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Research Report

Differential magnitude coding of gains and omitted rewards in the ventral striatum

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ABSTRACT

Physiologic studies revealed that neurons in the dopaminergic midbrain of non-human primates encode reward prediction errors. It was furthermore shown that reward prediction errors are adaptively scaled with respect to the range of possible outcomes, enabling sensitive encoding for a large range of reward values. Congruently, neuroimaging studies in humans demonstrated that BOLD-responses in the ventral striatum encode reward prediction errors in similar fashion as dopaminergic midbrain neurons, suggesting that these BOLD-responses may be driven by dopaminergic midbrain activity. However, neuroimaging results are ambiguous with respect to the adaptive scaling of reward prediction errors, leading to the conjecture that under certain circumstances other than dopaminergic midbrain input may drive ventral striatal BOLD-responses. The goal of this study was to substantiate whether BOLD-responses in the ventral striatum rather respond to adaptively scaled reward prediction errors or absolute reward magnitude. In addition, we aimed to identify neuronal structures modulating activity in the ventral striatum. Sixteen healthy participants played a wheel of fortune game, where they could win three differently valued rewards while being scanned. BOLD-responses increased after gaining rewards; this gain was however independent of the absolute reward magnitude. In contrast BOLD-responses upon reward omission decreased with reward magnitude. A psychophysiological interaction analysis identified a cluster in the brainstem in proximity of the dorsal raphe nucleus, a cluster in the lateral orbitofrontal cortex, and a cluster in the rostral cingulate zone. These clusters changed their connectivity with the ventral striatum in relation to the absolute reward magnitude in reward omission trials.

1. Introduction

Seminal experiments have demonstrated that dopaminergic midbrain cell firing patterns are related to reward processing, in particular to the encoding of the difference between expected reward and experienced reward, thus represent reward prediction errors (RPE) (for a review see Schultz, 2000). It has been shown that RPEs are modulated by means of the expected probability, delay of occurrence and the magnitude of the reward (Fiorillo et al., 2003; Schultz, 1998; Schultz et al., 1997; Tobler et al., 2005). It has been furthermore demonstrated that dopaminergic RPE-signals are scaled with respect to

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known alternatives (Tobler et al., 2005). Specifically, the authors established that when three cues predicted pairs of rewards of different magnitudes, the better outcome always elicits the same positive reward prediction error signal, irrespective of the absolute reward magnitude. This scheme also applies to negative outcomes that are followed by the same negative RPE-signal. As a consequence of this "gain adaptation" the neural response discriminates equally well between two potential outcomes, regardless of their absolute differences in magnitude. In this manner, the ability to sensitively encode rewards is maintained over a large range of reward values (Tobler et al., 2005).

A recent study of Bunzeck et al. (2010) investigated adaptive coding of RPEs in humans using functional magnetic resonance imaging (fMRI). Similar as in the study of Tobler et al. (2005) subjects were presented three different cues, which predicted two rewards with different magnitudes but identical probability. They could elegantly demonstrate that bold oxygenation level dependent (BOLD) responses in common target areas of the dopaminergic midbrain such as the ventral striatum reflect scaled adaptive coding of reward prediction errors, such that irrespective of the difference of the absolute magnitude, the better outcome elicits the same increase in BOLD-response compared to the lesser outcome. Thus, it was shown that BOLD-responses in the ventral striatum encode reward magnitudes with respect to the known alternatives and not at an absolute scale. Many other studies investigated BOLD-responses to differentially rewarding (and punishing) outcomes, although not with the specific goal to investigate "gain adaptation". If different rewards (which are fully known to the subject) can be won or lost, prediction errors should be scaled to the absolute difference between winning and losing, and hence BOLD-responses in the ventral striatum should not differ between the absolute magnitudes of different rewards. In contrast to this notion, a number of studies reported reward magnitude dependent hemodynamic responses in the ventral striatum (e.g. Rolls et al., 2008; Yacubian et al., 2006), whereas others showed magnitude *in*dependent differences between favorable and unfavorable outcomes (e.g. Delgado et al., 2003; Elliott et al., 2003; Bunzeck et al., 2010). One plausible explanation for the discrepancy between results could be that task specific differences impede "gain-adaptation". Alternatively, depending on the experimental task, the BOLD signal itself may be driven by different sources of neuronal activity.

Current standard of knowledge is that the BOLD signal is most strongly related to synaptic current; therefore, it may reflect afferent input to neuron populations *and/or* local intrinsic processing (e.g. Logothetis et al., 2001; Viswanathan and Freeman, 2007). Looking at the ventral striatum, BOLD-responses are suggested to arise from stimulation of postsynaptic D1 receptors through dopamine release as inferred from a pharmacological MRI study (Knutson and Gibbs, 2007). Significantly correlating BOLD-responses between the ventral tegmental area and the ventral striatum in response to reward prediction errors (D'Ardenne et al., 2008) and dopamine release in both structures (Schott et al., 2008) corroborate the idea of dopaminergic midbrain-driven BOLD-responses in the ventral striatum. Furthermore, at the level of single-unit activity reward prediction errors are generally not seen in the ventral striatum (Niv and Schoenbaum, 2008), thus arguing against intrinsically driven BOLD-responses. Nonetheless, a proportion of neurons in the ventral striatum signal the value of rewards and cues that predict reward (Niv and Schoenbaum, 2008). Congruently, in some neuroimaging studies the BOLD-signal in the ventral striatum correlates with reward magnitude (McClure et al., 2004, Tanaka et al., 2004) and not reward magnitude dependent prediction errors. Thus, the BOLD-signal in the ventral striatum might reflect cortical input or intrinsic activity if reward absolute reward magnitudes are correlated, whereas it might reflect dopaminergic input if reward prediction errors are related to hemodynamic responses (Daw and Doya, 2006).

In the present study we aimed to explore, whether reward and omission of reward of subjectively different magnitudes modulate BOLD-responses in the ventral striatum. If BOLD-responses are scaled to the magnitude of rewards, we speculate that other than dopaminergic midbrain input may modulate the BOLD signal. To further test this hypothesis we use psychophysiological interaction analysis to derive the neuronal sources of such putative variations.

