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Subregions of the ventral striatum show preferential coding of reward magnitude and probability

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As shown in non-human primate and human fMRI studies the probability and magnitude of anticipated rewards modulate activity in the mesolimbic dopaminergic system. Importantly, non-human primate data have revealed that single dopaminergic neurons code for both probability and magnitude of expected reward, suggesting an identical system. Using a guessing task that allowed the independent assessment of the factors probability and magnitude we were able to assess the impact of reward probability and magnitude in ventral striatal subregions in a large sample ($n=98$). We observed more anterior and lateral peak activation foci in the ventral striatum for reward probability and a more posterior and medial activation peak for reward magnitude, suggesting a functional segregation at the mesoscopic level. Importantly, this functional bias observed for the group average was also tested in each individual subject, allowing for proper random effects inference for the spatial dissociation. Taken together, our data point toward a functional dissociation of neuronal assemblies suggesting that certain populations of neurons are more sensitive to expected reward probability and other populations are more sensitive to reward magnitude.

Keywords: Ventral striatum; Reward; fMRI; Probability; Magnitude

Introduction

The behavioral goal to seek out rewards is ubiquitous throughout the realm of locomotive organisms, including non-human primates and humans. Two important characteristics determine which rewards are behaviorally sought after (Rescorla and Solomon, 1967; Dickinson and Balleine, 1994; Schultz, 2006): reward magnitude and reward probability. While the former determines how much of a particular reward is expected, the latter informs about the likelihood of obtaining it.

Economists and psychologists have long studied how humans and animals utilize such information. Probability theory, initially developed by Blaise Pascal, offers a framework for understanding how organisms deal with uncertainty in a macroscopically nondeterministic world (Machina, 1987). Pascal combined probability and magnitude to a single value called expected value to determine the mathematical value of any gamble or lottery (Pascal and Fermat, 1654). Daniel Bernoulli (1954) then developed this concept into "utility" of outcome, the subjective value that humans use when choosing between outcomes with different probabilities and magnitudes. These concepts form some of the basics of current economic decision-making theory (Kahneman and Tversky, 2000).

In biological terms, the past decade has witnessed the emergence of compelling evidence from single-unit recording in non-human primates for the involvement of mesolimbic dopaminergic neurons in the midbrain for the representation of reward probability and reward magnitude. Using appetitive classical conditioning, it has been demonstrated that the firing rate of these neurons is correlated with both the probability (Fiorillo et al., 2003) and magnitude (Tobler et al., 2005) of a reward signaled by different conditioned stimuli, which predict the magnitude or probability of anticipated future rewards. Thus, it appears that both reward magnitude and probability are encoded by these neurons when a reward-predicting stimulus is encountered. Importantly, single dopaminergic neurons seem to encode both reward probability and magnitude, suggesting that for this group of neurons at a cellular level these two components may not be segregated. However, this does not rule out a subtle bias of certain dopaminergic neuronal populations for either expected reward magnitude or probability.

Inspired at least in part by the findings in animal experiments and economic theory, recent fMRI experiments have recognized the importance of distinguishing between magnitude and probability of reward and have tested directly for their separate influence on reward-related brain activity (O'Doherty et al., 2001, 2002; Knutson et al., 2001, 2005; Elliot et al., 2003; Dreher et al., 2006; Abler et al., 2006; Preuschoff et al., 2006; Tobler et al., 2007). Activity changes in ventral striatum directly scale with the absolute magnitude of

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monetary rewards (Knutson et al., 2005; Elliot et al., 2003). In contrast, the orbitofrontal cortex, which also responds to magnitude of rewards either to the appetitive value of food reward (O'Doherty et al., 2002; Small et al., 2001) or to secondary reinforcers such as money (O'Doherty et al., 2001), seems to code relative, rather than absolute values of reward as also demonstrated in non-human primates by single cell recordings from orbitofrontal cortical neurons (Tremblay and Schultz, 1999). On the other hand the probability of obtaining a monetary reward was found to be correlated with activity in medial prefrontal cortex (Knutson et al., 2001) and to increase linearly with the fMRI signal in the ventral striatum (nucleus accumbens) (Abler et al., 2006). Consistent with previous findings, a recent study by our group (Yacubian et al., 2006) demonstrated ventral striatal responses coding both reward probability and magnitude during anticipation, permitting the local computation of gain-related expected value, the product of reward probability and magnitude. A similar result was recently demonstrated by Tobler et al. (2007) showing that striatal regions were sensitive to individual variations in magnitude and probability confirming that the striatum seems to combine reward magnitude and probability multiplicatively into a common signal of expected value, although in this study the anticipation of rewards was not separated from reward outcome. Furthermore, Preuschoff et al. (2006) showed that activations related to expected reward and risk were segregated spatio-temporally within the ventral striatum.

