Attentional Modulation of Reward Processing in the Human Brain

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Abstract: Although neural signals of reward anticipation have been studied extensively, the functional relationship between reward and attention has remained unclear: Neural signals implicated in reward processing could either reflect attentional biases towards motivationally salient stimuli, or proceed independently of attentional processes. Here, we sought to disentangle reward and attention-related neural processes by independently modulating reward value and attentional task demands in a functional magnetic resonance imaging study in healthy human participants. During presentation of a visual reward cue that indicated whether monetary reward could be obtained in a subsequent reaction time task, participants either attended to the reward cue or performed an unrelated attention-demanding task at two different levels of difficulty. In ventral striatum and ventral tegmental area, neural responses were modulated by reward anticipation irrespective of attentional demands, thus indicating attention-independent processing of reward cues. By contrast, additive effects of reward and attention were observed in visual cortex. Critically, reward-related activations in right anterior insula strongly depended on attention to the reward cue. Dynamic causal modelling revealed that the attentional modulation of reward processing in insular cortex was mediated by enhanced effective connectivity from ventral striatum to anterior insula. Our results provide evidence for distinct functional roles of the brain regions involved in the processing of reward-indicating information: While subcortical structures signal the motivational salience of reward cues even when attention is fully engaged elsewhere, reward-related responses in anterior insula depend on available attentional resources, likely reflecting the conscious evaluation of sensory information with respect to motivational value. *Hum Brain Mapp* 35:3036–3051, 2014. © 2013 Wiley Periodicals, Inc.

Key words: ventral striatum; anterior insula; fMRI; reinforcement; attention; visual cortex
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INTRODUCTION

The ability to detect potential rewards in the environment is a vital function for any organism. Individuals must be capable of discerning reward-indicating stimuli in the environment in order to prepare appropriate behavioral responses. As motor actions may have to be generated quickly or with high precision in order to actually obtain a reward, it is particularly important to anticipate potential rewards. Thus, the brain's processing resources have to be utilized in an efficient way to achieve the best possible outcome. Previous research has identified a widely distributed set of brain regions involved in the processing of reward-indicating information, including ventral striatum [VS; particularly the nucleus accumbens, which forms the medial portion of VS (Schultz et al., 1992)], medial prefrontal cortex (mPFC), anterior insula (aINS), and anterior cingulate cortex (ACC) [e.g., Bjork and Hummer, 2007; Ernst et al., 2004; Knutson et al., 2000, 2001a,b, 2003, 2005; Rademacher et al., 2010; Schultz et al., 1998; Smith et al., 2009; Yacubian et al., 2006]. Moreover, reward anticipation also modulates neural responses in sensory cortical areas [Apitz and Bunzeck, 2012; Doñamayor et al., 2012; Pessoa and Engelmann, 2010; Shuler and Bear, 2006; Tallon-Baudry et al., 2011; Weil et al., 2010].

While it is thus well established that the anticipation of rewards involves a large network of brain regions, less is known about the distinct roles of these regions in reward anticipation. Most notably, it is difficult to distinguish reward-related neural signals from those related to attentional processes [Maunsell, 2004]. Reward-indicating sensory information is motivationally salient and it has been demonstrated repeatedly that attention is allocated preferentially towards stimuli with high motivational salience [Della Libera and Chelazzi, 2006; Engelmann and Pessoa, 2007; Engelmann et al., 2009; Mohanty et al., 2008; Small et al., 2005]. Previously, it has been shown that even subliminally presented reward cues can elicit reward-related activity in VS [Pessiglione et al., 2007, 2008]. This, however, does not rule out the possibility that reward signals are mediated by attentional processes, since attentional biases towards motivationally relevant stimuli can also proceed in the absence of awareness [Jiang et al., 2006]. Furthermore, attention and awareness rely on distinct neural processes [Lamme, 2003; Wyart and Tallon-Baudry, 2008]. Thus, the exact role of attention in the anticipation of reward has remained elusive: Is attention to reward cues an essential component of reward anticipation? Or does reward anticipation proceed in an automatic fashion, that is, independent of the deployment of attention to the reward cue?

In the present functional magnetic resonance imaging (fMRI) study, we sought to disentangle potential automatic processes from attention-dependent processes in the anticipation of reward by manipulating reward value and attention independently of each other. During the anticipation

phase of a monetary incentive delay task [Knutson et al., 2000], participants' degree of attentional resources available for the reward cue was modulated by an additional task, similar to attentional manipulations applied in previous studies [Pessoa et al., 2002, 2005]. Brain regions engaged in attention-independent processing of reward information should show enhanced responses to reward-indicating vs. neutral cues irrespective of whether the reward cue is attended. Conversely, attention-dependent processing of reward would be demonstrated if neural responses to reward-indicating vs. neutral cues were modulated by attentional task demands. Beyond the perspective of regional brain activations, interactions between attention and reward anticipation could arise from influences that nodes of a neural network exert over each other. We thus performed dynamic models of effective connectivity to examine whether the impact of brain regions involved in attention-independent processing of reward cues on regions showing attention-dependent reward processing is modulated by available attentional resources.

MATERIALS AND METHODS

Participants

Twenty-eight participants volunteered for the study. Three participants had to be discarded from all analyses. One participant was excluded due to incomplete data collection. Two participants were excluded due to excessive head motion during fMRI, exceeding an a priori defined motion threshold of 3 mm within one run. The final sample consisted of 25 participants (18 females) with a mean age of 24 years (S.E.M.: 0.74 years). All participants had normal or corrected-to-normal vision. They were paid on the basis of their winnings during the experiment ($M = 25.95 \text{ €} \pm 0.41 \text{ S.E.M.}$). Written informed consent was obtained from all participants before the experiment. The study was approved by the local Ethics committee.

