and the catechol-O-methyltransferase (*COMT*) gene. The DAT1 (*SLC6A3*) Variable Number Tandem Repeat (*VNTR*) (Vandenbergh et al., 1992) located in the 3′UTR, modulates gene expression and transporter density in vitro (Van Ness et al., 2005), midbrain activation (Schott et al., 2006) and in vivo transporter availability (Schott et al., 2006; van Dyck et al., 2005). A recent study (Zhong et al., 2009b) finds that subjects with the 9-repeat allele are more risk tolerant than those with the 10-repeat allele for risks over gains, but not over losses. The catechol-O-methyltransferase (*COMT*) enzyme provides the main metabolic route for degradation of released *DA* in the prefrontal cortex (Matsumoto et al., 2003), and striatum (Huotari et al., 2002). A common functional polymorphism in codon 158 (Val158Met) of the *COMT* gene leading to an amino acid substitution (valine [Val] to methionine [Met]) results in the Met/Met variant showing 40% less enzymatic activity than the Val/Val (Chen et al., 2004) and presumably enhanced dopamine signaling (Gogos et al., 1998). In a recent imaging genetics study (Yacubian et al., 2007), carriers of the Met allele show enhanced responses in the prefrontal cortex and the ventral striatum compared to subjects homozygous for the Val allele, in response to expected reward processing.

Two candidate genes of interest relevant to 5HT neurotransmission are the serotonin transporter (*SLC6A4*) and monoamine oxidase A (*MAOA*) genes. The serotonin transporter gene (*SLC6A4*) is characterized by a 44 bp insertion/deletion (*5-HTTLPR*) in the promoter region (Canli and Lesch, 2007; Lesch et al., 1996). This polymorphism has been associated with harm avoidance and aversive behavior (Canli and Lesch, 2007; Lesch et al., 1996). More recently, *5-HTTLPR* has been shown to be associated with financial risk attitude (Crisan et al., 2009; Kuhnen and Chiao, 2009). The serotonin transporter gene (*SLC6A4*) is also characterized by a second intronic (*STin2*) 17 bp variable number of tandem repeat (Lesch et al., 1994). Evidence suggests that this *VNTR* region may act as a transcriptional regulator of *SLC6A4*, with the 12-repeat allele having stronger enhancer-like properties than the 10-repeat allele (Hranilovic et al., 2004). *STin2* was found to be significantly associated with risk attitude over losses, but not for risk attitude over gains (Zhong et al., 2009b). *MAOA* is an isozyme of monoamine oxidase, which deaminates monoamines including norepinephrine, epinephrine, serotonin, and dopamine. The (*MAOA*) gene encodes an enzyme which is the main metabolic route for inactivation of *5-HT* and is characterized by a functional promoter region VNTR (Deckert, 1999; Sabol et al., 1998). The longer 4 allele is more transcriptionally active than the shorter 3 allele with consequences for behavior, viz. carriers of this allele are less likely to develop antisocial problems when interacting with specific family environment (Caspi et al., 2002). Furthermore, the low expression allele predicts limbic volume reductions and hyperresponsive amygdala during emotional arousal, with diminished reactivity of regulatory prefrontal regions (Meyer-Lindenberg et al., 2006). In a study of attitude towards longshot risk, *MAOA* is significantly associated with skewed prospects and subjects with the 4 allele were characterized by a preference for longshot (Zhong et al., 2009a). From a 325-subject sample used in our earlier studies on the neurogenetics of risk taking (Zhong et al., 2009a,b), we selected 41 subjects with fairly balanced allelic distribution of *DAT1* to investigate the underlying neurochemical pathways, regulating brain activity linked to utility of risks over gains and losses.

Experimental procedures

Subjects

From a group of 325 Han Chinese subjects in our earlier studies (Zhong et al., 2009a,b), we selected 41 right-handed subjects for the present study (20 females, age 22.3 ± 2.40; see Table S1). Subjects were selected to accomplish a balanced distribution of DAT1 variants, viz. 10/10 and 9/10, which has been shown to be associated with risk attitude in the gain domain (Zhong et al., 2009b). All subjects had a bachelor degree, a master degree or were in the process of obtaining one. Each subject's informed consent was obtained and the experimental protocol was approved by the Institutional Review Board at the Hong Kong University of Science and Technology and Beijing Normal University.

Experimental paradigm

The experiment comprises an instruction phase, a scanning phase, and a post-scan questionnaire phase. Subjects first familiarize themselves with the decision-making tasks during the instruction phase. During the 20-minute scanning phase, in each trial subject chooses between betting on an even chance lottery and receiving a specific amount of money for sure. Each trial lasts about 15 s as follows (Fig. 1). After a 2-second random jitter fixation, the participant sees an even-chance risk – either a prospect or a hazard – for 6 s followed by another 2-second random jitter before the participant sees an amount of money that can be received for sure. At this point, the participant makes a decision within 5 s whether to choose the amount of money for sure or the lottery. Should a choice not be made within 5 s, the computer will implement a choice randomly on behalf of the participant. For the experiment, the magnitudes of expected values (*EV*) are Y*20* and Y*50* for both gain and loss trials. For each EV, there are four even-chance lotteries with its high outcome and low outcome being given respectively by $EV(1+d)$ and $EV(1-d)$ with $d = 0.1$, 0.4, 0.7, and 1. Each such lottery is compared with five sure amounts given by $EV[(1-(1-2k)d)]$ with $k = 0.2$, 0.3, 0.4, 0.5, and 0.6 for prospects and equals 0.3, 0.4, 0.5, 0.6 and 0.7 for hazards. Each subject receives the payoff based on his/her decision made in a randomly selected trial. This payoff is added to or deducted from the show-up fee of *Y120*, depending on whether the selected trial is a gain trial or a loss trial.

