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Functional Lateralization of the Anterior Insula During Feedback Processing

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Abstract: Effective adaptive behavior rests on an appropriate understanding of how much responsibility we have over outcomes in the environment. This attribution of agency to ourselves or to an external event influences our behavioral and affective response to the outcomes. Despite its special importance to understanding human motivation and affect, the neural mechanisms involved in self-attributed rewards and punishments remain unclear. Previous evidence implicates the anterior insula (AI) in evaluating the consequences of our own actions. However, it is unclear if the AI has a general role in feedback evaluation (positive and negative) or plays a specific role during error processing. Using functional magnetic resonance imaging and a motion prediction task, we investigate neural responses to self- and externally attributed monetary gains and losses. We found that attribution effects vary according to the valence of feedback: significant valence × attribution interactions in the right AI, the anterior cingulate cortex (ACC), the midbrain, and the right ventral putamen. Self-attributed losses were associated with increased activity in the midbrain, the ACC and the right AI, and negative BOLD response in the ventral putamen. However, higher BOLD activity to self-attributed feedback (losses and gains) was observed in the left AI, the thalamus, and the cerebellar vermis. These results suggest a functional lateralization of the AI. The right AI, together with the midbrain and the ACC, is mainly involved in processing the salience of the

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outcome, whereas the left is part of a cerebello-thalamic-cortical pathway involved in cognitive control processes important for subsequent behavioral adaptations. *Hum Brain Mapp 35:4428–4439, 2014.*

Key words: feedback; agency; error processing; salience; insula; functional magnetic resonance imaging

INTRODUCTION

Feedback monitoring is an executive function essential to guide behavior. When the outcome is caused by our own action (self-attributed), positive and negative feedback is important to signal the continuation or the adjustment of the current behavior to improve subsequent performance (Chambon et al., 2012; Danielmeier and Ullsperger, 2011; Klein et al., 2007; Li et al., 2008). During a fast reaction time task, response time on trials immediately following an error is usually longer. This post-error slowing is interpreted as a sign of ongoing cognitive processes important for behavioral adjustment (Danielmeier and Ullsperger, 2011; Klein et al., 2007; Li et al., 2008). Positive and negative feedback, however, can also be caused by an externally generated mechanism (externally attributed) and thus be independent of our actions. In the context of feedback monitoring, an appropriate agency attribution allows us to take responsibility for our errors and credit for our successes (Haggard and Tsakiris, 2009), and to alter our behavioral and emotional response when a feedback is related to an external event that is out of our control (Ochsner and Gross, 2005; Ochsner et al., 2004).

The insula is considered to play an important role in the self-agency experience (David, 2012; Sperduti et al., 2011)—'*the experience of controlling one's own actions, and, through them, events in the outside world*' (Haggard and Chambon, 2012). Together with the anterior cingulate cortex (ACC) and the medial prefrontal cortex (PFC), the insula has been widely involved in self-referential processing (Craig, 2009; Northoff et al., 2006; van der Meer et al., 2010). Recent evidence, however, shows that extensive bilateral damage of the insula, the ACC and the medial PFC is associated with impairments in updating the knowledge about the self but does not affect basic self-awareness or sense of self-agency (Khalsa et al., 2009; Philippi et al., 2012). These findings are consistent with the hypothesis that the insula, specifically the anterior insula (AI), may have a more essential role in evaluating the consequences of our intentional actions (Brass and Haggard, 2010).

Activation of the AI, the ACC, and the pre-supplementary motor area (pre-SMA) has also been reported in error processing studies. These regions are activated when uncertainty about performance is high and thus an external feedback is required to assess performance (Ullsperger and von Cramon, 2003), and when performance is internally detected but no external feedback (confirming the correctness of the response) is provided (Hester et al., 2004). Importantly, activation of the AI has been specifically found when errors are consciously perceived or performance monitoring is required (Hester et al., 2004, 2005; Ullsperger et al., 2010). This has led to the hypothesis that the AI may have a crucial role in processing conscious error, i.e., in error awareness (Klein et al., 2013). Moreover, recent findings point to a functional lateralization of the AI during error processing, where the right AI seems to modulate salience processing, whereas the left AI may be 'important for moment-to-moment adjustments in behavioral control' (Ham et al., 2013a). This functional dissociation is consistent with evidence of a right hemisphere lateralization in attentional processes and a left lateralization for fine motor coordination (Gotts et al., 2013; Menon and Uddin, 2010; Sridharan et al., 2008; Thiebaut de Schotten et al., 2011). Activation of the AI, however, has also been reported for monetary gains during gambling tasks (Clark et al., 2009; Izuma et al., 2008). In addition, recent electrophysiological findings in nonhuman primates show that neurons in the AI respond during reward delivery (Mizuhiki et al., 2012). Based on this evidence, it is unclear if the AI has a specific role in error processing, or a more general role in feedback evaluation (positive and negative) when the outcome is associated with our own actions (self-attributed).