2. Results

2.1. *Voxel-wise analysis*

We conducted a whole brain analysis that examined significant activity in the ventral striatum for the four conditions of interest ($AnR_{1,2,3}$ $AR_{1,2,3}$ $OwR_{1,2,3}$ $OnwR_{1,2,3}$); we then compared these results to the analog conditions, in which participants played for no rewards (AnR_n, AR_n, OwR_n, $OnwR_n$). See Table 1 for a description of contrasts and conditions.

Significantly more ventral striatal activity was found in the anticipation phase when playing for rewards compared to no rewards with clear bilateral activation (MNI: –10, 16, –6, t=5.77, p<0.001; MNI: 10, 10, –10, t=7.33, p<0.001, complete list of clusters: Table 2). There was no significant difference in ventral striatal activity between rewards and no rewards during the won outcome phases. Similarly, no significant differences were found in response to the announcement of differently rewarded trials. However, activity in the ventral striatum was significantly smaller when participants did not win a potential reward compared to not winning in a no-reward control trial (bilateral NAcc, (MNI: –8, 12, –10, t=5.52,

Table 1 – Contrasts of the first level analysis, testing for activity in the ventral striatum.

Contrasts	
$[AnR_1, AnR_2, AnR_3] > AnR_n$	
$[AR_1, AR_2, AR_3] > AR_n$	
$[OwR_1, OwR_2, OwR_3] > OwR_n$	
$[OnwR_1, OnwR_2, OnwR_3] < OnwR_n$	
Description	
An:	Announcement
A:	Anticipation phase
Ow:	Outcome phase (won trials)
Onw:	Outcome phase (not won trials)
R_x:	Reward magnitude(1 = high, 2 = intermediate, 3 = low)
R_n:	No reward

Table 2 – Group maximum t-values and MNI coordinates oF fMRI activity during the anticipation [*AR1, AR2, AR3*]>*AnRn* (p<0.001 uncorrected, cluster size >30 voxels).

Region	Right/left	Cluster size (voxels)	Coordinates			t-value	p <
			X	Y	Z		
Brainstem	R	3911	12	−26	−10	7.46	0.001
Pallidum	L		−14	−6	−6	5.34	0.001
Caudate	L		−8	4	0	5.60	0.001
Accumbens	L		−10	16	−6	5.77	0.001
Accumbens	R		10	10	−10	7.33	0.001
Caudate	R		10	4	2	6.63	0.001
Superior frontal gyrus	R	1070	24	−8	56	7.32	0.001
Thalamus	R	120	18	−22	12	7.16	0.001
Lateral occipital cortex, superior division	L	924	−12	−66	62	4.62	0.001
Middle frontal gyrus	L	1282	−28	−4	48	6.72	0.001
Supramarginal gyrus	L	153	−46	−34	36	6.37	0.001
Superior parietal lobule	R	861	22	−56	56	6.30	0.001
Postcentral gyrus	R	216	32	−34	46	6.05	0.001
Frontal pole	R	114	46	44	24	5.73	0.001
Lateral occipital cortex, inferior division	R	463	42	−66	−2	5.56	0.001
Frontal pole	R	146	34	52	10	5.34	0.001
Lateral occipital cortex, superior division	L	87	−32	−70	14	5.09	0.001

p<0.001; MNI: 14, 12, −10, t=4.56, 0.001, complete list of clusters: Table 3).

2.2. *Region of interest analysis*

2.2.1. *Anticipation phase*

Analysis of individual FIR time-courses during the anticipation phase (Fig. 1, A) (duration 10–12 s) extracted from the bilateral NAcc ROI yielded a significant interaction of condition (3)×epoch (10), (F (3.9, 47.4)=2.636, p<0.0046), indicating that certain conditions differed significantly over time. Post hoc paired t-tests at the time-point of the highest peak of the signal (12.5 s) revealed significant differences between R_1 (high reward magnitude) and R_3 (low reward magnitude) (t (df=12)=4.228, p<0.001), and a trend for differences between R_1 and R_2 (intermediate reward magnitude) (t (df=12)=1.759, p<0.0502).

2.2.2. *Outcome won*

No significant activity within the ventral striatum was found for the outcome phase of rewarding won trials (Fig. 1, B) when compared to non-rewarding won trials in the whole brain analysis. Nevertheless, a repeated measure ANOVA revealed a significant main effect of the factor epoch (10), (F (2.456, 24.563)=9.066, p<0.001) but no significant interaction between condition (3) and epoch (10); thus, indicating that the signal time courses changed significantly over time without differing between conditions. A post hoc single sample t-test at the peak of the mean of all signal time courses indicated a significant increase in signal change (t (df=10)=3.404, p<0.007)). The FIR time course of the won, although not rewarded, trials differed significantly at the onset of the outcome phase and 2.5 s thereafter from the time courses of mean of all rewarded conditions (0 s=(t (df=10)=2.457, p<0.034), 2.5 s=(t (df=10)=3.106, p<0.01). This indicates that the hemodynamic response started in not rewarded trials at lower levels, compared to rewarded trials.

2.2.3. *Outcome not won*

The analysis of individual FIR time-courses during the outcome phase of not won trials (Fig. 1, C) (duration 3 s) extracted from the bilateral NAcc ROI, yielded a significant interaction of condition (3)×epoch (10), (F (4.815, 67.411)=3.2, p<0.013); therefore, indicating that particular conditions differed significantly over time. Post-hoc paired t-tests at the time-point of the most negative signal change (R_1=10 s,

Table 3 – Group maximum t-values and MNI coordinates of fMRI "deactivation" after the omission of rewards [*OnwR1, OnwR2, OnwR3*]<*OnwRn* (p<0.001 uncorrected, cluster size >30 voxels).