Genotype

The genotyping method is the same as described in previous publications by our group (Zhong et al., 2009a,b). We do not examine the *5-HTTLPR* polymorphism given that its allele frequency is highly unbalanced in the Han Chinese population (Li et al., 2007). The short allele of *5-HTTLPR* is known to be the dominant allele (Canli and Lesch, 2007) and we have only 2 subjects with long/long genotype versus 39 subjects with either short/long or short/short. As such, *5-HTTLPR* was not included in the data analysis. The genotype frequency is presented in Table 1. We further test the correlation between genotypes, and find no significant correlation (Table S2). None of the polymorphisms were correlated with demographic information (Table S3), suggesting that the effect of the genes on brain activation in neuroimaging analysis is unlikely to be driven by demographic stratification. For *MAOA* and *COMT* polymorphisms, we compare the homozygous genotype of the major allele with the homozygous genotype of the minor allele and heterozygous genotype in the analysis. All the analyses are conducted by comparing the major genotype to other genotypes, to maximize the statistical power.

Image acquisition

Images were acquired with subjects in the supine position observing the rear-projected computer screen via a 45° mirror mounted above their faces on the head coil. Subjects' choices were

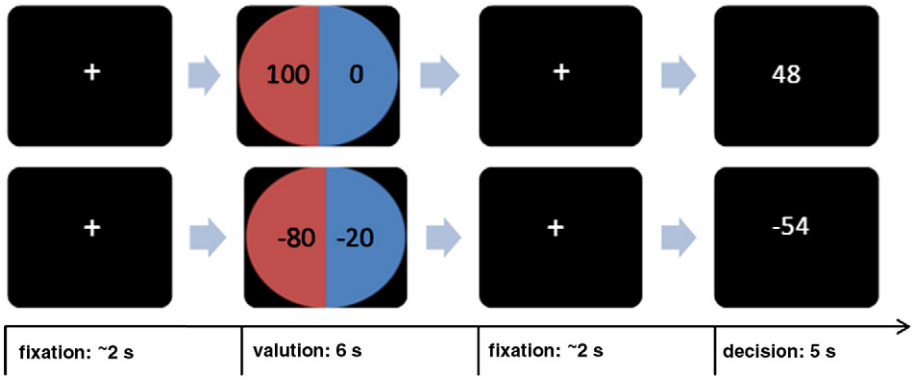

Fig. 1. Timeline of experimental design. Each 15-second trial begins with a 2-second random jitter fixation followed by a 6-second display of the image of an even-chance lottery. This is followed by another 2-second random jitter fixation which is in turn followed by the display of a sure amount of money for 5 s during which the subject chooses between receiving the lottery and receiving the sure amount. For both gain and loss trials, the magnitudes of expected value (*EV*) are 20 and 50. Each *EV* yields four even-chance lotteries with outcomes given by $EV(1-d)$ and $EV(1+d)$ ($d=0.1, 0.4, 0.7, 1$). Each lottery is compared with five sure amounts given by $EV[(1-(1-2k)d)]$ with k taking the values of 0.2, 0.3, 0.4, 0.5, and 0.6 for prospects and 0.3, 0.4, 0.5, 0.6 and 0.7 for hazards.

registered using two MRI-compatible button boxes. High-resolution T1-weighted scans ($1.3\times1.0\times1.3$ mm) were acquired on Siemens 3T scanners. Functional images details: echo-planar imaging; repetition time (TR) = 2000 ms; echo time (TE) = 30 ms; flip angle = 90° and functional $3.4\times3.4\times4$ mm3 voxels.

Imaging data analysis

Imaging data are processed and analyzed using *SPM8*. Functional images are realigned using a six-parameter rigid-body transformation. Each individual's structural T1 image is co-registered to the average of the motion-corrected images using 12-parameter affine transformation. Individual T1 structural images are segmented into gray matter, white matter, and CSF before the individual gray matter is nonlinearly warped into MNI gray matter template. Functional images are then slice-timing artifact corrected, normalized into MNI space by applying the transformation matrix adopted from previous T1 warping. Images are then smoothed with an 8 mm isotropic Gaussian kernel.

Pre-processed imaging data are analyzed by specifying a separate general linear model for each subject, followed by random effect analysis performed at the second level. One subject's fMRI data are excluded due to potential motion artifacts, since he suffered from light claustrophobia. All images are high-pass filtered in the temporal domain (filter width 128 s). Autocorrelation of the hemodynamic responses is modeled as an AR(1) process. In a single GLM model, both utility for prospects and utility for hazards are added to the main regressors using parametric modulations to test for how brain activity relates to sensitivity towards utility for prospects as well as hazards.

Table 1
Genotype frequencies. The first column is the name of the polymorphism; the second column is the name of allele; the third column is the number of subjects in each allele; the last column shows how we group different allele for the individual difference analysis.

Gene	Genotype	No. of subject	Group
DAT	9/10	13	1
	10/10	28	2
COMT	Val/val	25	1
	Val/met	11	2
	Met/met	4	2
STin2	10/12	6	1
	12/12	35	2
MAOA	3/3	20	1
	3/4	12	2
	4/4	8	2

All analyses are conducted in the valuation epoch with duration of 6 s as in Fig. 1, when subjects see the gambles. The full brain search results are reported in Tables S5 and S6 with a threshold of $p<0.005$. In addition, we apply small volume corrections (*SVC*) regarding striatum and amygdala activation with a sphere of radius 10 mm. and a threshold of $p<0.05$. We center the *SVC* on the coordinates based on previous research on the role of striatum in the valuation of gains and losses (Knutson et al., 2001) and amygdala in the effect of loss–gain framing (De Martino et al., 2006).