Procedure

Participants performed a modified version of the monetary incentive delay (MID) task [Knutson et al., 2000]. In a standard MID task, participants are provided with a visual cue informing them about the valence and the magnitude of an upcoming potential outcome. After a variable delay a target appears requiring participants to respond as fast as possible by button press in order to obtain a reward or to avoid punishment. Task difficulty, that is, participants' required reaction time, is individually titrated to each participant's performance, so that they succeed on 66% of all trials approximately. A trial sequence of the modified MID task used in our study is depicted in Figure 1. We used two different female faces taken from a standardized set of human faces [Ekman and Friesen, 1976] as reward cues to specifically investigate neural responses in high-level

Figure 1.

Trial sequence of the experimental task design. At the beginning of each trial, participants were provided with a verbal instruction for 1 s indicating the task for the current trial (face task, bar color task, or bar orientation task). After a variable delay of 2–5 s, a face was presented in the center of the screen along with two peripheral colored bars for 150 ms. The face served as a cue signaling whether participants could obtain a reward in the current trial or not. After another variable delay of 2–5 s, participants were required to give their response within 1.5 s to the task according to the instruction at the beginning of the trial. Another delay of 2.125–5 s followed. Next, the target appeared, which required participants to respond as fast as possible in order to receive the reward. Target duration was individually adapted to participants' performance so that they would succeed in 66% of the trials. Finally, feedback was provided for 1 s. An inter trial interval with 2–5 s duration followed before the start of the next trial.

face-responsive visual cortex. While one face signaled a potential reward, the other face indicated a neutral trial, in which no reward could be obtained. The association of each face to its respective reward condition was counter-balanced across participants. Simultaneously to the faces, two colored bars were presented, one in the left half and one in the right half of the screen (eccentricity: 4.5° of visual angle).

At the beginning of each trial, an instruction prompt presented for 1 s indicated the task for the upcoming cue

phase. Participants either had to indicate whether the face was associated with an upcoming reward or not (instruction: “face”); or to perform a simple or difficult task on the colored bars. The intention of these tasks was to manipulate the degree of attention available for the processing of the reward cue. Such task manipulations have previously been proved to be effective in modulating attentional resources available for the processing of visual stimuli [Pessoa et al., 2002, 2005]. The simple bar task was to indicate whether the bars had the same color (instruction: “color”). For the difficult task, participants had to indicate whether the two bars had the same spatial orientation (instruction: “orientation”). Orientation differences were individually adjusted to each participant's performance in order to keep task difficulty comparable across participants. To this end, if participants achieved accuracy levels of above 85% or below 65% in a particular run, the difference in spatial orientation of the two bars was reduced or increased by three degrees, respectively, for the subsequent run. The face stimulus and the surrounding bar stimuli were shown for a short period of 150 ms to prevent eye movements towards the peripheral bars. Additionally, we recorded eye movements to rule out that varying levels of attention were confounded with systematic eye movements (see section “Eyetracking data acquisition and analysis”). After the cue phase, a “Wait!” prompt appeared for a variable interval of 2–5 s, which was intended to prevent immediate manual responses, in order to disentangle neural signals related to the reward cue from button presses. Subsequently, a question related to the task instruction at the beginning of the trial (e.g., “Color: Same or different?”) was displayed for 1.5 s and indicated the period, during which participants were requested to give their response. After another variable delay of 2.125–5 s, a white square was shown as the target stimulus, to which participants had to respond as fast as possible by button press. The duration of the target was constantly adapted throughout the experiment so that participants succeeded in 66% of the reward trials. Lower or higher performance rates led to an increase or decrease, respectively, of the target duration by one frame (i.e., 33 ms) in the subsequent trial. Across task conditions, one algorithm was used for the adaptation of target duration in the reward trials. For neutral trials, target duration was the same as in the preceding reward trial. At the end of each trial, feedback was given for 1 s about the monetary outcome of the trial. An inter trial interval (ITI) with a duration of 2–5 s followed before the start of the next trial. For successful reward trials, participants received 75¢. To render the face and bar tasks sufficiently relevant to effectively guide participants' attention, participants were informed that they would receive only that proportion of their monetary outcome that corresponded to their overall performance in all three attention tasks. Participants' potential and actual winnings were displayed after each run.

Participants first performed a practice session consisting of 48 trials inside the scanner but without fMRI acquisition. From this session, performance parameters regarding

the difficulty of the bar orientation task and target duration were derived. Subsequently, five runs with 24 trials each were conducted while participants underwent fMRI. The order of attention and reward conditions was counter-balanced and randomized across trials for each participant. The main session lasted for about 40 min.

fMRI Acquisition

Functional and anatomical images were acquired on a Siemens 3T TRIO system (Erlangen, Germany) equipped with a 12-channel head coil. Functional scans were acquired using a T2*-weighted echo-planar sequence (TR: 2.26 s, TE: 25 ms, flip angle: 90°). Images were collected from 38 contiguous slices covering the entire brain (voxel size: 3 × 3 × 3 mm³). Slices were oriented parallel to the intercommisural line (AC-PC line). In the main experiment 200 volumes were acquired per run. After the experimental runs, a high-resolution T1-weighted structural image (MPRAGE, voxel size: 1 × 1 × 1 mm³) was acquired.

fMRI Data Analysis

fMRI preprocessing

fMRI data were analyzed with SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/>) for Matlab (The MathWorks Inc.). fMRI preprocessing included slice time correction, realignment to the mean volume, coregistration to the first functional image, segmentation, spatial normalization to standard MNI space, and smoothing using an 8 mm full-width-half-maximum (FWHM) kernel. For each run, the first 4 images were discarded to allow for T1-equilibration effects.