Region	Right/left	Cluster size (voxels)	Coordinates			t-value	p <
			X	Y	Z		
Superior frontal gyrus	L	214	−20	22	60	5.73	0.001
Accumbens	L	92	−8	12	−10	5.52	0.001
Accumbens, putamen	R	33	14	12	−10	4.56	0.001

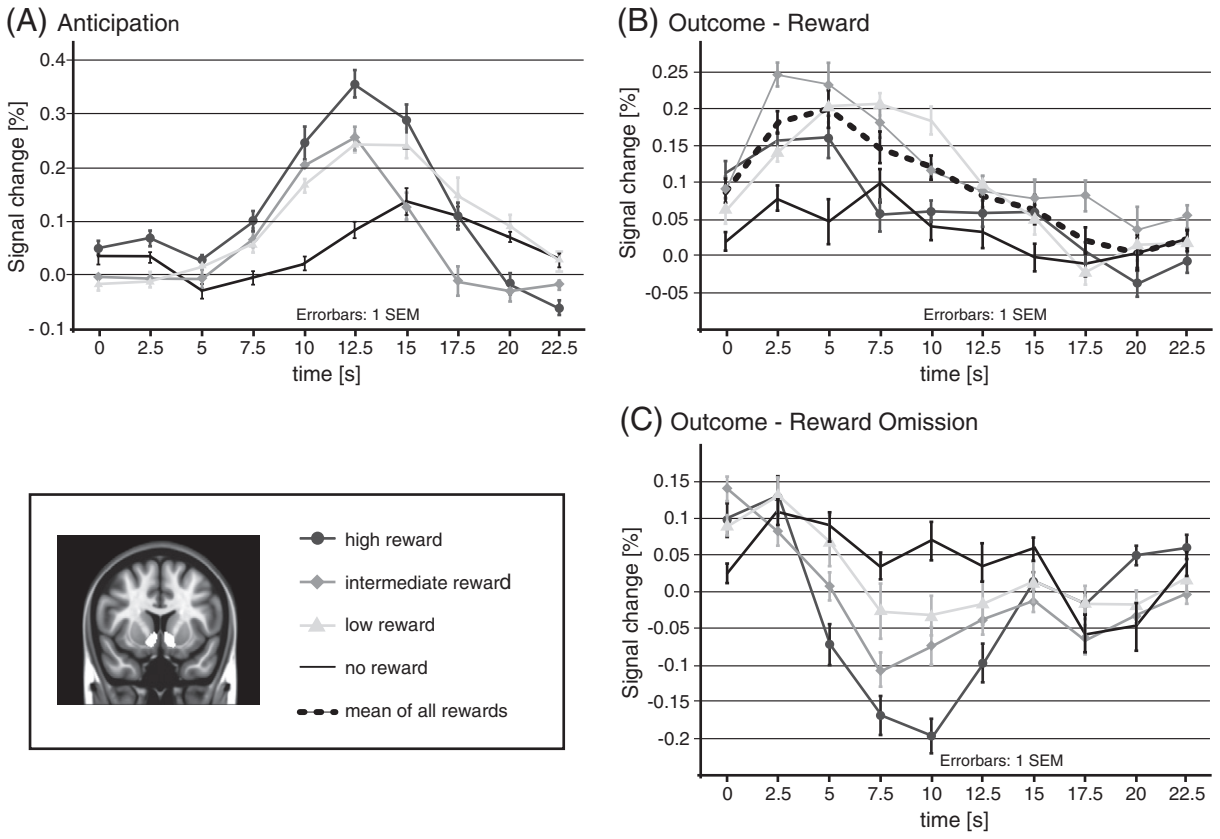

Fig. 1 – Event-related hemodynamic responses to different reward magnitudes (reward magnitude). A, Hemodynamic responses during the anticipation phase are modulated by reward magnitude. B, Hemodynamic responses after rewarded outcomes are not influenced by reward magnitude. Averaged time-courses of all rewarded trials (dashed line) exhibit significant differences to non-rewarded trials. C, After reward omission, signal time-courses significantly decrease in a reward magnitude-dependent fashion. (Note the different scalings in A, B and C).

R_2=7.5 s, R_3=10 s) revealed significant differences between R_1 and R_3 (t (df=14)=4.006, $p<0.001$), as well as significant differences between R_2 and R_3 (t (df=14)=2.383, $p<0.032$). No significant difference was observed between R_1 and R_2 (t (df=14)=1.521, $p<0.150$).

2.3. *PPI of reward magnitude and the NAcc after not won outcomes*

We discovered that neural responses in the dorsal raphe nucleus (dRN), rostral cingulate zone (RCZ), and the right lateral orbitofrontal cortex (lOFC) covaried more negatively with neural activity in the NAcc as a function of the magnitude of omitted rewards (Table 4). The precise localization of dRN activation is difficult to ascertain with standard MRI techniques. However, previous imaging studies have identified the dorsal raphe nucleus within close range to the cluster in the brainstem, which was found in our study (Lanzenberger et al., 2009; Tanaka et al., 2004). A repeated measures ANOVA ($p<0.05$) with factors preference levels (3)×cluster location (3) was performed using the mean of the estimated beta weights; it revealed a significant main effect for the factor preference levels (F (101.7, 1.67)=5.69, $p=0.007$). Post-hoc paired t-tests of the beta estimates in the dRN indicated significant differences between R_1 and R_2 (t (df=61)=2.144, $p<0.036$) and R_1 and R_3 (t (df=61)=2.802, $p<0.0035$). With regard to the beta estimates of the lOFC cluster, post-hoc paired t-tests revealed a trend for significant differences

Table 4 – Brain areas showing significant negative changes in connectivity at $p<0.001$. Uncorrected, cluster size >30 voxels, except for the dorsal raphe nucleus (cluster size >10).