Since the initial introduction of the concept of the ventral striatum and limbic striatal integration by Heimer and Wilson in 1975 this structure and its connections have been a research focus of the neurobiological mechanisms underlying not only the normal responses in relation to reward, decision-making and reinforcement learning but also in relation to drug addiction and other psychiatric disorders (Robbins and Everitt, 1996). The ventral striatum refers to a continuum of neural tissue that extends into the ventromedial parts of the putamen and caudate and includes the nucleus accumbens (Gray, 1999). It has long been associated with a group of structures thought to mediate reward and goal-directed behaviors. This association is partly based on its input connections from structures such as the amygdala and prefrontal cortex, as well as dopaminergic afferents from the ventral tegmental area, which are considered to be involved in mechanisms of reward and positive reinforcement (Wise and Rompre, 1989; Haber, 2003).

Taking into account the functional and anatomical regional differences within the ventral striatum (that has representational topographies related to its midbrain and cortical inputs); and the differences between reward probability and reward magnitude properties predicated by economic and decision making theories, we asked the question whether the ventral striatum responses for probability and magnitude of rewards are identically encoded across the ventral striatum, or whether a consistent response preference for magnitude and probability coding can be established at the single subject level. A large sample of volunteers ($n=98$) that was investigated to study the link between genetic variation in dopamine metabolizing enzymes and transporters was reanalyzed for this purpose (Yacubian et al., 2006, 2007).

Materials and methods

Participants

Ninety-eight healthy male volunteers were investigated. We focused our study on male volunteers, to exclude gender effects, because it has been suggested that women have an increased endogenous striatal dopamine concentration (Pasqualini et al., 1996). All volunteers underwent a structured psychiatric interview performed by an experienced psychiatrist and urine drug screening to exclude cocaine, amphetamine, cannabis and opiate use. Additionally, all subjects were asked to not smoke or drink alcoholic beverages at least 24 h prior to evaluation.

The age range of the sample was 18–46 years (mean, 26.2 ± SD 5.4) and 8–20 years of education (mean, 14.9 ± SD 1.7). The study was approved by the Ethics Committee of the Medical Board in Hamburg (Germany) and all subjects gave written informed consent.

Task

We employed a simple guessing task subdivided into choice/anticipation and outcome (Yacubian et al., 2006). Each trial began with the presentation of the backside of eight playing cards. Volunteers had to place a given amount of money (€1.00 or €5.00) on individual playing cards, allowing for the control of reward magnitude. In some trials, the bet had to be placed on the corners of four adjacent cards and in others only on single cards, which allowed for the control of reward probability (low for a single card and high for four cards). Altogether, volunteers played a series of 200 trials. Due to trial randomization, the probability for the low probability trials was 26% and 66% for the high probability trials. This is a small deviation from the graphically expected probabilities of 1/8 (i.e. 0.125) and 4/8 (i.e. 0.5), which was necessary to avoid a rapid decrease in balance due to the unfortunate average gain/loss ratio of 31.25%/68.75% when the individual gain probabilities are 12.5% and 50%.

Initial credit was set to €20.00 and continuously displayed on the screen. The money presented was either a €1 coin or a €5 bill. Volunteers were able to place their bet using an MR compatible optical mouse for 3034 ms. After placing the bet, the display was kept constant during an additional anticipation period of 4207 ms, after which all cards were flipped and the volunteers could see the outcome of the trial. Another 2015 ms later, the continuously visible credit display was updated and another 3006 ms (in 171 trials) or 12,262 ms (in 29 trials) later, the next trial began. This resulted in 171 trials with an inter stimulus interval (ISI) of 12.26 s and 29 trials with a longer ISI (21.46 s), introducing 14.6% null events.

Seven of eight cards were black, the remaining one was a red ace. If the red ace was touched by the bet, the volunteer gained the amount of money, and otherwise lost the money. The order of trials was pseudorandomized and predetermined, i.e. the volunteer had no influence on the probability and the magnitude of each individual trial.

Before entering the scanner, subjects received a standardized verbal description of the task and completed a practice session including all possible combinations of probability, magnitude and outcome.