In the second level analysis on individual differences, we perform region of interest (*ROI*) analysis using Marsbar (Brett et al., 2002) to extract beta values of striatum and amygdala. The regions of interest are the same as those we used in *SVC*. We further use the beta values from the ROI analysis to test for association of brain activations in the striatum and the amygdala with risk attitudes towards prospects and hazards as well as with the four candidate polymorphisms.

We further conduct psycho-physiological interaction (*PPI*) analyses (Friston et al., 1997) to examine whether these polymorphisms are associated with striatum–amygdala coupling during decision making. First, we compute individual average time-series within a 6 mm sphere surrounding the peaks within the functional mask of right striatum shown in Figs. 2A/C. The *GLM* includes different levels of utility for prospects/hazards. The peak activation of each subject within the right striatum mask is identified based on the regions having the strongest response to utility for prospects and for hazards. Second, we estimate a *GLM* with the following regressors: 1. an interaction between the neural activity in the seed region and the utility for prospects/hazards; 2. a function for different levels of utility for prospects/hazards; 3. the original *BOLD* eigenvariate (i.e. the average time-series from the 6 mm sphere). Note that the first regressor identifies areas that exhibit task-related functional connectivity with the right striatum. In particular, it identifies areas in which the correlation in *BOLD* activity with right striatum increases with higher magnitudes of utility for prospects/hazards. Third, single subject contrasts for the first regressor were calculated, and then a second-level regression analysis is performed to examine whether there is significant difference in functional connectivity for subjects with 4-repeat allele and those without 4-repeat allele of *MAOA* gene.

Results

Behavioral results

We assume a utility function U (as in Kahneman and Tversky, 1979) which comprises x^{γ} for $x>0$ and $-(-x)^{\lambda}$ for $x<0$. For $x>0$, $\gamma<1$ ($=1, >1$) corresponds to subjects being risk averse (neutral,

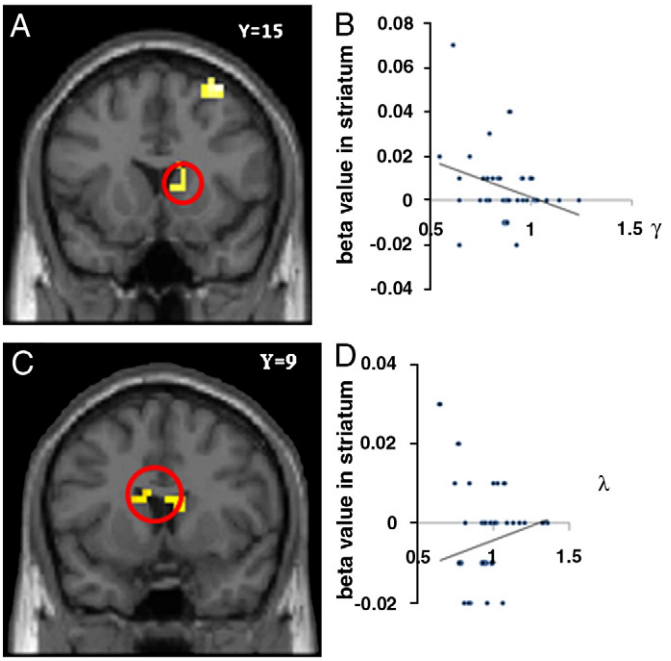

Fig. 2. (A) Coronal section showing the striatum whose activation correlates significantly with increased in the magnitude of the utility for prospects. The threshold is set at uncorrected $p<0.005$, and cluster size $k>10$ for illustration. (B) The beta value of striatum activation is significantly negatively correlated with the index γ of the utility function over gains, x^{γ}, in which lower values of γ represent greater degrees of risk aversion ($p<0.057$, two-tailed). (C) Coronal section of striatum whose activation correlates significantly with increased magnitude of utility for hazards. The threshold is set at uncorrected $p<0.005$, and cluster size $k>10$ for illustration. (D) The beta value of striatum activation is not significantly positively correlated with the index λ of the utility function over losses, $-(-x^{\lambda})$, in which higher values of λ represent greater degrees of risk aversion ($p<0.363$, two-tailed).

tolerant) and for $x<0$, $\lambda>1$ ($=1$, <1) corresponds to subjects being risk averse (neutral, tolerant). To estimate the risk aversion coefficients in Table S4 at both group and individual levels (as in Harrison and Rutstrom, 2008; Hey and Orme, 1994), we use *Stata 9* with the program code as documented in (Harrison, 2008) based on the following probabilistic choice model:

$$\text{Prob(choosing the lottery)} = \Phi((EU(\text{Lottery}) - U(\text{Certainty}))/\mu),$$

where μ is a 'noise' term (Harrison and Rutstrom, 2008; Hey and Orme, 1994). As expected, subjects are on average risk averse over prospects ($p<0.001$, one-tailed) and risk tolerant over hazards ($p<0.033$, one-tailed). There is no significant correlation between risk attitude over prospects and hazards (Spearman correlation $=0.176$, $p=0.149$). We exclude one subject who chose the lottery all the time and two subjects whose decisions violated stochastic dominance too often to estimate the risk attitude.

Behavior and gene association

To test the effect of genotypes on individual risk aversion coefficients reported in Table S4, we use linear regression with robust standard error. The statistical results are reported in Table 2. Not unexpectedly, considering the small sample size of 37 in the imaging protocol, we do not find significant association between genes and behavior, except for *MAOA*. The current study is built on our previous genetic association study with a much larger sample size ($N=325$) (Zhong et al., 2009b) in which significant associations were observed between *DAT1* and *STin2*, and risk attitudes over prospects and over hazards. More specifically, subjects with the 9-repeat allele of *DAT1* are more risk-tolerant over gains than subjects with the 10-repeat

Table 2
Genetic association between candidate genes and risk attitude in gain domain and in loss domain.