Region (negative PPI)	Right/left	Cluster size (voxels)	Coordinates			t-value	$p <$
			X	Y	Z		
Rostral cingulate zone	–	545	0	34	12	7.39	0.001
Lateral orbitofrontal cortex	R	341	34	28	−22	6.06	0.001
Dorsal raphe nucleus	L	16	−2	−32	−16	3.73	0.001

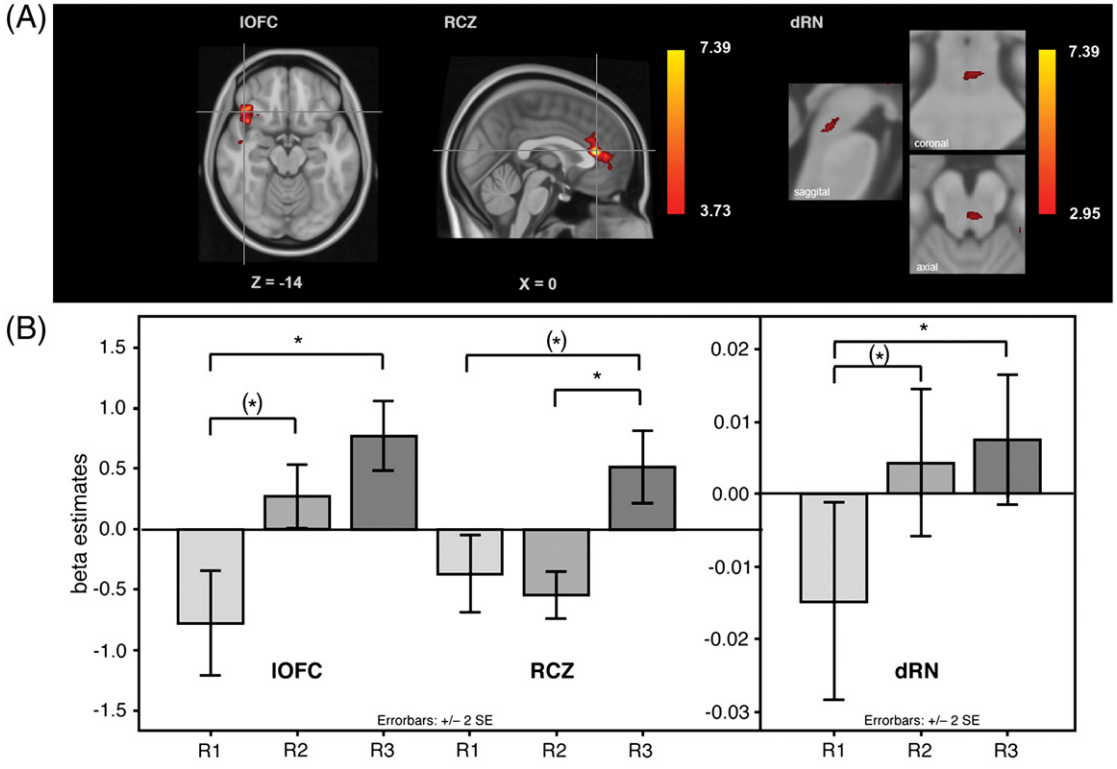

Fig. 2 – PPI results. A, Brain structures significantly changing co-activity with NAcc as an inverse function of reward magnitude (voxel height threshold: $p<0.001$, voxel extent threshold, $p<0.05$ family-wise error (FWE) corrected, lOFC, lateral orbitofrontal cortex, RCZ, rostral cingulate zone, dRN, dorsal raphe nucleus (cluster extent threshold >10 voxel)). B, Mean beta estimates of the NAcc ROI–PPI regressors. Positive values indicate positively correlating co-activity, whereas negative values indicate negatively correlating co-activity. Asterisks indicate significant differences *($p<0.05$, one-sided, corrected for multiple comparisons). A trend for a significant difference is indicated by asterisks within parenthesis (*) ($p<0.05$, one sided, uncorrected for multiple comparisons).

between R_1 and R_2 ($t\ (df=61)=1.9962$, $p<0.051$) and R_1 and R_3 ($t\ (df=61)=3.038$, $p<0.004$). Mean beta estimates of the RCZ cluster showed significant differences between conditions R_1 and R_3 ($t\ (df=61)=2.184$, $p<0.033$) and R_2 and R_3 ($t\ (df=61)=3.401$, $p<0.002$) (Fig. 2).

3. Discussion

The goal of this study was to examine whether BOLD-responses in the ventral striatum might be mainly driven by RPE-related neuronal activity in the dopaminergic midbrain or neuronal activity, related to absolute magnitude coding. We used individual ratings of rewards and associated these to Nucleus Accumbens (NAcc) activity to assure that rewards truly differ in the subjectively perceived magnitude. Our analysis focused on the NAcc, since this part of the ventral striatum was most consistently activated across experimental conditions. Furthermore, we employed a NAcc probability map, in order to circumvent the problem of non-independence between analysis levels.

Amplitudes of BOLD-responses in the NAcc reflected the expected reward magnitude while subjects were anticipating rewards. This is in line with previous studies, indicating magnitude dependent reward prediction error signals in the dopaminergic midbrain (e.g. Tobler et al., 2005) and ventral striatum (e.g. Delgado et al., 2003; Knutson et al., 2001). The same area exhibited BOLD-responses during reward delivery and was unaffected by reward magnitude; thus, supporting the previously reported effect of reward prediction error "gain adaptation" (Bunzeck et al., 2010; Tobler et al., 2005). We further identified significant negative deviations in BOLD-responses in the NAcc after the omission of rewards. Interestingly, this decrease in BOLD-responses was found to be magnitude-dependent. This finding argues in favor of reward magnitude coding at an absolute scale for the case of reward omission. A psychophysiological interaction analysis implies that the differences in BOLD-responses, related to the magnitude of omissions are predominantly driven by other structures than the dopaminergic midbrain.

3.1. *Reward anticipation*

During the anticipation phase, there was a clear difference in hemodynamic responses in trials in which rewards could be anticipated compared with control trials without reward. Furthermore, at the peak of the signal change curve (12.5 s

after spinning wheel onset) significant differences were evident between large and intermediate reward magnitude and large and small reward magnitude, but not between intermediate and small reward magnitude. Thus, this finding of reward magnitude-dependent activity in the ventral striatum during anticipation is consistent with previous imaging studies (Breiter et al., 2001; Galvan et al., 2005; Knutson et al., 2001) reporting a general albeit not necessarily linear dependence of reward magnitude and ventral striatal activity. It is noteworthy that the observed effect of anticipatory reward magnitude coding may be conceptualized as a magnitude dependent reward prediction error signal. Since subjects did not know the exact moment of the beginning of a trial (random inter-trial-interval), the presentation of the reward-predicting cue reflects a prediction error, which is scaled to the magnitude of the probable forthcoming reward. The observed response pattern complies with reward prediction error-dependent dopaminergic midbrain-spiking patterns evidenced in non-human primates during the anticipation of different rewards (Bayer and Glimcher, 2005; Tobler et al., 2005). This suggests strong dopaminergic innervation of the ventral striatum.