Volunteers were told explicitly before the experiment that they would receive their balance in cash. In case of a negative balance they were told that the amount would be deducted from the payment offered for participating in this study. Volunteers ended the game with a negative balance of €8.00, which was waived.

Imaging and statistics

MR scanning was performed on a 3 T MR Scanner (Siemens Trio, Erlangen, Germany) with a standard head coil. Thirty-eight continuous axial slices (slice thickness: 2 mm) were acquired using a gradient echo echo-planar T_2*-sensitive sequence (TR=2.22 s, TE=25 ms, flip angle 80°, matrix 64*64, field of view 192*192 mm). Subjects viewed the backprojected stimuli via a 45° mirror placed on top of the head coil. The task presentation and the recording of behavioral responses were performed with Cogent 2000v1.24 (www.vislab.ucl.ac.uk/cogent/index.html).

Image processing and statistical analyses were carried out using SPM2 (www.fil.ion.ucl.ac.uk/spm). All volumes were realigned to the first volume, spatially normalized to an EPI template in the standard MNI coordinate system. We extracted data from a smaller field of view (x: −36 to 36, y: −26 to 30 and z: −24 to 18 mm) from the originally normalized functional images and renormalized those to the mean of all images using an affine transformation. This last step was intended to further improve the alignment of subcortical structures. After this second normalization, data were resampled to a voxel size of 2×2×2 mm and slightly smoothed with a Gaussian kernel of 4 mm FWHM. In addition, each individual structural T_1-weighted MRI was coregistered to the renormalized individual functional images using an information theoretical approach as implemented in SPM2.

The employed paradigm has a 2×2×2 factorial design with the factors probability (high or low), magnitude (€1.00 or €5.00) and outcome (gain or loss), resulting in eight different conditions. All eight conditions were modeled separately in the context of the general linear model as implemented in SPM2. The anticipation and the outcome phase were modeled as individual hemodynamic responses (3034 and 7241 ms after trial onset), leading to 16 regressors (2×2×2 conditions times 2 regressors, anticipation and outcome). An additional covariate was incorporated into the model, representing the early response (3034 ms after trial onset) modulated by the total amount of mouse movements in the choice period of this trial. This ensured that movement related activation during the early trial period is modeled independently from the regressors of interest. The outcome phase (i.e. reward delivery) was modeled but not taken into account in this analysis.

Data were analyzed for each subject individually applying a high pass filter with a cut-off of 120 s to remove baseline drifts. Based on the ensuing parameter estimates, contrasts of interest were generated (i.e. main effect of anticipation related responses against baseline and parametric increase for higher and more likely rewards). For an additional group analysis the ensuing contrast images were then entered into a second level analysis with subjects as a random effect.

To test for a spatial segregation of reward magnitude and reward probability associated activations at the single subject level, we used a volume of interest approach. In a first step we identified a point halfway between the peak of magnitude and probability within the ventral striatum of the group data, separately for the right and left hemisphere. Around this point (x=±16, y=13, z=0 mm), we defined a volume of interest (VOI; sphere with a diameter of 24 mm) that comprised both peaks. We then identified the location of the highest t-value in each volunteer related to probability and to magnitude in this VOI. The ensuing x, y and z coordinates were then analyzed separately using a paired t-test. For this analysis, the threshold was set to $p<0.05$.

Results

Main effect of reward magnitude and reward probability

The average peak of the magnitude related activation was located in bilateral posterior ventral striatum (peak x, y, z: 8, 6, 2 mm; z=10.0, peak x, y, z: −10, 4, 0 mm; z=9.7, both $p<0.05$, corrected). The average peak of the probability related activation was located in the anterior ventral striatum (peak x, y, z: 12, 19, −6 mm; z=6.7, peak x, y, z: −14, 14, −2 mm; z=5.4, both $p<0.05$, corrected).

Spatial relationship between effects

When directly comparing the probability and magnitude related activation from the group analysis, we observed a spatial segregation within the ventral striatum (Fig. 1) for reward probability and magnitude. The main effect of magnitude during the anticipation phase was located posterior and medially in the ventral caudate adjacent to the lateral ventricle (green) and extended posteriorly along the ventromedial surface of the ventral caudate. In contrast, the main effect of probability (blue) was located further anterior, lateral and ventral.