fMRI statistical analysis

fMRI-data were analyzed in a two-level procedure. At the first level, a general linear model (GLM) was estimated for each participant individually. At the second level, parameter estimates resulting from first-level analyses were subjected to random-effects analysis across the whole group. At the first level, we pursued a parametric approach modeling the different attention tasks during the cue phase as a variation on one dimension [Büchel et al., 1998; Wood et al., 2008]. The rationale behind this approach was that available attentional resources for the processing of the reward cue are maximal during the face task and minimal during the bar orientation task. In comparison, in the bar color task an intermediate level of attentional resources is available for the reward cue, since spatial attention is drawn away from the cue that can—due to the low difficulty of the task—still be processed to some degree [Lavie, 1995]. As a consequence, we modeled a linear relation between the three levels of attention available for the processing of the reward cue and the respective attention task conditions. Additionally, we followed an ANOVA approach treating the attention tasks as dis-

crete conditions. The statistical analysis and results of this approach are reported in the Supporting Information. For each of the two approaches, a GLM was first estimated for each participant. High-pass filters with a cutoff at 128 s were applied to correct for low-frequency fluctuations and temporal autocorrelations were removed by using autoregressive models of order one (AR(1)). Note that responses in fusiform gyrus (FFG) were analyzed on the basis of individually defined maxima (see section *Regions of interest* for further details).

First level GLMs and second-level analyses for the parametric approach

Within the individual GLMs, two regressors were defined, each modeling the onsets of reward-indicating and neutral cues, respectively. One parametric regressor for each reward condition was included to model varying levels of attentional task demands: (1) bar orientation task, (2) bar color task, and (3) face task. The numbers in brackets indicate the weights of the levels of attention within the parametric regressors. Variance resulting from instruction and feedback phase as well as motoric influences were partialled out by including the following regressors of no interest: (1) 3 regressors for the instruction phase (face task, bar color task, and bar orientation task), (2) 3 regressors for motor responses to the attention tasks, (3) 1 regressor for target presentation, (4) 9 regressors for feedback phase (i.e., 3 regressors for neutral condition, 3 regressors for successful reward, and 3 regressors for unsuccessful reward), (5) 6 realignment parameters. All regressors were modeled as stick functions convolved with the canonical hemodynamic response function. In order to disentangle attention-independent from attention-dependent reward processing, contrast maps were computed for the following regressors from the GLM containing parametric regressors: (1) reward condition, (2) neutral condition, (3) reward condition parametrically modulated by attention, (4) neutral condition parametrically modulated by attention. For second-level random-effects analyses, a flexible factorial analysis of variance was performed including the individual contrast maps. Main effect of reward processing was probed by applying a T-contrast to the first two regressors of the second-level model [1 -1 0 0]. For the assessment of parametrically modulated reward processing, a T-contrast was applied to the last two regressors [0 0 1 -1].

Parametric main effects of attention were probed by applying a T-contrast with a weight of 1 to all parametric regressors within the individual GLMs. For second-level analyses, the resulting contrast images were subjected to a one-sample *t*-test. A T-contrast with the weight of 1 was used to identify brain regions exhibiting increasing activation with decreasing attentional task demands (i.e., face task > bar color task > bar orientation task). Brain regions showing increasing activation with increasing attentional task demands (i.e., bar orientation task > bar color task > face task) were identified by a T-contrast with a weight of -1.

Regions of interest (ROIs)

Our analyses were focused on brain regions previously implicated in reward processing, namely VS, mPFC, aINS, and ACC. In order to examine neural responses in these a priori defined regions, we constructed binary masks based on reward-related activations in previous studies for VS [Carlson et al., 2011; Croxson et al., 2009; Guitart-Masip et al., 2012; Knutson et al., 2001a; Pedroni et al., 2011; Rolls et al., 2008; Sescousse et al., 2010; Wimmer et al., 2012; Wrase et al., 2007], mPFC [Ballard and Knutson, 2009; Carlson et al., 2011; Knutson et al., 2000, 2001b, 2003, 2005; Knutson and Wimmer, 2007; Mowrer et al., 2011; Pochon et al., 2002; Tobler et al., 2007; Ursu and Carter, 2005; Wu et al., 2011], aINS [Davey et al., 2010; Downar et al., 2003; Harrison et al., 2009; Jensen et al., 2007; Kim et al., 2011; Knutson et al., 2000, 2001b; O'Doherty et al., 2003; Prövest et al., 2010; Rolls et al., 2008; Shulman et al., 2003; Venkateraman et al., 2009; Wiech et al., 2010; Yacubian et al., 2006], and ACC [Basten et al., 2010; Croxson et al., 2009; Elliott et al., 2004; Kable and Glimcher, 2007; Knutson et al., 2001a, 2005; Marsh et al., 2007; Rogers et al., 2004; Sescousse et al., 2010]. To this end, all coordinates for a given region were pooled. The probability that a particular voxel lay within the respective area was estimated by calculating a 3D Gaussian distribution, the boundaries of which were defined by a threshold of two standard deviations [see Schubert et al., 2008, for a detailed description]. Univariate fMRI statistics were family-wise error (FWE) corrected for each respective ROI. The resulting p-values were corrected for the number of ROIs by applying Bonferroni correction.

We were further interested in the relation of attention- and reward-related signals in high-level visual cortex. As we used faces as reward cues, we focused on face-responsive voxels in fusiform gyrus (FFG), a brain region that is known to be selectively involved in face processing [Kanwisher et al., 1997]. For each participant, we individually identified voxels that were maximally sensitive to the presentation of faces in the cue phase across all conditions by setting contrast weights for all cue regressors to 1. As anatomical constraint, a binary mask of the fusiform gyrus, derived from WFU pickatlas (<http://fmri.wfubmc.edu/software/PickAtlas>), was used. Parameter estimates of all conditions were derived from the most anterior peak voxel within this mask for each hemisphere and analyzed by means of a $2 \times 2 \times 3$ repeated-measures ANOVA with factors hemisphere (left, right), motivation (reward, neutral), and task (face task, bar color task, bar orientation task). Note that due to spatial smoothing this voxel represents a weighted average of neighboring voxels.