A better understanding of the AI's role during self-attributed outcomes may help shed light on feedback processing abnormalities reported in several neuropsychiatric disorders. Patients with schizophrenia, major depression and drug addiction, for instance, show altered response to feedback (Eshel and Roiser, 2010; Li et al., 2006; Luo et al., 2013; Mathalon et al., 2009; Ziauddeen and Murray, 2010), as well as an abnormal sense of agency. Schizophrenic patients often report delusion of control (Moore and Fletcher, 2012), while depressed and addicted patients show loss of control and helplessness (Pryce et al., 2011). It is known that these disorders are associated with functional and structural abnormalities of the AI (Diener et al., 2012; Hatton et al., 2012; Naqvi and Bechara, 2009; Palaniyappan and Liddle, 2012; Shepherd et al., 2012). It is, therefore, possible that an abnormal agency attribution interferes with feedback processing in these disorders.

To assess the role of the AI during feedback processing, we factorially manipulated agency and valence of monetary feedback while measuring subject's blood-oxygen-level-dependent (BOLD) response with functional magnetic resonance imaging (fMRI). Specifically, we modified a

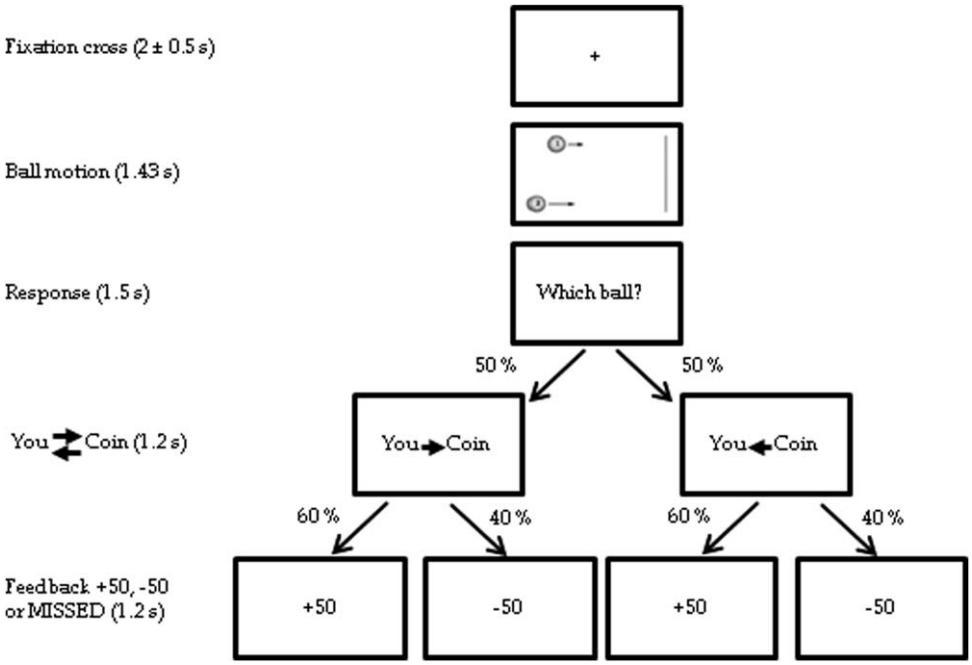

Figure 1.
Timing of the modified dynamically adaptive motion prediction task.

dynamically adapted motion prediction (DAMP) task (Ullsperger and von Cramon, 2003) to investigate whether the neuronal responses to feedback are sensitive to agency, and whether this sensitivity is valence-specific. Our modified motion prediction task allows the investigation of self-attributed (SA) and externally attributed (EA) feedback (contingent/non-contingent on performance) while holding motor output, perceptual stimulation, gain/loss probability, and gain/loss uncertainty ('risk') constant between.

METHODS

Participants and Task

Participants were 25 healthy right-handed subjects (10 males, 21–45 years of age, mean age: 29.8 years ± 7.9 SD) without any psychiatric, neurologic, or medical illness as confirmed by the Structured Clinical Interview for Axis I Disorders. The study was approved by the University of Zurich's Institutional Review Board, and all subjects gave written informed consent.