The analysis of single subjects confirmed this finding, showing a spatial segregation between magnitude and probability. Significant spatial differences were confirmed in the x and y coordinates, representing right to left and anterior to posterior dimensions, respectively (Table 1; Fig. 2). Directly comparing x, y and z coordinates revealed a significant difference for x, with reward probability being more lateral (right: $t(97)=5.1$, $p<0.05$; left: $t(97)=3.5$, $p<0.05$) than reward magnitude. In addition a significant anterior–posterior segregation was observed with reward probability being located anterior compared to reward magnitude (right: $t(97)=3.7$, $p<0.05$; left: $t(97)=4.8$, $p<0.05$). No difference with respect to the z coordinate was observed (right: $t(97)=0.3$, n.s.; left: $t(97)=0.8$, $p<0.05$).

Discussion

Using a large data set comprising 98 volunteers and individual analyses, our data show a robust spatial segregation of the peak activations related to the main effect of anticipated reward magnitude and probability in the ventral striatum. Peak responses for magnitude were located posterior and medial to the area that showed the maximal activation for the probability of the anticipated reward. The former effect could be localized within the posterior medio-ventral caudate nucleus, whereas probability mostly activated the ventral striatum in the lateral-anterior region. This observation suggests that certain populations of neurons within the ventral striatum are more sensitive to expected reward probability and other populations are more sensitive to reward magnitude.

Refined analysis of connectivity as well as the histochemical profile revealed that the ventral striatum is composed of different subregions (Kelley, 2004). The nucleus accumbens is classically divided into the core (tissue surrounding the anterior commissure) and the shell, a region extending medially, ventrally and laterally

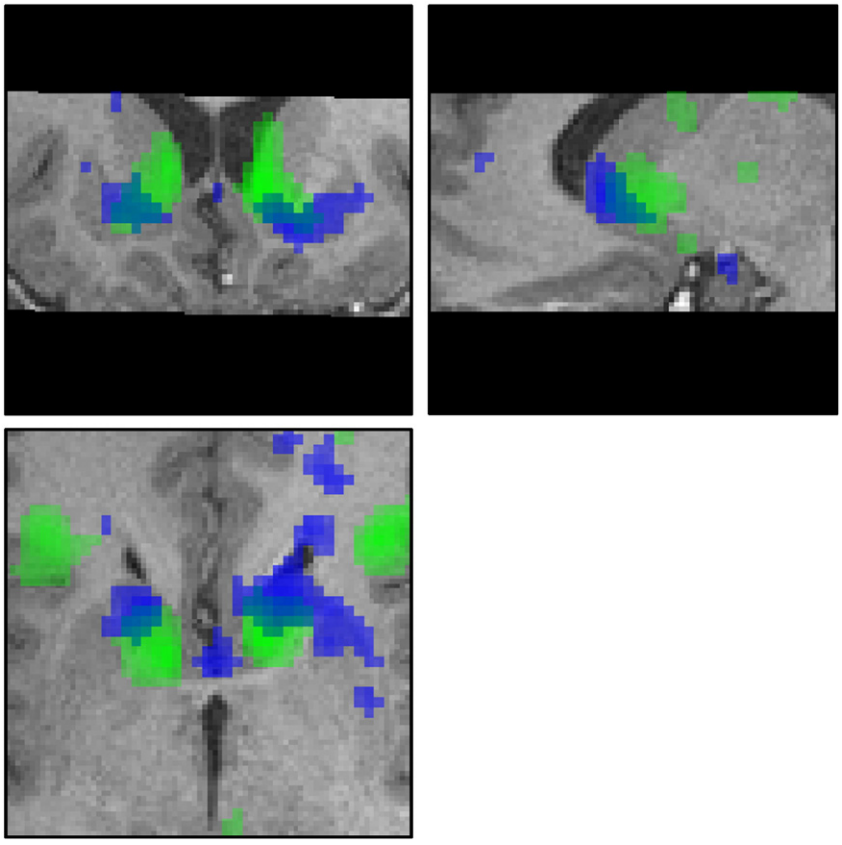

Fig. 1. Spatial dissociation of expected reward magnitude and probability. Activation for reward magnitude and probability in right and left ventral striatum are overlaid on a normalized T1-weighted image from a representative volunteer at $\times=-13$, $y=10$, $z=-3$. The probability related activation is depicted in blue and magnitude-related responses are shown in green. The average coordinate for reward probability in the right hemisphere was located at $\times=15.9\pm0.6$, $y=13.6\pm0.5$, $z=-0.5\pm0.5$ mm, the corresponding average peak for magnitude was located at $\times=11.9\pm0.5$, $y=10.6\pm0.5$, $z=-0.3\pm0.5$ mm. In the left hemisphere the peak for reward probability was located at $\times=-16.5\pm0.6$, $y=13.8\pm0.5$, $z=-0.7\pm0.5$ mm and the peak for reward magnitude was located at $\times=-13.7\pm0.5$, $y=10.2\pm0.6$, $z=-0.2\pm0.5$ mm.