Dynamic Causal Modeling (DCM)

Model construction

We used DCM as implemented in SPM8 to model effective connectivity between brain regions found in our univariate fMRI analysis. DCM provides a framework to infer

how experimental variables can impact on the coupling between brain regions [Friston et al., 2003]. Although a widely-used technique, the reliability of DCM has also been called into question regarding its physiological and mathematical foundations [Daunizeau et al., 2011]. Yet, there is empirical evidence that DCM is well suited to identify meaningful models of effective connectivity [David et al., 2008]. Within this framework, each model consists of context-independent intrinsic connections between different brain regions. Experimental manipulations are incorporated either as driving inputs (i.e., direct influences on single brain regions) or as modulatory inputs (i.e., context-dependent changes of intrinsic connectivity). Based on our univariate fMRI results (see Figs. 3 and 4), we constructed an initial model (M1) consisting of FFG, VS, and aINS as nodes. The generation of a model based on these three regions represents the most parsimonious approach in order to probe the influence of attentional modulation on reward-related brain areas. In accordance with anatomical evidence, bidirectional intrinsic connections were modeled between all three regions. In monkeys, it has been shown that several sites of the striatum receive fibers from visual areas in temporal cortex [Kemp and Powell, 1970; Saint-Cyr et al., 1990] and that visual cortical areas are target regions of the striatum [Middleton and Strick, 1996]. The anterior insular cortex projects to the ventral striatum [Chikama et al., 1997; Eblen and Graybiel, 1995; Fudge et al., 2005]. Conversely, projections to anterior insula also arise from ventral striatum [Dupont et al., 2003; Parent and Hazrati, 1995]. Finally, reciprocal connections have also been demonstrated between insula and visual cortex [Mesulam and Mufson, 1982]. Driving sensory input, that is, the onset of face stimuli in all conditions was directed to FFG. Further, we incorporated modulation of VS activity by reward into the model. Finally and critically, the main effect of attention modeled as a parametric regressor was used as modulatory input on the forward connection from VS to aINS. The initial model is depicted in Figure 6A. We then constructed alternative models (M2 - M12; see Figure 6C), in which the position of the modulatory input of attention to intrinsic connections was systematically varied. A constraint of this model space was that at least one of the intrinsic connections directed to aINS was modulated by attention. No attentional modulation was placed on the intrinsic connections between FFG and VS, as the effect of reward did not interact with attention in these two regions.

Time series extraction

In a first step, individual peak voxels were identified for time series extraction. For FFG, the same peak voxels were used that had been identified in the univariate SPM analysis. For VS and aINS, individual maxima were defined by the contrasts reward > neutral (VS) and reward modulated by attention > neutral modulated by attention (aINS). Each maximum was required to be within the probabilistic mask of the respective region that was also used for the

group analysis. In a second step, for all three regions (FFG, VS, and aINS) the first Eigenvariates were calculated across all voxels within a sphere of 5 mm around the individually defined maxima in the right hemisphere.

Model selection

To identify the best fitting model Bayesian model selection was performed as implemented in SPM8, using a second level random-effects approach. Bayesian model selection takes into account the fit and the complexity of each model. This procedure results in an exceedance probability for each model, which denotes the probability that a particular model is more likely than any other model [Stephan et al., 2009]. After identification of the model with the highest exceedance probability, parameter estimates of the respective model were tested using one sample *t*-tests with Bonferroni correction.

Analysis of Behavioral Data

We analyzed participants' accuracy in the attention tasks by means of a one-way repeated measures ANOVA. Due to a programming error, target reaction times were not properly recorded in eight participants. For the remaining participants reaction times were analyzed with a 2 × 3 repeated-measures ANOVA with factors motivation (reward, neutral) and task (face task, bar color task, bar orientation task).

Correlation Between Behavioral Data and fMRI Signals

In order to explore whether neural signals of attention-dependent reward processing are related to individual attentional demands elicited by our attention tasks, we probed a correlation between participants' performance in the attention tasks and neural responses in aINS, where an attentional modulation of the processing of reward-indicating cues was observed. We performed a regression of each participant's accuracy in the attention tasks against levels of attentional task demands analogously to our fMRI analysis (i.e. "3" for face task, "2" for bar color task, and "1" for bar orientation task). The resulting slopes were used as indices for individual attentional task demands. Greater slopes imply stronger performance drops for increasing levels of attention directed away from the reward cue. These regression slopes were correlated with parameters estimates derived from the group maximum in aINS where an effect of attentional modulation of reward processing was observed. Numerically greater fMRI parameter estimates imply a stronger attentional modulation of reward processing.

Eyetracking Data Acquisition and Analysis

Eyetracking data were collected by means of an fMRI-compatible infrared video eyetracker (iView XTM MRI, Sen-

soMotoric Instruments, Teltow, Germany). Prior to each run, participants performed a nine-point calibration. During each run, eye position data were recorded with an acquisition rate of 50 Hz and analyzed offline using Matlab (The MathWorks Inc.). In five participants eyetracking data could not be collected due to insufficient eyetracker calibration. For the remaining participants, eyetracking data were collapsed across runs. Artifacts, such as blinks, were removed and the data were mean-corrected. The following analyses are based on eyetracking data during time windows of 500 ms before cue onsets until 500 ms after cue onsets to be maximally sensitive to anticipatory as well as responsive eye movements. In order to determine whether participants kept fixating the screen centre during the cue phase throughout all tasks, gaze positions were plotted and visually inspected for each participant. We then examined possible differences in eye movements between attention conditions by collapsing horizontal gaze positions across all participants and plotting the distributions along the horizontal axis of the screen for each task separately with a bin size of 0.2 degree of visual angle. Two-sample Kolmogorov-Smirnov tests were used to compare the distributions of gaze positions between tasks.