The fMRI paradigm consisted of 130 trials and 12 randomly interspersed non-events of 10 s each. The stimuli were presented using Presentation 0.45 (Neurobehavioral Systems, San Francisco, CA) and appeared on goggles suitable for use inside the scanner bore. A modified version of the DAMP task (Ullsperger and von Cramon, 2003) was used. Each trial started with two balls moving at different speeds and from different starting points toward a finish line. For every trial of the experiment, the balls were on the screen for 1.43 s and the task was to predict, which ball would cross the finish line first, then indicate the decision by a left or right button press done with the left or right hand, respectively. Only after this decision were subjects instructed whether their response was relevant or irrelevant to the upcoming feedback. Specifically, subjects were told that on each trial they would gain or lose 50 cents indicated by "+50" or "−50" feedback. On a random 50% of the trials feedback was performance-dependent (SA gains or losses, i.e., correct or error). On the other 50% of trials feedback was dependent on chance, being randomly selected by the computer with a probability tailored to match their success-rate in performance-dependent trials (EA negative or positive feedback was determined by a biased virtual coin flip). 750 ms after the response, a picture with the words "You" and "Coin" and an arrow pointing toward either word was presented on the screen to indicate if the following feedback was associated with the subject's performance or not. Finally, feedback about winning (+50) or losing (−50) was presented (Fig. 1). The next trial started after 2000 ± 500 ms. If the subject failed to respond, the arrow pointed towards the word "You" followed by the feedback "Missed". During the fMRI paradigm, task difficulty was adapted for each participant such that the error rate was between 35 and 50%, thus uncertainty about performance was high. Difficulty levels (defined as the difference in arrival time of the two balls at the finish line, given a different speed and starting

position for each ball) were dynamically adapted for each participant, such that the error rate was constant (Ullsperger and von Cramon, 2003). To keep the error rate high during the first trials of the experiment, difficulty levels were first determined individually using a training session of 100 trials performed during the anatomical scans, during which the subjects received only a performance feedback (correct: smiley face, incorrect: unhappy face). Participants were unaware that the difficulty of the task was manipulated, were told to do their best at winning and were paid based on performance in addition to an hourly rate (25 Swiss francs) for participation in the study. The chance of monetary gain for EA and SA feedback were (mean ± SD) 59.5 % ± 5.3 and 58.6 % ± 5.6, respectively; percent difference between SA and EA gains was −0.9 ± 1.1, percent of missed trials was 0.8 ± 1.4.

Image Acquisition

Images were acquired on a Philips Achieva TX 3T whole-body MR unit equipped with an eight-channel head coil. Functional time series were acquired with a sensitivity encoded single shot echo-planar sequence (echo time = 35 ms, 80 × 80 voxel matrix, interpolated to 128 × 128, voxel size: 2.75 × 2.75 × 4 mm^3, SENSE acceleration factor $R = 2.0$). Thirty six contiguous axial slices were placed along the anterior–posterior commissure plane covering the entire brain and acquired in ascending order (repetition time = 2,000 ms). The first four acquisitions were discarded due to T1 saturation effects. T1-weighted high-resolution images were also acquired for each participant.

Data Analysis

Behavioral data were analyzed using StatView 5.0.1 (SAS Institute, Cary, NC). All data were reported as mean ± standard error of the mean (SEM), and significance was set at $P < 0.05$ two-tailed. Mean reaction time differences for correct and incorrect trials were analyzed with paired t test. Reaction time slowing for trial following a negative feedback was calculated separately for SA and EA losses and was defined as difference in reaction time between post-SA losses and post-SA gains and between post-EA losses and post-EA gains, respectively.

Image processing was carried out using MATLAB R2012a (The Mathworks, Natick, MA) and Statistical Parametric Mapping (SPM8; Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl. ac.uk). Functional volumes were spatially realigned to the location of the first image in the time series. For each subject, the first functional image was coregistered to the subject's T1 anatomical image and normalized into standard stereotactic space (template provided by the Montreal Neurological Institute; MNI). The remaining functional images were then normalized accordingly. All functional images were spatially smoothed using a 8 mm full width at half maximum Gaussian kernel. No subjects demonstrated greater motion than 2.5 mm in any direction (less than the size of one voxel). The time series were high-pass filtered to eliminate low-frequency components (filter width 128 s). Statistical analysis was performed by modeling the feedback events in different conditions convolved with a hemodynamic response function and its temporal derivative as explanatory variables within the context of the general linear model on a voxel-by-voxel basis.