around the core (Zahm and Brog, 1992). In humans the tissue corresponding to the rat nucleus accumbens may extend through a lateral location (Holt et al., 1997). Thus, the shell of the nucleus accumbens seems to be in a ventral-to-ventrolateral position in the human as opposed to the ventromedial position seen in the rat, which would be consistent with the possibility that the region in the ventrolateral human striatum is shell-like tissue (Holt et al., 1997). The shell region receives a specific and limited afferent projection most closely linked to the amygdala and hypothalamus (Haber and McFarland, 1999).

Additionally, in the human it is supposed that the parts of the striatum closely related to the limbic system occupy a region that extends beyond the boundaries of what is traditionally considered the nucleus accumbens proper (Eblen and Graybiel, 1996).

Comparing the activation pattern found in our experiment with known anatomy and connections of different subregions within the ventral striatum, the peak activation of magnitude coincides with the region of the ventral striatum that receives input from orbital and medial prefrontal cortex (OMPFC). This is consistent with the view that activation in this region represents stimulus reward value (Elliot et al., 2003). Although activity in the medial prefrontal cortex has also been related to reward probability (Knutson et al., 2005), new data from immunocytochemical experiments in non-human primates suggest that there may be a number of pathways

Table 1
Spatial difference between reward magnitude and probability within ventral striatum

	Right ventral striatum			Left ventral striatum		
	x	*y*	*z*	*x*	*y*	*z*
Average distance mean±SD (mm)	4.0±7.7	−3.0±8.1	−0.2±7.6	2.5±8.5	3.6±7.5	−0.5±6.7
SE (mm)	±0.8	±0.8	±0.8	±0.9	±0.8	±0.7
t(97)	5.1 *	3.7 *	0.3	3.5 *	4.8 *	0.8

SD—standard deviation; SE—standard error.
* $p<0.001$.

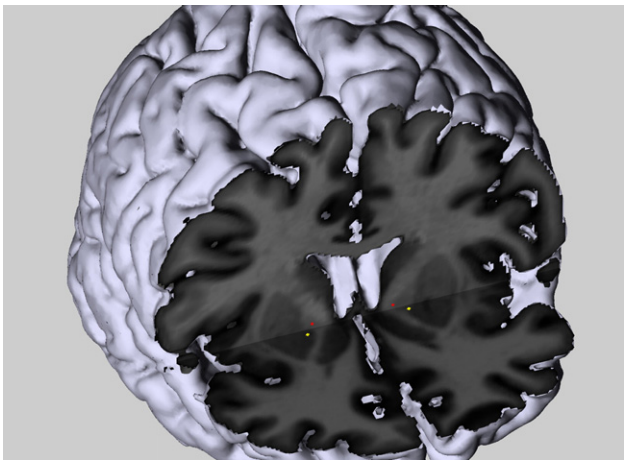

Fig. 2. Differential representation sites of reward magnitude and probability in right and left ventral striatum overlaid on a 3D-rendered brain. The probability-related peak activation is depicted in yellow and is situated more lateral (x-axis: right: $t(97)=5.1$, $p<0.05$; left: $t(97)=3.5$, $p<0.05$) and anterior (y-axis: right: $t(97)=3.7$, $p<0.05$; left: $t(97)=4.8$, $p<0.05$) than the magnitude-related peak activation shown in red.

by which different corticostriatal loops interact. Some of these corticostriatal loops involve projections from the medial PFC to the ventromedial striatal position, which in our data correspond to the magnitude activation, while projections from the orbital PFC are widely distributed throughout the ventral striatum (Haber et al., 2006). Yet, the peak activation for probability in our data corresponds to the antero-lateral region of the ventral striatum that might be considered as the lateral shell (Groenewegen et al., 1999). This area is richly connected with subcortical areas (lateral ventral tegmental area and thalamus) and amygdala (basal amygdaloid complex) (Groenewegen et al., 1999).

Furthermore, corticostriatal loops were also traced in humans with a diffusion tensor imaging axonal mapping technique (Lehericy et al., 2004) showing direct connections from the OMPFC, the amygdala and the hippocampus to the ventral striatum.