A substantial difference between Tobler et al.'s (2005) study and our study was the longer delay between reward predicting stimulus and reward (11.5–16 s in our study compared to approximately 2 s in Tobler's study). We initially expected hemodynamic responses to the onset of the announcement of the reward. However, our analysis did not indicate significant responses to this reward-predicting stimulus. This lack of finding may be due to decreases in dopaminergic response in relation to expected longer delays of rewards as reported by Kobayashi and Schultz (2008). Nevertheless, as dopamine responses have been frequently observed to generalize to stimuli resembling reward predictors (Ljungberg et al., 1991; Schultz and Romo, 1990) the late peaking hemodynamic response in the ventral striatum could reflect a later reward-predicting cue. This cue might be the slowing of the wheel of fortune; it likely represents a more salient and temporally closer predictor for future reward. Future studies will be necessary to better understand the influence of different delays between cues and rewards on the signal time course of hemodynamic signals in the ventral striatum, as well as spike signaling of dopaminergic neurons.

3.2. *Outcome won*

The analysis of event-related FIR time-courses of rewarded outcome trials indicates a significant signal change in the NAcc with a BOLD-response characteristic that could possibly reflect activity in relation to the processing of positive RPEs. Unlike the reward magnitude-dependent responses in the ventral striatum during anticipation, the FIR time-courses did not differ between absolute reward magnitudes after rewarded outcomes. The fact that signal time courses gradually increased irrespective of reward magnitude lends support to the previously reported effect of "gain-adaptation" of RPEs (Bunzeck et al., 2010; Tobler et al., 2005). In these two studies, subjects (humans and non-human primates) were presented three cues predicting pairs of rewards of different magnitudes. They could nicely demonstrate that the pattern of prediction errors is adaptively scaled with respect to the possible alternatives. In other words, winning vs. not winning a reward always elicits the same neuronal response, independently of the absolute magnitude. In contrast, in our study, to play for a reward of specific magnitude always meant that this reward could be won or not won. Similarly as in the studies of Tobler et al. (2005) and Bunzeck et al. (2010) the range of outcomes was known. Thus, a positive RPE (e.g. winning) may normalize to the absolute difference between two outcomes (e.g. gain of a large reward vs. omission of a large reward), thereby resulting in a magnitude-indifferent increase in hemodynamic response. However, deducing this interpretation from the non-finding of differences is obviously problematic from a statistical point of view.

Regarding previous research, a number of studies did find reward magnitude dependent hemodynamic responses in the ventral striatum (Rolls et al., 2008; Yacubian et al., 2006). Other studies showed magnitude *in*dependent differences between favorable and unfavorable outcomes (e.g. Bunzeck et al., 2010; Delgado et al., 2003; Elliott et al., 2003). The discrepancy between the results might be explained by differences in the experimental tasks. For instance, in the study of Rolls et al. (2008) and Yacubian et al. (2006) subjects could choose between alternatives with different reward magnitudes in combination with different reward probabilities. The outcome was always probabilistic and hence the needed knowledge about alternative outcomes for reward prediction gain adaptation was possibly not met. In contrast, in the studies of Delgado et al. (2003), Elliott et al. (2003) and Bunzeck et al. (2010) only two known alternative outcomes per trial were possible, thus RPE–gain adaptation was possibly feasible. In addition, lending further support to our interpretation, there exists a general agreement that the human reward system largely encodes reward values in relation to possible outcomes and not on an absolute scale (De Martino et al., 2009; Elliott et al., 2008; Fujiwara et al., 2009; Nieuwenhuis et al., 2005).

3.3. *Outcome not won*

Our findings reveal that hemodynamic responses upon reward omission gradually decrease in relation to the reward magnitude. This is in contrast to the hypothesis of gain-adaptation, which also applies to negative prediction errors, as shown in midbrain dopamergic firing rates which were also scaled to the difference between alternative outcomes and thus did not differentiate between the absolute magnitudes of outcomes (Tobler et al., 2005). In light of this and the finding of magnitude independent BOLD-responses after gaining rewards, our result of a reward magnitude-dependent decrease in BOLD-response was surprising. However, alternatively to spike-frequency reward prediction error magnitude coding in the dopaminergic midbrain, which is anyway limited in the case of spiking depression in response to negative prediction errors, RPE-magnitude-dependent graded responses in dopaminergic midbrain neurons have been reported in terms of the *duration* of the below base-rate spiking depression (Bayer et al., 2007). This may have affected BOLD-responses in synaptic target regions, such as, the NAcc. However, it is not yet clear how longer suppression influences the amplitude of negative hemodynamic responses.

Compared to the hemodynamic response after won outcomes the negative BOLD-response peaked 2.5–5 s later. The physiological meaning of the latency of BOLD-responses is only scarcely investigated but it has been conjectured that prolonged neuronal activity would produce both larger and relatively delayed peaking of the BOLD-response (Henson et al., 2002). Adopting this idea to later peaking *negative* BOLD-responses could indicate that reward omissions elicit longer deactivations in the ventral striatum after reward omissions, compared to activation due to gains. However, to our knowledge, latency effects of negative hemodynamic responses have not yet been investigated and it is therefore impossible to draw conclusions on this difference.

Rather than the dopaminergic system, it may be the serotonergic system (e.g., the dorsal raphe nucleus (dRN)) that sends strong projections to the ventral striatum (Azmitia and Segal, 1978) and influences the encoding of negative RPE; thereby, affecting the graded decrease in hemodynamic signal in the NAcc. However, evidence that phasic serotonergic signaling drives negative RPEs has only been deduced from computational models (Daw et al., 2002) so far and has yet to be proven physiologically.