RESULTS

Eyetracking

The distributions of gaze positions along the horizontal axis of the screen are plotted in Figure 2A for each task separately. Two-sample Kolmogorov-Smirnov tests revealed no differences between any of the distributions (all $P > 0.9$).

Behavioral Data

Anticipation phase

The proportion of correct manual responses for the attention tasks during the anticipation phase is depicted in Figure 2B. A one-way repeated-measures ANOVA yielded significant differences in performance between tasks ($F(2,48) = 11.26$, $P < 0.001$). Post-hoc paired sample *t*-tests with Bonferroni correction revealed that participants' performance was significantly reduced in the bar orientation task compared with the face task ($t(24) = 3.66$, $P = 0.004$) and to the bar color task ($t(24) = 4.25$, $P = 0.001$). There was no difference in accuracy between face task and bar color task ($t < 1$).

Target response

Participants were able to obtain a reward in $M = 65.6\%$ ($SEM = 0.7\%$) of all trials predicting a potential reward, indicating a successful adjustment of positive feedback rate to two thirds of all reward-related trials. Response times for the target are illustrated in Figure 2C. A repeated-measures ANOVA with factors task (face task, bar color task, bar orientation task) and motivation

Figure 2.

Eyetracking and behavioral data. **A:** Distributions of horizontal gaze positions for the three attention tasks. **B:** Mean accuracy of participants' responses for the attention tasks. **C:** Mean target reaction times in reward-related and neutral trials for each attention condition. Error bars denote within-subject standard errors [Cousineau, 2005].

(reward, neutral) revealed a significant main effect of task ($F(2,32) = 3.48$, $P = 0.043$). However, post-hoc comparisons of reaction times between tasks did not survive Bonferroni correction (paired t -tests: all $P > 0.10$). Furthermore, this analysis yielded a main effect of motivation ($F(1,16) = 7.29$, $P = 0.016$) indicating shorter reaction times for trials with a potential monetary gain. No interaction was found between task and motivation ($F(2,32) = 1.79$, $P = 0.196$).

FMRI Results

Parametric effects of attention

Correlations of neural activity with parametric levels of attentional task demands are listed in Table I.

Neural responses in FFG

Mean MNI coordinates for the individually defined face-responsive voxels in visual cortex were $x = -37.4 (\pm 0.7)$, $y = -51.4 (\pm 0.8)$, $z = -19.0 (\pm 0.5)$ in the left hemisphere and $x = 36.6 (\pm 0.8)$, $y = -49.2 (\pm 1.3)$, $z = -19.0 (\pm 0.5)$ in the right hemisphere. Parameter estimates were subjected to a repeated-measures ANOVA with factors hemisphere (left, right), motivation (reward, neutral), and task (face task, bar color task, bar orientation task). No main effect of hemisphere was observed ($F(1,24) = 1.32$; $P = 0.261$). A main effect was found for motivation ($F(1,24) = 9.73$; $P = 0.005$) indicating stronger responses to faces predicting a potential reward compared to faces predicting no outcome. Furthermore, there was a main effect of task ($F(2,48) = 3.35$; $P = 0.044$) and a task-by-hemisphere interaction ($F(2,48) = 4.15$; $P = 0.022$). There were no other significant interaction effects (hemisphere $\times$ motivation: $F(1,24) = 1.19$; $P = 0.286$; task $\times$ motivation: $F(2,48) = 0.54$; $P = 0.584$; hemisphere $\times$ task $\times$ motivation: $F(2,48) = 0.17$; $P = 0.845$). Separate repeated-measures ANOVAs for each hemisphere revealed that neural responses in the right hemisphere ($F(2,48) = 5.69$; $P = 0.006$), but not in the left hemisphere ($F(2,48) = 0.39$; $P = 0.683$) were modulated by task. In order

TABLE I. Brain regions showing a parametric modulation of fMRI signal by attentional task demands

Brain region	L/R	Peak voxel (MNI coordinates)			T	$p_{(FWE)}$
		x	y	z		
(A) Face task > Bar color task > Bar orientation task						
Middle temporal gyrus	L	-66	-34	-8	7.25	0.004
Inferior parietal lobule	L	-42	-62	43	6.21	0.050
(B) Bar orientation task > Bar color task > Face task						
Intraparietal sulcus	R	36	-43	49	9.49	< 0.001
Inferior frontal gyrus	R	48	8	25	7.36	0.003
Superior parietal lobule	R	18	-64	55	7.00	0.008
Posterior temporal cortex	R	57	-58	-8	6.85	0.011

Figure 3.

Univariate fMRI results for responses in fusiform gyrus (FFG) and attention-independent reward processing. **A:** Neural responses derived from the individually defined face-responsive voxels in FFG showed main effects of motivation and attention, but no interaction between the two factors. The white ellipse superimposed on a horizontal and sagittal section of a T1-weighted structural scan indicates the 3D Gaussian distribution of the individually defined right FFG with a threshold of two standard deviations. **B:**

Attention-independent processing of reward was found in ventral striatum (VS) and ventral tegmental area (VTA) bilaterally. Parameter estimates are plotted for the group maximum in the left VS and left VTA. The activation map is superimposed onto a horizontal, sagittal, and coronal section of a T1-weighted structural scan, thresholded at $P < 0.001$ (uncorrected) for illustration purposes [Cousineau, 2005]. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

to further qualify task modulations in the right hemisphere, we conducted post-hoc paired t -tests with Bonferroni correction. They revealed significantly weaker responses in the bar orientation task compared to the face task ($t(24) = 3.42$; $P = 0.007$). There was a main effect of reward both in right and left FFG (right: $F(1,24) = 11.28$; $P = 0.002$; left:

$F(1,24) = 4.61$; $P = 0.042$). Significant task-by-reward interactions were neither observed in right nor in left FFG (right: $F(2,48) = 0.32$; $P = 0.728$; left: $F(2,48) = 0.66$; $P = 0.523$). Thus, responses in the right FFG were modulated by task and reward independently of each other. Parameter estimates are displayed in Figure 3A.