Gene	Gain			Loss		
	Coef	Std. err	p-value	Coef	Std. err	p-value
DAT1	0.006	0.046	0.901	0.046	0.051	0.371
COMT	0.028	0.050	0.572	0.011	0.055	0.847
STin2	0.050	0.053	0.358	0.021	0.058	0.720
MAOA	−0.104	0.049	0.042	0.025	0.056	0.653

allele, and that subjects with the 10-repeat allele of STin2 are more risk-tolerant over losses than subjects with the 12-repeat allele. While we did not replicate this direction of effect for *DAT1* in this current small sample, we replicated the direction of effect for *STin2*. As the genes contributing to complex traits are characterized by small effect sizes (odds ratio between 1 and 2; see Jakobsdottir et al.,2009), we exercise considerable caution in interpreting the behavior–gene association observed with the current small sample. Hence, for the behavior–gene association we refer to our previous study that is ipso facto more reliable. That being said, our initial hypotheses in the current paper were based on our previous observations in the larger sample.

Neural activation

In the gain domain, we find increased activation of striatum and dorsolateral prefrontal cortex, as well as decreased activation of insula, when the utility over prospects increases in the full brain search (Table S5). The striatal activation survives a *SVC* with coordinate ($x=12$, $y=18$, $z=-1$) as reported in previous literature (Knutson et al., 2001) (Fig. 2A). Additionally, the beta value of the striatal activation from *ROI* analysis using the same coordinate ($x=12$, $y=18$, $z=-1$) correlates positively with the degree of risk aversion, showing more risk averse subjects have higher activations in the striatum ($p<0.057$) (Fig. 2B).

In the loss domain, we find increased activation of striatum, inferior frontal gyrus and dorsolateral prefrontal cortex, and decreased activation of amygdala, insula and orbitofrontal cortex when the magnitude of utility over hazards increases in the whole brain search (Table S6). We perform a conjunction analysis (Price and Friston, 1997) for both prospects contrast and hazards contrast, which reveals a common region of striatum with peaks at $x=15$, $y=15$and $z=14$ (uncorrected $p<0.005$, voxel size >10). Again the striatal activation survives a *SVC* performed at coordinate ($x=8$, $y=4$, $z=11$), which reported to be correlated with valuation of losses (Knutson et al., 2001) (Fig. 2C). The striatal activation ($x=8$, $y=4$, $z=11$) from *ROI* analysis shows no significant correlation with risk aversion in the loss domain ($p>0.3$) (Fig. 2D). The amygdala activation also survives a SVC performed at coordinate ($x=-14$, $y=2$, $z=-24$), which is shown to be associated with framing effect of gains and losses (De Martino et al., 2006) (Fig. 3A). Notably, the amygdala activation from *ROI* analysis ($x=-14$, $y=2$, $z=-24$) correlates negatively with risk aversion in the loss domain ($p<0.071$) (Fig. 3B). Risk-tolerant subjects show greater amygdala activation compared to risk-averse subjects.

Neural activation and gene association

To test association between striatum and amygdala with the four candidate polymorphisms, we perform an *ROI* analysis using the coordinates from the *SVC* to extract beta values of the brain regions, and further test the effect of the gene using simple linear regression. The striatal responses of subjects with the *DAT1* 10/10 are significantly higher than the responses of the ones with the 9/10 genotype (two-tailed, $p<0.004$). No such association is observed for *COMT*, *STin2* and

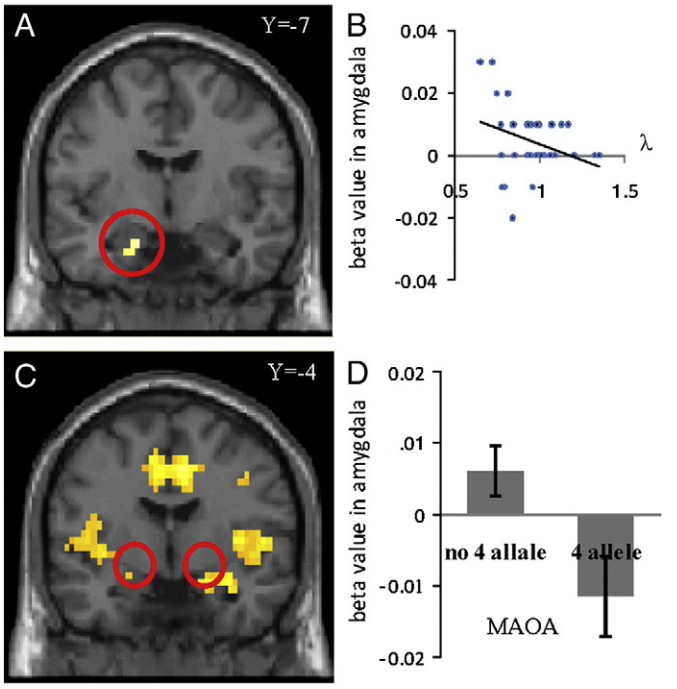

Fig. 3. (A) Coronal section of amygdala whose activation correlates negatively with increased magnitude of utility for hazards. The threshold is set at uncorrected $p<0.005$, and cluster size $k>10$ for illustration. (B) The beta value of amygdala activation is significantly negatively correlated with the index λ of the utility function over losses, $-(-x^{\lambda})$, in which higher values of λ represent greater degrees of risk aversion ($p<0.071$, two-tailed). (C) Subjects with 4-repeat allele of *MAOA* have lower functional connectivity between striatum and brain regions including bilateral amygdala, bilateral insula, and cingulate cortex activation than subjects without 4-repeat allele (*FDR* corrected $p<0.040$, cluster size $k>10$).