3.4. *Psychophysiological interaction analysis (PPI)*

In order to explore which structures modulate the graded negative responses in the NAcc, we performed a psychophysiological interaction analysis (PPI) isolating those structures that change their functional connectivity to the NAcc as an inverse function of reward magnitude in reward omission trials. The analysis revealed, that activity in the brainstem, possibly the dorsal raphe nucleus (dRN), rostral cingulate zone (RCZ), and in the right lateral orbitofrontal cortex (OFC) covaries with neural activity in the NAcc as the magnitude of the omitted reward increases.

Experiments conducted with monkeys have suggested a strong interaction between the dopaminergic and serotonergic system. For example, it has been shown that the serotonin system, which originates in the dRN, inhibits dopaminergic function in the midbrain (Dray and Straughan, 1976; Trent and Tepper, 1991), as well as at the terminal dopaminergic fields, namely, the NAcc and striatum (Kapur and Remington, 1996). Further evidence for a mechanism, which subserves serotonin's inhibitory effect on dopamine, comes from an electrophysiological study by Jones and Kauer (1999), demonstrating that the excitatory glutamatergic synaptic transmission onto VTA neurons is depressed through the activation of serotonin receptors. This is in contrast to the interaction between dRN activity and dopamine, and suggests their involvement in the processing of negative prediction errors. Recent studies have revealed that dRN neurons respond to expected and received rewards (Lanzenberger et al., 2009; Nakamura et al., 2008), as well as to the evaluation of delayed rewards (Tanaka et al., 2004). In view of this, we can only conjecture that the dRN "down-regulates" (probably through serotonergic input) activity in the NAcc, which may account for the graded decreases in hemodynamic responses.

An important role in monitoring the rewarding features of stimuli is attributed to the OFC because of its extensive multisensory connections (Padoa-Schioppa and Assad, 2006; Walton et al., 2004). More specifically, the lateral OFC receives input from visual areas (Ongur and Price, 2000), and it is active during evaluation of punishing stimuli (Kringelbach and Rolls, 2004; Seymour et al., 2005). Prominent projections from the lateral OFC to the NAcc (Haber et al., 1995) provide further support for the concept of a modulating impact produced by the lateral OFC on the NAcc. We suggest that after receiving sensory information about a punishing event, the lateral OFC evaluates this information in terms of its rewarding value and subsequently down-regulates activity in the NAcc and dopaminergic midbrain structures.

The RCZ is often co-active with the lateral OFC during evaluation of negatively valued events (Kringelbach, 2005). As shown in non-human primates, these two structures maintain strong anatomical interconnections (Ongur and Price, 2000), suggesting that they operate as a linked pair (Kringelbach and Rolls, 2003). The RCZ also receives projections from limbic structures, such as, the ventral striatum (Kunishio and Haber, 1994) and amygdala (Barbas and De Olmos, 1990); it generally represents a main target area of the mesocortical dopamine system, which originates in the ventral tegmental area (Gaspar et al., 1989). It has been previously suggested that pyramidal cells in the RCZ are disinhibited by phasic decreases of mesencephalic dopaminergic inputs, which result in error related negativity (ERN), that is a negative deflection in the ongoing electroencephalogram (EEG) emerging when humans evaluate events, which are inconsistent with their expectations (Holroyd and Coles, 2002). In line with this theory, Münte et al. (2007) conducted a study employing simultaneous intraoperative recordings and EEG in an awake human patient. These researchers found decreases in the local field potential within the NAcc, which were highly correlated to the ERN signal in the EEG recordings. Furthermore, they showed that the error-related activity in the NAcc precedes the ERN by 40 ms; thus, suggesting a directional influence of the NAcc to the RCZ. In our experiment, if a highly preferred reward was not obtained, then it represented a more relevant violation of what had been expected, in contrast with the omission of a less preferred reward. Neurons in the RCZ may process this violation and trigger the subsequent (re)formation of future expectations, this resulting in an outcome-based optimization of forthcoming behavior. In our study, the participants had no means of influencing the outcome of the wheel of fortune game; therefore, they were unable to optimize future behavior. Nevertheless, this basal learning mechanism may be triggered irrespective of whether future behavior can be optimized on the basis of outcome.

In conclusion, ventral striatal BOLD-responses during anticipation and after gain of different rewards exhibit response patterns of RPEs as shown before (Bunzeck et al., 2010; Delgado et al., 2003; Tobler et al., 2005). Thus, in these phases, the BOLD signal in the ventral striatum likely reflects predominantly innervation of activity of the dopaminergic midbrain. In contrast to dopaminergic midbrain responses to the omission of rewards, hemodynamic responses were scaled to the absolute reward magnitude, suggesting that activity in the NAcc may be modulated through inputs of other than dopaminergic midbrain neurons. The PPI analysis used in our study has revealed that activity in the dRN, lateral OFC, and RCZ was negatively related to BOLD-deactivations in the NAcc in association with the omission of rewards of different magnitudes. We suggest

that the dRN and lateral OFC have a graded inhibitory effect on NAcc after reward omission whereas RCZ is disinhibited by the deactivation of neural activity in the NAcc. Intracranial recordings could possibly yield evidence for this proposal.

4. Experimental procedures

4.1. Participants

Sixteen healthy adult voluntary participants (9 female and 7 male, mean age of 24±4) were recruited from the University of Zurich and ETH Zurich, Switzerland. In contrast to previous studies, we manipulated reward magnitude on a subjective, individual scale; this required the selection of participants based on specific criteria. In our previous studies (Koeneke et al., 2008), we were able to show (1) that – within a certain product category, e.g., chocolate bars or sneakers – different brands can be arranged in a preference hierarchy for each individual and (2) that this individual brand preference hierarchy is reflected in the pattern of brain activity during a gambling paradigm. Neural structures whose activity was modulated by individual brand preferences were similar to structures identified in previous studies that manipulated the reward according to an objectively quantifiable scale, for example, monetary rewards. The aspect of modulating reward values through brand preferences will be published elsewhere.