Figure 4.

Univariate fMRI results for attention-dependent reward processing. Activation in right anterior insula (aINS) revealed a parametric modulation of reward processing by attentional task demands. A statistical trend towards this effect was further found in anterior cingulate cortex (ACC). Parameter estimates are plotted for the group maxima. The activation map is super-

imposed onto a coronal, horizontal, and sagittal section of a T1-weighted structural scan, thresholded at $P < 0.001$ (uncorrected) for illustration purposes. All error bars indicate within-subject standard errors [Cousineau, 2005]. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Attention-independent reward processing

Parametric analysis. Greater fMRI responses to faces indicating reward compared with neutral faces irrespective of attention condition was observed in VS bilaterally (left peak voxel: $x = -12, y = 8, z = -8$; $T = 6.40$; $P < 0.001$, FWE small-volume-correction; right peak voxel: $x = 9, y = 11, z = -5$; $T = 5.24$; $P < 0.001$, FWE small-volume-correction; see Fig. 3B). This contrast yielded robust activations throughout our whole *a priori* defined ROI, including nucleus accumbens. Furthermore, attention-independent reward processing was found in ventral tegmental area (VTA) bilaterally (left peak voxel: $x = -9, y = -22, z = -11$; $T = 6.32$; $P < 0.001$, FWE whole-brain-correction; right peak voxel: $x = 9, y = -22, z = -8$; $T = 5.50$; $P = 0.010$, FWE whole-brain-correction).

Attention-dependent reward processing

Parametric analysis. In order to identify brain regions that process reward information in dependence on current attentional task demands, we probed a parametric decrease of reward processing with increasing attentional task demands. This analysis yielded a significant effect in

right aINS (peak voxel: $x = 36, y = 11, z = 7$; $T = 4.14$; $P = 0.038$, FWE small-volume-correction; see Fig. 4), reflecting a reward-related modulation of the response when attention was directed to the reward value of the face, but not when attention was directed to the simultaneously presented bars. A statistical trend was observed in ACC (peak voxel: $x = -12, y = 35, z = 7$; $T = 3.91$; $P = 0.074$, FWE small-volume-correction). No such task-dependent modulation of reward processing was detected in the VS within the *a priori* defined ROI, or the VTA using small-volume correction within spherical ROIs (diameter 10 mm) centered on the peak voxels showing a main effect of reward (all $P > 0.2$).

Relation between individual attentional task demands and neural signals of task-dependent reward-processing

To explore whether the neural effect of attention-dependent reward processing is related to the individual degree of attentional task demands, we performed an across-subjects correlation between parameter estimates

Figure 5.

Across-subjects correlation between behavioral task performance and fMRI signals in right anterior insula. The x-axis represents individually derived parameter estimates for the effect of task-dependent reward processing at the group maximum in the right anterior insula. The y-axis represents regression slopes resulting from a linear regression of each participant's performance in the attention tasks against attention levels. Greater slopes signify sharper performance drops in the bar orientation task compared to the face task. Data points displayed in grey denote statistical outliers.

derived from right aINS and the slopes resulting from single regressions of individual task performance against attention levels. Four data points were more than two standard deviations above or below the mean and hence defined as statistical outliers (gray circles in Fig. 5). We computed Spearman's rank order correlation, which is less sensitive to outliers compared to the standard Pearson correlation. A significant positive correlation was observed ($\rho = 0.458$, $P = 0.021$) indicating that a greater increase of task difficulty for the bar orientation task vs. face task is related to a stronger suppression of reward signals in aINS.

DCM results

On the basis of our univariate fMRI results, we constructed an initial model with FFG, VS, and aINS as nodes (Fig. 6A). Eleven additional models were set up by varying which intrinsic connections were modulated by attention. These models are depicted in Figure 6C. We performed Bayesian model selection in order to identify the model with highest model evidence. The exceedance probability of our initial model (M1) was $\phi_1 = 0.32$. All other models had lower exceedance probabilities ranging from 0 to 0.23 (see Fig. 6B). Thus, Bayesian model selection favored the model in which only the forward connection from VS to aINS was modulated by attentional task demands. Interestingly, the other three models with exceedance probabilities of $\phi > 0.20$ yielded a very similar

model structure: all models contained an attentional modulation of the connection between VS and aINS as in our initial model (M1) and variable additional attentional modulations of the connections from aINS to VS (M2), aINS to FFG (M4), or on both of these connections (M6).

Parameter estimates of model M1 were tested with Bonferroni-corrected one-sample t -tests and are reported in Table II. For intrinsic connections all parameter estimates were significant, except for the connection between FFG and VS, which did not survive Bonferroni correction. Critically, we found a significant modulation of the forward connection from VS to aINS by attention, indicating that the attention-dependent reward effect in aINS was mediated by differences in VS-aINS effective connectivity. In other words, the more attention was directed towards the reward cue, the stronger was the coupling between VS and aINS.

We additionally performed Bayesian Model Averaging for the four models yielding exceedance probabilities of $\phi > 0.20$ to examine which of the attentional modulations contributed strongest to models evidence across the four models. In concordance with our initial DCM analysis, Bayesian Model Averaging revealed that the connection from VS to aINS was most strongly modulated by attention ($M = 0.18 \text{ Hz} \pm 0.054 \text{ (SEM)}$; Bonferroni-corrected one sample t -test: $t(24) = 3.36$, $P = 0.008$), while attentional modulation of the other two connections was not significant (aINS to VS: $M = 0.013 \text{ Hz} \pm 0.005$, $t(24) = 2.46$, $P = 0.064$; aINS to FFG: $M = 0.009 \text{ Hz} \pm 0.05$, $t(24) = 1.78$, $P = 0.264$). Bonferroni-corrected paired sample t -tests further showed that parameters for the attentional modulation of the connection from aINS to VS ($t(24) = 3.19$, $P = 0.008$) and from aINS to FFG ($t(24) = 3.23$, $P = 0.007$) were significantly lower compared to the modulation of the connection from VS to aINS.