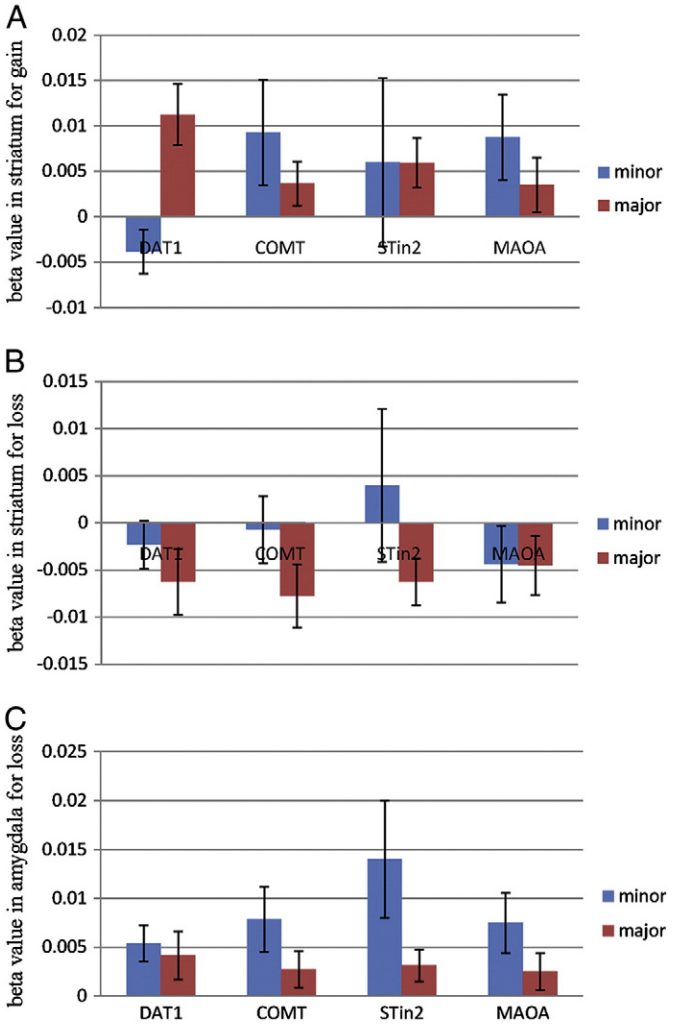

Fig. 4. (A) Striatal activation for prospects and genes. The striatal responses to increased utility for prospects for subjects with the *DAT1* 10/10 are significantly higher than the responses of the ones with the 9/10 genotype (two-tailed, $p<0.004$), and no significant association is found for *COMT*, *STin2* and *MAOA*. (B) Striatal activation for hazards and genes. Striatal activation in response to increased utility of hazards is not significantly associated with each of the four polymorphisms. (C) Amygdala activation for hazards and genes. Amygdala activation towards increased utility for losses for subjects with the *STin2* 10/12 genotype is significantly higher than the ones with the 12/12 genotype (two-tailed, $p<0.028$), and no significant association is found for *DAT1*, *COMT*, and *MAOA*.

MAOA (Fig. 4A). We do not find striatal activation responding to changes in utility of hazards being associated with any of the four polymorphisms (Fig. 4B). However, subjects with the STin2 10/12 genotype have significantly higher amygdala response than the ones with the 12/12 genotype (two-tailed, $p<0.028$). No such association is observed with *DAT1*, *COMT*, and *MAOA* (Fig. 4C).

Using psycho-physiological interaction (*PPI*) analysis with right striatum as seed, we find functional connectivity between right striatum and bilateral amygdala in the loss domain and importantly, this connectivity is mediated by *MAOA*. Subjects with the *MAOA* 4-repeat allele show lower functional connectivity between striatum and bilateral amygdala, bilateral insula as well as cingulate cortex, than subjects without the 4-repeat allele (Fig. 3C). We conduct similar analysis in the gain domain using right striatum as seed, and do not find significant functional connectivity between right striatum and any of these regions.

Discussion

At the neuroanatomical level, we find that the striatum encodes utility of both gain and loss oriented risks. This is consistent with reported evidence regarding striatal activation responding positively to the magnitude of both anticipated gains and anticipated losses (Carter et al., 2009; Knutson et al., 2001). By contrast, a recent imaging study of valuation towards gains and losses using mixed risks around the status quo (Tom et al., 2007) reports that the striatum showed increased activity as potential gains increased and decreased activity as the size of the potential loss increased and no association with regions regulating emotion including amygdala and insula. Tom et al. interpreted their result in terms of a single reward mechanism that codes for both gains and losses. This divergent finding may be attributed to the fact that the lotteries used in Tom et al. are mixed ones involving both gains and losses while the lotteries used in Knutson et al. (2001), Carter et al. (2009), as well as the current study involve pure-gain and pure-loss lotteries but not mixed ones. Using a mixed lottery paradigm limits the ability to identify a dual system involving gains and losses. Indeed, in using both pure-gain and pure-loss lotteries, our design enables us to identify a dual striatum–dopamine and amygdala–serotonin system.