Similar to our previous work, we used different product brands to represent various reward magnitudes in the present study. Determining the individual brand hierarchies required a detailed assessment of brand preferences embedded in a two-stage selection procedure. During the first stage, a paper and pencil questionnaire was distributed to students in different courses of the Psychology Department of the University of Zurich. Two-hundred students completed the questionnaire, from which 50 respondents indicated that they (a) wore sneakers at least from time to time, (b) cared about sneakers, (c) cared about brands when it came to sneakers, and (d) expressed differentiated brand preferences in a constant sum point allocation "chip game" between different sneaker brands. These 50 respondents were invited to the second round. Twenty-seven of the pre-selected participants accepted the invitation and filled out a second, computer-based questionnaire that aimed to measure individual brand preferences in more detail with a choice-based procedure (the GfK Price Challenger, GPC, Wildner, 2003), and another constant sum chip game. Of those, 18 respondents were invited to our fMRI study. These participants expressed preferences that were consistent across the two measures and widely dispersed, in order to allow for clear brand differentiation. Two participants dropped out due to personal reasons. Based on the preference data gathered in the second stage of the selection procedure, three sneaker brands were determined for each subject: (1) her/his favorite brand (high reward: R_1), (2) her/his least preferred yet still acceptable brand (low reward: R_3), as well as (3) one intermediate brand (intermediate reward: R_2) that ranked between the top and the bottom brand. Hence, reward magnitude in the present study had three parameter values.

The local ethics committee approved our study and the research participants gave written informed consent. The tasks and testing procedures were in accordance with institutional guidelines and the study conformed to the Declaration of Helsinki. Participation was compensated with 50.00 CHF, and if during the experiment a pair of sneakers was won, then research participants received a voucher worth 150 CHF.

4.2. Design and procedure

Participants played a virtual wheel-of-fortune game projected onto a translucent screen that could be viewed inside the scanner via a mirror. The experiment consisted of four runs with 25 trials each. Individual T1-weighted anatomic brain images were recorded after the actual experimental sessions. The total scanning time was approximately 50 min. Before being scanned, participants were briefly informed about MRI/fMRI methodology; then each participant was instructed to (1) complete a questionnaire that tested for individual MR-suitability and (2) to give his/her informed consent. Next, participants were requested to read a short instruction manual, which explained the procedures of the experiment. Participants then completed two test trials of the wheel-of-fortune game outside the scanner, in order to assure that they had understood the task correctly. The overall prize that could be won in our experiment was a voucher (worth 150 CHF) for a particular brand of sneakers. The subjects played for this voucher in a lottery, which took place after the scanning session. During the scanning session, the subjects were able to win lottery tickets that increased their chances of winning in the subsequent lottery. In other words, a won trial in the wheel-of-fortune game increased the probability of winning the voucher for a certain brand of sneakers.

In each wheel-of-fortune trial, one out of 25 lottery tickets per brands could be won (i.e., 75 lottery tickets in total). Trials were brand-specific, meaning that a won trial increased the chances of winning a voucher for one specific brand (R_1, R_2 or R_3), which was announced at the beginning of the trial. During the scanning session, the number of won lottery tickets for each brand was displayed. After the scanning session, the subjects were presented with three pots (one for each brand) that each contained 25 lottery tickets, with one lottery ticket being the joker. The subjects then drew the amount of won lottery tickets separately for each brand. If the joker was drawn, participants received the voucher for the particular brand. If more than one voucher was won, they could freely choose one to take home. The chance to win was pseudo-randomly varied at a chance of 50%. Thus, participants had the cumulative chance to win one of the three vouchers of 87.5%. The sequence of the brands the participants played for were pseudo-randomly distributed, to ensure enough trials of every possible combination (brand, outcome) for the analysis. In addition, 25 trials in which no lottery tickets could be won were randomly interspersed in the experiment, in order to detect brain areas responding to the wheel-of-fortune game itself; this resulted in a total of 100 trials.

A trial consisted of a brand announcement phase (0.5–2 s), a response phase (choice between green and red; 1–2 s), a prospect phase (wheel of fortune spins; 10–12 s), an outcome phase (outcome is presented; 3 s), a blank screen with a fixation cross (4–5 s), a picture of the actual balance (2 s), and a blank screen with a fixation cross (6 s) (Fig. 3). During the announcement phase, the logo of the brand that subjects were playing for in the current trial was presented in the center of a wheel-of-fortune

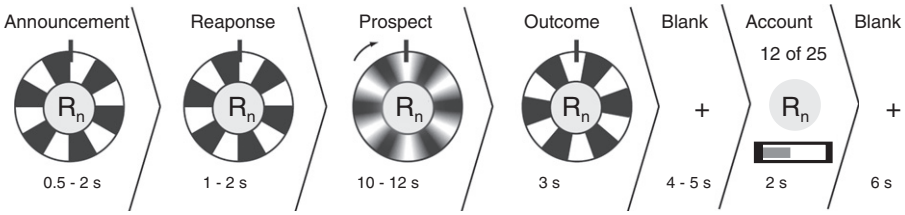

Fig. 3 – Experimental design of the wheel-of-fortune game.

that consisted of twelve colored (6 green and 6 red) fields. During the response phase, participants could choose one color by pressing a button. The button-to-color assignment was kept constant across the trials. The chosen color field remained visible underneath the wheel while the other color field disappeared so that participants did not have to memorize their choice. The anticipation phase started with the wheel-of-fortune rotating and slowing down to a halt after 10–12 s. The wheel-of-fortune slowed down asymptotically, to simulate a realistic roulette-like game. The ensuing outcome-phase started after the wheel had stopped. The outcome achieved was indicated by a field that came to a halt under a pin at the top of the wheel, as well as by a text box (i.e., "You have won 1 lot/ You have not won"). During the outcome-phase the logo at stake was still visible. A trial was won when the color chosen by the subject was consistent with the color of the field that came to a halt under the pin. To avoid participants memorizing account balances, the balance of the number of lottery tickets for the respective brand, which had been acquired thus far, was indicated in each trial. This number was also translated into the probability of winning a voucher and was represented as a bar chart. A blank screen with a fixation cross was presented for 6 s before the next trial started, in order to ensure that the fMRI signal could level back to a task-unspecific baseline.