DISCUSSION

In this study, we investigated the influence of attention on reward processing in the human brain. In VS and VTA, we found a strong modulation of fMRI responses by reward cues irrespective of the attention task, indicating

TABLE II. DCM parameters of the best fitting model

DCM parameter	Mean (Hz) $\pm$ SEM	T	$p(\text{Bonferroni corr.})$
(A) Driving and modulatory effects			
Faces on FFG	1.346 ± 0.019	14.28	<0.001
Reward on VS	0.377 ± 0.012	6.52	<0.001
Attention on VS $\rightarrow$ aINS	0.181 ± 0.011	3.38	0.007
(B) Intrinsic connections			
FFG $\rightarrow$ VS	0.047 ± 0.004	2.56	0.102
FFG $\rightarrow$ aINS	0.211 ± 0.005	8.67	<0.001
VS $\rightarrow$ FFG	0.096 ± 0.003	5.49	<0.001
VS $\rightarrow$ aINS	0.064 ± 0.003	4.11	0.002
aINS $\rightarrow$ FFG	0.044 ± 0.001	7.82	<0.001
aINS $\rightarrow$ VS	0.018 ± 0.001	6.54	<0.001

attention-independent processing of reward cues in subcortical regions of the reward system. In contrast, both reward and attention modulated responses in high-level visual cortex, but independently of each other. Finally and critically, neural responses in right aINS and ACC showed a modulation of reward processing by attention: Responses to reward-indicating vs. neutral cues were enhanced when participants attended to the reward cues, but not when attention was directed to peripheral bar stimuli. This effect was mediated by a modulation of effective connectivity between VS and aINS by attentional task demands.

Reward and Attention Signals in FFG

Previous neuroimaging studies have provided evidence for an involvement of visual areas in reward processing [Apitz and Bunzeck, 2012; Pessoa and Engelmann, 2010; Weil et al., 2010]. Extending these earlier findings, our results now demonstrate that reward and attention contribute independently to neural signals in FFG, similar to previously observed additive effects of emotion and attention in high-level visual cortex [Gomez et al., 2011; Vuilleumier et al., 2001]. This finding argues for independent sources for the influence of attention and motivational information. The attentional modulation of FFG activation is most likely exerted by top-down control from frontoparietal areas [Corbetta and Shulman, 2002; Reddy et al., 2007], which also exhibited increasing activations in response to increasing task demands in our study. The attention-independent responses to reward in FFG could be mediated by feedback signals originating from VS and VTA, which would be in accordance with neuroanatomical evidence [Middleton and Strick, 1996]. We interpret the additive modulation of FFG responses by attention and reward as reflecting a mechanism by which the brain copes with two concurrent tasks that compete for sensory processing resources.

Attention-Independent Processing of Reward Information in Subcortical Structures

It is well known that dopaminergic neurons in VTA play a crucial role for signaling predictions about future rewarding events [Cohen et al., 2012; Schultz et al., 1997]. Axons of these neurons project to other brain regions, especially to the basal ganglia and frontal cortex, and are thus directly involved in the initiation of goal-directed behavior towards behaviorally relevant stimuli. As such, this region is considered to play a causal and basic role for the generation of reinforcement learning behavior [Fields et al., 2007]. According to findings reported by Mireniewicz and Schultz [1996], dopaminergic neurons in VTA respond preferentially to rewarding rather than aversive events. Based on these results, Schultz [2000] has suggested that reward-related activity in VTA and VS is more likely to

reflect processing of reward information rather than attention induced by the salience of the reward stimulus. In contrast, more recent studies propose that dopaminergic neurons are additionally involved in the processing of signals arising from salient but non-rewarded events, such as novelty [see Bromberg-Martin et al., 2010, for a review]. However, these studies do not provide unequivocal evidence for the question whether reward signals in VS and VTA are encoded independent of attentional task demands. Previously, Pessiglione et al. [2007] have shown that VS responds to reward-indicating stimuli even when their visibility is strongly reduced through visual masking, albeit to a substantially lesser extent than to fully conscious stimuli. Still, such residual reward signals could reflect attentional orienting towards motivationally relevant stimuli, which has also been demonstrated for invisible stimuli [Jiang et al., 2006]. In contrast to the previous finding of a strong reduction of neural responses to reward cues in the absence of awareness [Pessiglione et al., 2007], we observed a robust modulation of neural signals in VS and VTA that was entirely unaffected by attentional task demands. This strongly supports the notion that these subcortical structures primarily respond to reward information rather than reflecting an attention-related process. It is also in line with the idea that subcortical learning signals primarily reflect a 'model-free' control in decision making systems while the prefrontal-parietal network represent the more 'model-based' aspects probably closely related to processes such as attention and working memory [Deserno et al., 2012; Gläscher et al., 2010].

Attentional Modulation of Reward Processing in aINS and ACC

Activation of aINS in response to stimuli with motivational or affective relevance has often been reported [e.g. Knutson et al., 2000, 2001b, 2003; see also Mizuhiki et al., 2012, showing responses to expected rewards in monkeys' aINS neurons]. However, a clear and distinctive role of this region for the processing of reward-indicating stimuli is still lacking. Our results demonstrate that aINS activation is not automatically driven by reward information, but rather depends on attentional resources available for processing of the reward cue. Its function for the anticipation of motivationally relevant events is thus distinct from VS and VTA. Our results are in agreement with recent notions suggesting aINS as a crucial node for the distribution of attentional resources and the implementation of responsiveness to sensory stimuli [Dosenbach et al., 2007; Eckert et al., 2009; Nelson et al., 2010; Sterzer and Kleinschmidt, 2010]. In their model of cognitive control, Tops and Boksem [2011] describe aINS as a central component of a system that guides behavior in low-predictable environments by adaptively focusing attention towards motivationally relevant stimuli while constantly

Figure 6.