Amygdala and striatum have a well understood anatomic connectivity and show a tight functional coupling (Adolphs, 2010) and it would make biological sense that an anatomical distinction between loss and gain could be encoded in the amygdala and striatum, respectively. Following Tom et al.(2007), a study using the same mixed lottery design (De Martino et al., 2010) on subjects with amygdala lesions reveals that they are more tolerant towards mixed risks. In an imaging study using a framing design in which the same lottery is framed as a gain-oriented risk as well as a loss-oriented risk, De Martino et al. (2006) find that amygdala activation is modulated by an interaction between gain–loss framing and risk attitude. A follow up imaging genetics study (Roiser et al., 2009) finds

that amygdala activation is mediated by the serotonin transporter gene. We further show that the functional connectivity between striatum and amygdala during evaluation of hazards is mediated by *MAOA* adding a neurochemical dimension to the anatomical separation in the neural response to risks involving gains and involving losses. Altogether, our finding contributes to a growing consensus that the amygdala is involved in the valuation of risks involving losses. This view is biologically plausible considering the well-established role of this brain region in anxiety and fear circuitry (Adolphs, 2010).

By stratifying brain activation to identify more precisely the neurochemical pathways underpinning risk over losses and gains, the present work directly links synaptic dopamine and serotonin availability, indexed by common functional polymorphisms, with *BOLD* signal changes in humans. In particular, our results suggest that individual differences in striatal *BOLD* signal responding to increased utility for prospects are associated with the dopaminegic polymorphism of *DAT*1 and more precisely that they reveal the role of *DA* pathways in mediating attitude towards economic risk taking. Our findings are consistent with the role of dopamine genes in modulating reward sensitivity that has been reported in previous imaging genetic studies (Yacubian et al., 2007). We do not find a direct link between the two *DA* polymorphisms and striatal activity in response to changes in the utility for hazards; although it is believed that the striatum receives afferent inputs from midbrain dopaminergic neurons (Carter et al., 2009; Knutson et al., 2001). Notwithstanding this, it has been reported that the administration of *DA* drugs affects decision making over gain oriented risks but not over loss oriented risks at both the behavioral and the neural levels (Pessiglione et al., 2006). Recently, Matsumoto and Hikosaka (2009) find that some *DA* neurons are activated by both reward and punishment while other *DA* neurons respond solely to reward signals and are suppressed by punishment signals. This reveals a richer picture of how *DA* neurons respond to reward and punishment. Some regions in the striatum appear to respond positively to the magnitude of reward as well as punishment, while other anatomically distinct regions within the striatum show increased activity as potential gains increased and decreased activity as the size of the potential loss increased. Follow-up studies are needed to gain a better understanding of *DA* in processing losses in decision making under risk.

Given our finding of association between amygdala response to loss and its correlation with a functional serotonergic polymorphism (*STin2*) in the serotonin transporter, it appears that a further loss–gain distinction can be made not only at the anatomical but also at the neurochemical level. Our findings support the notion of a role for serotonergic pathways in the amygdala response to utility for hazards, and dopaminergic pathways underlying striatal response to utility for prospects and possibly hazards. These conclusions are consistent with previous imaging genetics evidence regarding the role of serotonin in amygdala function encoding negative emotion and the effect of loss–gain framing (Hariri et al., 2002; Hariri and Weinberger, 2003; Roiser et al., 2009). The present study supports the idea of a serotonin–amygdala system having a role in processing utility for hazards. Interestingly, serotonergic pathways inhibit dopamine neurotransmission in key brain regions such as the nucleus accumbens allowing for a direct opponency between these two signaling molecules at the synaptic level. In particular, the central serotonin *5-HT$_{2C}$* receptor is now well established as a modulator of dopamine neuron function in the mammalian brain (Alex et al., 2005; Berg et al., 2008).

Building on the interaction at the synaptic level, *5-HT* has been linked to *DA* in an "opponent partnership" in reinforcement learning (Boureau and Dayan, 2011; Cools et al., 2010; Daw et al., 2002; Dayan and Huys, 2009; Rogers, 2011). For an updated view of the 'opponent partnership' hypothesis, the reader is referred to a recent review of Cools et al. that lays forth the arguments about how the two neuromodulators interact and provides a more comprehensive understanding regarding the joint role of *DA* and *5-HT* in encoding reinforcement learning. As noted by Cools et al., computational modeling of the role of *DA* in reinforcement learning has made great strides in the past decade. On the other hand, our understanding of the role of *5-HT* in these processes has lagged behind. Boureau and Dayan take a complementary approach, basing their thinking on a refined analysis of the interactions between *DA* and *5-HT*, and between reward and punishment from the perspective of various components of conditioning. We suggest the notion that striatal activation responding to loss may be driven by serotonergic inhibition, specifically by *5-HT$_{2C}$* receptors, of dopaminergic neurotransmission. Our paper adds to this ongoing debate and supports the idea that opponency between *DA* and *5-HT* has a role in decision making under risk. Addressing this complexity appears to offer a fruitful direction for future research.

Acknowledgment

We thank Zhu Xingtian for assistance in conducting the experiment. We would like to acknowledge the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University for facilitating the fMRI experiment. We are also grateful to Steven Graham, Nicolas Hon, Hsu Ming, O'Dhaniel Mullette-Gillman, Trevor Penney, and Annett Schirmer Li Jian for helpful comments. Financial supports from the Hong Kong University of Science and Technology (project title: Neuroeconomics and Decision making), Ministry of Education, Singapore (project title: Biological Economics and Decision Making), and AXA Research Fund (project title: Biology of Decision Making under Risk) are also gratefully acknowledged.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2011.07.031.