4.3. *fMRI acquisition*

A Philips Intera 3T whole-body MR unit (Philips Medical Systems, Best, The Netherlands), equipped with an eight-channel Philips SENSE head coil was used, to acquire magnetic resonance images. Anatomical images of the whole brain were obtained by using a T1-weighted three-dimensional, spoiled, gradient echo pulse sequence (repetition time (TR)=20 ms, echo time (TE)=2.30 ms, flip angle 20°, field of view (FOV)=220 mm, acquisition matrix=224×224, voxel size=1 mm×1 mm 0.75 mm, 180 slices, slice thickness=0.75 mm). Functional data for the behavioral tasks were obtained from 280 whole-head scans per run using a Sensitivity Encoded (SENSE) (Pruessmann et al., 1999) single-shot echoplanar imaging technique (TR=2500 ms, TE=35 ms, flip angle=78°, FOV=220 mm, acquisition matrix=80×80, 33 transverse slices, voxel size=1.72 mm×1.72 mm×4 mm).

4.4. *Data analysis*

4.4.1. *Preprocessing*

Artifact elimination and MRI data analysis were performed using MATLAB 2006b (Mathworks Inc., Natick, Massachusetts, USA), and the SPM5 software package (Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm/software/spm5). The first three images were discarded, to allow for steady-state magnetization. All images were realigned to the first image of the first run, slice time corrected and spatially normalized into standard stereotactic MNI space (EPI template provided by the Montreal Neurological Institute), interpolated to a voxel size of 2×2×2 mm and spatially smoothed using a 8-mm full-with-at-half-maximum Gaussian kernel.

4.4.2. *Voxel-wise analysis*

Whole brain analysis was performed using a general linear model as implemented in SPM5. The design matrix included regressors modeling the onsets and durations of the announcement phase, response phase, anticipation phase, the two possible types of outcome (won/ not won) and the actual balance. Separate regressors were introduced for each preference level and the non-rewarding condition in the announcement phase, the anticipation phase, and the two outcome phases. The announcement, response and anticipation phases, as well as the blank screen between the outcome and balance varied in duration. Also, the time lag between motor response that occurred when choosing a color and at the onset of the anticipation phase (the start of the spinning of the wheel-of-fortune) was temporally jittered. This was implemented, since our aim was to temporally de-correlate two ensuing regressors and avoid inflation of variance; thereby, increasing model-sensitivity. The resulting regressors were convolved with SPM's canonical difference of gamma hemodynamic response function. After high-pass filtering (cut-off of 128 s), an individual statistical model was computed for each participant.

The goal of the whole-brain analysis was to assure significant activity in the ventral striatum, in order to further analyze region-specific hemodynamic signal time courses. Thus, contrasts were calculated for the announcement, the anticipation phases, between R_1, R_2, R_3 and the non-rewarding (R_n) trials, for the two outcomes (won/not won) R_1, R_2, R_3 and the non-rewarding trials (R_n) (Table 1). To allow for a population level inference, the maps of contrast coefficients, which were controlled for random effects, were collectively submitted to one-sample t-tests against the null hypothesis of no activation.

4.4.3. *Regions of interest analysis*

Region of interest (ROI) analyses were performed using MARSBAR, the ROI toolbox for SPM; version 0.41 (http://marsbar.sourceforge.net/), and SPSS (Rel. 16.0, SPSS). Since the NAcc (bilaterally) was found to be consistently activated

within the ventral striatum, we chose the bilateral NAcc of the Harvard–Oxford subcortical probabilistic atlas, provided by the FSL Software Library (Analysis Group, FMRIB, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html). We made this choice, instead of defining our ROI from activation patterns, because the former involves a risk that may have resulted in non-independence between test hierarchies. A finite impulse response (FIR) model was employed since we intended to extract event-related time courses of each experimental condition (10 time bins of 2.5 s); thereby, calculating the best estimate of the fMRI signal for each scan after adjusting for other effects of the model.

The analysis targeted preference-dependent FIR signal time courses of the anticipation phase (A), the outcome phase of won trials (OW), and the outcome phase of not won trials (OnW). The resulting FIR-time courses, which were time-locked to the onsets of the three phases were analyzed by using a repeated-measures ANOVA ($p<0.05$) with the within-subject factors: preference-level ($n=3$) and epoch ($n=10$). If one single FIR value was above or below 3 * interquartile range, then FIR signal time courses of those subjects were excluded from the analysis. Average signal changes were compared across condition types at the time of positive or negative peaks (depending on the overall time-course) by using paired t-tests. Unless otherwise indicated, significance thresholds were set at $p<0.05$ and Bonferroni-corrected for the number of paired t-tests.

4.4.4. *Psychophysiological interaction analysis (PPI)*

A psychophysiological interaction means that the connectivity of one area to another changes significantly in relation to an experimental variable (Friston et al., 1997). However, it should be kept in mind that PPI analyses do not inform us about causality. In our study, we aimed to reveal which neural structures may have influenced reward-magnitude-specific decreases in neural activity in the NAcc during the outcome phase of not won trials (OnW); subsequently, suggesting the role of inhibitory interactions. In order to accomplish this goal, individual time series were extracted from the bilateral NAcc ROI (which we also used for the standard ROI analyses) by using the first eigentimeseries (principal component). The PPI is defined as the interaction between the NAcc time series and the preference levels introduced as a first order parametric modulation in not won trials. To test for group effects, single-subject first-order parametric modulatory contrasts were subjected to a one-way ANOVA. If clusters demonstrated significant connectivity ($p<0.001$, voxel extent threshold, $p<0.05$ family-wise-error (FWE) corrected), then mean beta weights of the clusters of the three different preference levels were extracted and further compared with paired t-tests. Because the dorsal raphe nucleus (dRN) has been previously suggested to influence the negative prediction error signal in the ventral striatum, the cluster extent threshold was lowered to a cluster size of 10 voxels for the brainstem region surrounding the dRN.

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