DCM models and results. **A:** Initial model with attentional modulation of the forward connection from ventral striatum to anterior insula. **B:** Exceedance probabilities for all tested models resulting from Bayesian model selection. **C:** Structure of alternative models M2–M12. In each model, sensory input (faces) was

directed to face-responsive fusiform gyrus (FFG) and reward was directed to ventral striatum (VS), as indicated by dotted arrows. Attentional modulations of intrinsic connections were systematically varied across models, as indicated by dashed arrows between model nodes.

monitoring available attentional resources (see also Hampshire et al., 2009). AINS probably fulfils such a function by the integration of interoceptive, sensory, and emotional/motivational information, which consequently mediates awareness of sensory stimuli with respect to their motivational relevance and thus facilitates their further processing [Craig, 2002, 2009; see also Critchley et al., 2004; Ploran et al., 2007; Menon and Uddin, 2010]. Accordingly, the absence of reward-related signals in aINS during the bar tasks in our study most likely reflects participants' restricted or abolished awareness of the motivational value indicated by the reward cue. Notably, such attentional

manipulations as implemented in our task design are known to cause drastic reductions of visual awareness for unattended stimuli [Lavie, 2006]. Furthermore, our results provide a link between neural signals in aINS and individual demands of attentional resources, suggesting that reward-related activity in aINS corresponds to the individual degree of awareness of motivationally salient information.

Notably, we only observed an attention-dependent reward effect in right, but not in left aINS. This selective activation of right aINS corresponds to previous research showing a lateralized functionality of this region. Neural

activations associated with the detection of motivationally salient events are commonly found in right aINS exclusively [Critchley et al., 2004; Eckert et al., 2009; Hampshire et al., 2009; Knutson et al., 2001, 2003]. By contrast, left aINS activation has been observed in association with rumination over negative emotional events [Shin et al., 2000; Simmons et al., 2012]. It has been suggested that such lateral asymmetries may arise from hemisphere-specific influences of sympathetic and parasympathetic activity [Craig 2002, 2009].

Remarkably, target reaction times were affected by reward independent of attentional task demands. Thus, reaction times were sensitive to reward even when attentional task demands were highest and reward-related signals in aINS were abolished. Note that this does not implicate that attention was not effectively diverted away from the reward cue in the bar tasks. Rather, the influence of reward on such simple motor tasks may predominantly rest upon subcortical reward signals and act even outside of awareness [Pessiglione et al., 2007]. More complex behaviour requiring an elaborate processing of the reward cue, in contrast, may possibly rely more on cortical processing resources. Support for this notion comes from findings by Bijleveld et al. [2010, 2012]. In tasks requiring both fast and accurate responses, unconscious reward cues incited participants to respond faster, whereas conscious reward cues led to a benefit in participants' accuracy probably reflecting the involvement of higher-level cognitive resources.

Along with aINS, albeit statistically weaker, we observed attention-dependent reward signals in ACC. Co-activation of ACC with aINS is often reported, giving support for the notion that these regions form two components of one network [Medford and Critchley, 2010]. This "salience network" is supposed to guide behavior by identifying the most relevant items in the environment [Seeley et al. 2007]. As suggested by our results ACC and aINS occupy similar functions for the processing of motivationally salient input. Yet, it has been argued that within this network aINS constitutes the input component by integrating cognitive, affective, and interoceptive information [Medford and Critchley 2010]. ACC, by contrast, may represent the output component by preparing motor responses for the selection of salient stimuli while taking into account the expected effort for the planned action [Croxson et al., 2009; Paus, 2001; Sheth et al., 2012].

Furthermore, both regions share a cytoarchitectonic commonality in that they contain von Economo neurons, projection neurons, which are considerably larger than pyramidal cells [Allman et al., 2010; Nimchinsky et al., 1999]. They possess larger dendrites and axons, which possibly facilitate a rapid transmission of neural signals to other cortical areas.

Attentional Modulation of Reward-Processing as a Result of Network Interactions

The model selection of our DCM analysis yielded highest model evidence for our initial model, while three other models showed exceedance probabilities greater than 0.20

but below the winning model. Notably, attentional modulation of the connection from VS to aINS was a common feature of all these high-ranking models. This indicates that the observed attention-dependent reward effect in aINS is mediated by attention-dependent modulation of effective connectivity from VS to aINS. In this context, the coupling between the two regions and hence the transmission of reward information from VS to aINS is stronger for a higher degree of attention directed towards the reward cue. Such attentional influences could potentially be elicited by higher cortical regions such as fronto-parietal regions, which are known to be involved in top-down allocation of attention [Corbetta and Shulman, 2002].

CONCLUSIONS

Taken together, our results demonstrate distinct roles of brain regions previously implicated in reward anticipation. We suggest that these diverging response profiles reflect how the brain exploits available processing resources when faced with multiple behaviorally relevant inputs: Sensory processing in visual cortex can be enhanced both by attention and by the motivational salience of a stimulus, but these influences seem to be mediated by independent sources rather than by a common pathway. Crucially, subcortical structures keep track of motivationally salient stimuli irrespective of current task demands, possibly in order to ensure sensitivity to behaviorally relevant input, which could facilitate simple or stereotypical motor responses. In contrast, aINS and ACC may have a key role in promoting more elaborate processing of motivationally relevant information by mediating the individual's awareness and the conscious evaluation of such information. Based on our DCM results, we propose that a modulation of effective connectivity from VS to aINS by attentional task demands underlies these distinct regional responses.

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