References

Adolphs, R., 2010. What does the amygdala contribute to social cognition? Ann. N. Y. Acad. Sci. 1191, 42–61.
Alex, K.D., Yavanian, G.J., McFarlane, H.G., Pluto, C.P., Pehek, E.A., 2005. Modulation of dopamine release by striatal 5 HT2C receptors. Synapse 55, 242–251.
Bayer, H.M., Glimcher, P.W., 2005. Midbrain dopamine neurons encode a quantitative reward prediction error signal. Neuron 47, 129–141.
Berg, K.A., Clarke, W.P., Cunningham, K.A., Spampinato, U., 2008. Fine-tuning serotonin2c receptor function in the brain: molecular and functional implications. Neuropharmacology 55, 969–976.
Boureau, Y.L., Dayan, P., 2011. Opponency revisited: competition and cooperation between dopamine and serotonin. Neuropsychopharmacology 36, 74–97.
Brett, M., Anton, J.L., Valabregue, R., Poline, J.B., 2002. Region of interest analysis using an SPM toolbox. Neuroimage 16, 1140–1141.
Canli, T., Lesch, K.P., 2007. Long story short: the serotonin transporter in emotion regulation and social cognition. Nat. Neurosci. 10, 1103–1109.
Carter, R.M., Macinnes, J.J., Huettel, S.A., Adcock, R.A., 2009. Activation in the VTA and nucleus accumbens increases in anticipation of both gains and losses. Front. Behav. Neurosci. 3, 21.
Caspi, A., McClay, J., Moffitt, T.E., Mill, J., Martin, J., Craig, I.W., Taylor, A., Poulton, R., 2002. Role of genotype in the cycle of violence in maltreated children. Science 297, 851–854.
Chen, J., Lipska, B.K., Halim, N., Ma, Q.D., Matsumoto, M., Melhem, S., Kolachana, B.S., Hyde, T.M., Herman, M.M., Apud, J., 2004. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. Am. J. Hum. Genet. 75, 807–821.
Cloninger, C.R., 1987. A systematic method for clinical description and classification of personality variants. A proposal. Arch. Gen. Psychiatry 44, 573–588.
Cools, R., Nakamura, K., Daw, N.D., 2010. Serotonin and dopamine: unifying affective, activational, and decision functions. Neuropsychopharmacology 36, 98–113.
Crisan, L.G., Pana, S., Vulturar, R., Heilman, R.M., Szekely, R., Druga, B., Dragos, N., Miu, A.C., 2009. Genetic contributions of the serotonin transporter to social learning of fear and economic decision making. Soc. Cogn. Affect. Neurosci. 4 (4), 399–408.
Daw, N.D., Kakade, S., Dayan, P., 2002. Opponent interactions between serotonin and dopamine. Neural Netw. 15, 603–616.
Dayan, P., Huys, Q.J., 2009. Serotonin in affective control. Annu. Rev. Neurosci. 32, 95–126.
De Martino, B., Camerer, C.F., Adolphs, R., 2010. Amygdala damage eliminates monetary loss aversion. PNAS 107, 3788–3794.