The OMPFC has been widely suggested to guide behavior based on the anticipated value of different actions (Nauta, 1971). It is a particularly strong candidate for a representation of incentive value as its neurons respond rapidly to changes in the reward value of specific foods (Cardinal et al., 2003). Neurophysiological studies of behaving monkeys and rats show that neurons in orbitofrontal cortex process motivating events, discriminate between appetitive and aversive conditioned stimuli (Thorpe et al., 1983) and are active during the expectation of outcomes (Schoenbaum et al., 1998). The activity of these orbitofrontal neurons does not appear to code the fixed physical properties of rewards, but rather reflects the motivational value of one reward relative to another, as expressed by the behavioral preference. Some orbitofrontal neurons may dynamically code the value of reward and lose their responses when the reward gets devalued, for instance when animals become satiated on particular food items (Critchley and Rolls, 1996). Human studies using fMRI showed that magnitude of rewards and punishments received is represented in medial and lateral orbitofrontal respectively (O'Doherty et al., 2001).

Of particular interest is that prefrontal cortical projections, including orbitofrontal fibres, extend dorsally and rostrally from the conventionally defined nucleus accumbens into the ventral caudate nucleus and throughout a large part of its rostral pole (Haber and McFarland, 1999, Haber et al., 2006). The demonstration that brain processes related to reward magnitude are localized in areas densely connected to the prefrontal cortical region is another indicator for the relationship between these regions and the ventral striatum in the estimation of reward value.

Expectation of increasing reward probabilities is related to increases in phasic dopamine responses in non-human primates (Fiorillo et al., 2003). However, reward-responsive tonically active neurons in the striatum do not appear to be sensitive to reward probability (Morris et al., 2004), indicating that not all neurons sensitive to reward may code its value in terms of probability. Our results show that activation associated with a high probability in comparison to a low probability of being rewarded is represented more laterally and ventrally in ventral striatum, comprising in part the lateral part of the shell of the nucleus accumbens, which receives massive input from amygdala, thalamus and ventral tegmental area (Groenewegen et al., 1999).

Moreover, our results are in agreement with a recent fMRI experiment (Preuschoff et al., 2006) that distinguished ventral striatum regions that specifically responded to either reward expectation or risk. Importantly, these areas showed activity that increased with the level of expected reward and perceived risk. Additionally, they found that the activation related to expected reward was immediate, while the activation related to risk was delayed. Along the same lines, Tobler et al. (2007) also showed that fMRI activations reflecting reward magnitude, probability and expected value can be distinguished by their localization within ventral striatum. Although the striatal anatomical segregation was not the main focus of these studies (Preuschoff et al., 2006; Tobler et al., 2007) it is clearly evident in both reports that the risk/probability signals are located more ventrally and laterally in relation to the expected reward signals.

According to decision theory all consequences that might result from certain actions should be reviewed and then, to the extent possible, their likelihood should be assessed (Slovic et al., 1977). Theoretical frameworks dealing with decision under risk like expected value (Pascal and Fermat, 1654), expected utility (Von Neumann and Morgenstern, 1944) and prospect theory (Kahneman and Tversky, 2000) have in common that a decision is based on the product of reward magnitude and probability. Yet, these theories differ with respect to the weighting of these two entities before being multiplied. Whereas the simplest form, expected value takes the simple product, prospect theory combines magnitude and probability using two non-linear functions (i.e. value and the weighting function). Crucially, the observation of prospect theory that two different functions are necessary to account for human choice behavior at least suggests that probability and magnitude processing could be separable in the human brain.

In addition, cognitive processes have been shown to individually modify parameters of the individual weighting or value function independently (e.g. framing) (Tversky and Kahneman, 1992). The adaptivity of this system would also benefit from the concept of segregated probability and magnitude coding, which would enlarge the flexibility necessary for decisions under changing circumstances.

Importantly, our data do not show that the ventral striatum contains two mutually exclusive nodes for magnitude and probability processing. Given previous observations in non-human primates (Schultz, 2006) it is more likely that although most neurons respond to changes in reward magnitude and probability,

they do so in a graded fashion, i.e. have a bias to preferentially encode either probability or magnitude in certain subregion of the ventral striatum.

In summary, our findings support the concept of at least partially dissociable modules for the processing of anticipated reward magnitude and probability within the ventral striatum. This dissociation is likely to be the result of differences in anatomical connectivity with respect to medial or lateral aspects of the prefrontal/orbital cortex as well as to reward-sensitive subcortical brain regions. Importantly, this segregation allows for a high degree of flexibility in the way how probability and magnitude are combined for instance in the framework of prospect theory to flexibly guide human choice behavior.

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