De Martino, B., Kumaran, D., Seymour, B., Dolan, R.J., 2006. Frames, biases, and rational decision-making in the human brain. Science 313, 684–687.
Deckert, J., 1999. Excess of high activity monoamine oxidase A gene promoter alleles in female patients with panic disorder. Hum. Mol. Genet. 8, 621–624.
Friston, K.J., Buechel, C., Fink, G.R., Morris, J., Rolls, E., Dolan, R.J., 1997. Psychophysiological and modulatory interactions in neuroimaging. Neuroimage 6, 218–229.
Gogos, J.A., Morgan, M., Luine, V., Santha, M., Ogawa, S., Pfaff, D., Karayiorgou, M., 1998. Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior. PNAS 95, 9991–9996.
Hariri, A.R., Mattay, V.S., Tessitore, A., Kolachana, B., Fera, F., Goldman, D., Egan, M.F., Weinberger, D.R., 2002. Serotonin transporter genetic variation and the response of the human amygdala. Science 297, 400–403.
Hariri, A.R., Weinberger, D.R., 2003. Functional neuroimaging of genetic variation in serotonergic neurotransmission. Genes Brain Behav. 2, 341–349.
Harrison, G.W., 2008. Maximum Likelihood Estimation of Utility Functions Using Stata. Working Paper.
Harrison, G.W., Rutstrom, E.E., 2008. Risk aversion in the laboratory. In: Cox, J.C., Harrison, G.W. (Eds.), Risk Aversion in Experiments. Emerald Group Publishing Limit.
Hey, J., Orme, C., 1994. Investigating generalizations of expected utility theory using experimental data. Econometrica 62, 1291–1326.
Hranilovic, D., Stefulj, J., Schwab, S., Borrmann-Hassenbach, M., Albus, M., Jernej, B., Wildenauer, D., 2004. Serotonin transporter promoter and intron 2 polymorphisms: relationship between allelic variants and gene expression. Biol. Psychol. 55, 1090–1094.
Huotari, M., Santha, M., Lucas, L.R., Karayiorgou, M., Gogos, J.A., Männistö, P.T., 2002. Effect of dopamine uptake inhibition on brain catecholamine levels and locomotion in catechol-O-methyltransferase-disrupted mice. J. Pharmacol. Exp. Ther. 303, 1309.
Jakobsdottir, J., Gorin, M.B., Conley, Y.P., Ferrell, R.E., Weeks, D.E., 2009. Interpretation of genetic association studies: markers with replicated highly significant odds ratios may be poor classifiers. PLoS Genet. 5, e1000337.
Kahn, I., Yeshurun, Y., Rotshtein, P., Fried, I., Ben-Bashat, D., Hendler, T., 2002. The role of the amygdala in signaling prospective outcome of choice. Neuron 33, 983–994.
Kahneman, D., Tversky, A., 1979. Prospect theory: an analysis of decision under risk. Econometrica 47, 263–291.
Knutson, B., Adams, C.M., Fong, G.W., Hommer, D., 2001. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. J. Neurosci. 21, 159.
Kuhnen, C.M., Chiao, J.Y., 2009. Genetic determinants of financial risk taking. PLoS One 4, e4362.
Lesch, K.P., Balling, U., Gross, J., Strauss, K., Wolozin, B.L., Murphy, D.L., Riederer, P., 1994. Organization of the human serotonin transporter gene. J. Neural Transm. Gen. Sect. 95, 157–162.
Lesch, K.P., Bengel, D., Heils, A., Sabol, S.Z., Greenberg, B.D., Petri, S., Benjamin, J., Muller, C.R., Hamer, D.H., Murphy, D.L., 1996. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 274, 1527–1531.
Li, J., Wang, Y., Zhou, R., Zhang, H., Yang, L., Wang, B., Faraone, S.V., 2007. Association between polymorphisms in serotonin transporter gene and attention deficit hyperactivity disorder in Chinese Han subjects. Am. J. Med. Genet. B Neuropsychiatr. Genet. 144, 14.
Matsumoto, M., Hikosaka, O., 2009. Two types of dopamine neuron distinctly convey positive and negative motivational signals. Nature 459, 837–841.
Matsumoto, M., Weickert, C.S., Akil, M., Lipska, B.K., Hyde, T.M., Herman, M.M., Kleinman, J.E., Weinberger, D.R., 2003. Catechol O-methyltransferase mRNA expression in human and rat brain: evidence for a role in cortical neuronal function. Neuroscience 116, 127–137.
Meyer-Lindenberg, A., Buckholtz, J.W., Kolachana, B., Hariri, A.R., Pezawas, L., Blasi, G., Wabnitz, A., Honea, R., Verchinski, B., Callicott, J.H., 2006. Neural mechanisms of genetic risk for impulsivity and violence in humans. PNAS 103, 6269–6274.
Pessiglione, M., Seymour, B., Flandin, G., Dolan, R.J., Frith, C.D., 2006. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature 442, 1042–1045.
Price, C.J., Friston, K.J., 1997. Cognitive conjunction: a new approach to brain activation experiments. Neuroimage 5, 261–270.
Rogers, R.D., 2011. The roles of dopamine and serotonin in decision making: evidence from pharmacological experiments in humans. Neuropsychopharmacology 36, 114–132.
Roiser, J.P., de Martino, B., Tan, G.C., Kumaran, D., Seymour, B., Wood, N.W., Dolan, R.J., 2009. A genetically mediated bias in decision making driven by failure of amygdala control. J. Neurosci. 29, 5985–5991.
Sabol, S.Z., Hu, S., Hamer, D., 1998. A functional polymorphism in the monoamine oxidase A gene promoter. Hum. Genet. 103, 273–279.
Schott, B.H., Seidenbecher, C.I., Fenker, D.B., Lauer, C.J., Bunzeck, N., Bernstein, H.G., Tischmeyer, W., Gundelfinger, E.D., Heinze, H.J., Duzel, E., 2006. The dopaminergic midbrain participates in human episodic memory formation: evidence from genetic imaging. J. Neurosci. 26, 1407–1417.
Schultz, W., 2002. Getting formal with dopamine and reward. Neuron 36, 241–263.
Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. Science 275, 1593–1599.
Seymour, B., Daw, N., Dayan, P., Singer, T., Dolan, R., 2007. Differential encoding of losses and gains in the human striatum. J. Neurosci. 27, 4826–4831.
Tobler, P.N., Dickinson, A., Schultz, W., 2003. Coding of predicted reward omission by dopamine neurons in a conditioned inhibition paradigm. J. Neurosci. 23, 10402–10410.
Tom, S.M., Fox, C.R., Trepel, C., Poldrack, R.A., 2007. The neural basis of loss aversion in decision-making under risk. Science 315, 515–518.
Tversky, A., Kahneman, D., 1992. Advances in prospect-theory — cumulative representation of uncertainty. J. Risk Uncertain 5, 297–323.
van Dyck, C.H., Malison, R.T., Jacobsen, L.K., Seibyl, J.P., Staley, J.K., Laruelle, M., Baldwin, R.M., Innis, R.B., Gelernter, J., 2005. Increased dopamine transporter availability associated with the 9-repeat allele of the SLC6A3 gene. J. Nucl. Med. 46, 745–751.
Vandenbergh, D.J., Persico, A.M., Hawkins, A.L., Griffin, C.A., Li, X., Jabs, E.W., Uhl, G.R., 1992. Human dopamine transporter gene (DAT1) maps to chromosome 5pl5. 3 and displays a VNTR. Genomics 14, 1104–1106.
van Ness, S.H., Owens, M.J., Kilts, C.D., 2005. The variable number of tandem repeats element in DAT1 regulates in vitro dopamine transporter density. BMC Genet. 6, 55.
Volkow, N.D., Fowler, J.S., Wang, G.J., Baler, R., Telang, F., 2009. Imaging dopamine's role in drug abuse and addiction. Neuropharmacology 56 (Suppl 1), 3–8.
Yacubian, J., Glascher, J., Schroeder, K., Sommer, T., Braus, D.F., Buchel, C., 2006. Dissociable systems for gain- and loss-related value predictions and errors of prediction in the human brain. J. Neurosci. 26, 9530.
Yacubian, J., Sommer, T., Schroeder, K., Glascher, J., Kalisch, R., Leuenberger, B., Braus, D.F., Buchel, C., 2007. Gene–gene interaction associated with neural reward sensitivity. PNAS 104, 8125–8130.
Zhong, S., Israel, S., Xue, H., Ebstein, R.P., Chew, S.H., 2009a. Monoamine oxidase A gene (MAOA) associated with attitude towards longshot risks. Plos ONE 4 (12), e8516.
Zhong, S., Israel, S., Xue, H., Sham, P.C., Ebstein, R.P., Chew, S.H., 2009b. A neurochemical approach to valuation sensitivity over gains and losses. Proc. Biol. Sci. 276, 4181–4188.