Our 2 × 2 factorial design independently manipulated the agency and valence of feedback. The four feedback conditions (SA losses, EA losses, SA gains, EA gains) were distributed pseudo-randomly throughout the session of 130 trials (Fig. 1). Several regressors were modeled as events including the four feedback conditions and the regressors of no interest [the missed feedback, the motor response (button press) and the realignment parameters (see also Supporting Information)]. As reported with original version of the DAMP task (Ullsperger and von Cramon, 2003), mean reaction time for incorrect trials was significantly longer than for correct trials (see Results), thus reaction time was included as a first order parametric modulator. A fixed-effect model at a single-subject level was specified, giving images of parameter estimates, which were then used for a second-level random effects analysis. For the second-level analysis, we used linear regression to model subject-specific contrast images in the following way: Contrast = b1 + b2*age + b3*gender + ε. This permitted us to identify reliable between-subject activations while controlling for age and gender, by use of a one-sample t test on b1. Unless otherwise specified, clusters of activation were identified with a global height threshold of $P < 0.001$ uncorrected and a spatial extent cluster size to achieve a family-wise error (FWE) corrected statistical threshold of $P < 0.05$ (Nichols and Hayasaka, 2003). Location of voxels significantly associated with contrasts of interest were determined by summarizing local maxima separated by at least 8 mm. Regions were anatomically labeled using the automatic anatomical labeling from the SPM toolbox and by visual inspection. The mean percent signal change across all voxels within a functional cluster was calculated using marsbar from the SPM toolbox, and a repeated-measures analyses of variance (RM-ANOVA) was then performed with subject as a random factor and attribution (self and external), and valence (negative and positive) as within-subject factors. Coordinates are reported in MNI space.

RESULTS

Behavioral Data

Independently of the feedback condition, mean reaction time for incorrect trials was significantly longer compared to reaction time for correct trials ($t(24) = 4.7$, $P < 0.001$; incorrect reaction time: 523.7 ± 20.9 ms, correct reaction time: 485.7 ± 18.5 ms). To assess if mean reaction time differed across the four feedback conditions, we conducted a RM-ANOVA

TABLE I. Brain activity associated with self-attributed feedback

Cluster (voxels)	*T* (peak)	*P* (cluster-level)	Region	*X*	*Y*	*Z*	Hem
SA > EA feedback							
499	6.65	$<0.001_{\text{-FWE-corrected}}$	Midbrain	−10	−26	−16	L
			Midbrain	10	−30	−20	R
			Midbrain	0	−18	−20	R/L
417	6.06	$<0.001_{\text{-FWE-corrected}}$	Anterior Cingulate G	2	32	24	R
501	5.55	$<0.001_{\text{-FWE-corrected}}$	Thalamus	2	−30	0	R
			Thalamus	2	−20	10	R
			Thalamus	−12	2	0	L
275	5.28	$<0.007_{\text{-FWE-corrected}}$	Insula	−36	18	−4	L
			Insula	−30	32	2	L
			Insula	−32	20	8	L
172	5.10	$<0.05_{\text{-FWE-corrected}}$	Vermis	4	−60	−36	R
			Vermis	4	−70	−40	R
202	4.93	$<0.03_{\text{-FWE-corrected}}$	Calcarine S	−2	−92	−2	L
			Calcarine S	−8	−86	−4	L
SA > EA gains							
209	4.84	$<0.02_{\text{-FWE-corrected}}$	Vermis	4	−62	−34	R
			Vermis	8	−56	−30	R
SA > EA losses							
531	6.68	$<0.001_{\text{-FWE-corrected}}$	Midbrain	8	−32	−20	R
			Midbrain	2	−20	−18	R
			Midbrain	−10	−24	−14	L
362	6.65	$<0.002_{\text{-FWE-corrected}}$	Insula	26	26	−8	R
			Insula	38	20	−6	R
			Insula	28	28	2	R
554	5.84	$<0.001_{\text{-FWE-corrected}}$	Anterior Cingulate G	6	30	24	R
			Anterior Cingulate G	−4	26	30	L
426	5.66	$<0.001_{\text{-FWE-corrected}}$	Thalamus	−12	2	0	L
			Thalamus	0	−30	0	R/L
			Thalamus	4	−22	8	R
221	4.96	$<0.02_{\text{-FWE-corrected}}$	Insula	−38	18	−4	L
			Insula	−34	30	−2	L

FWE = family-wise error, G = gyrus, S = sulcus, Hem = hemisphere, L = left, R = right.

analysis and found a significant valence x attribution interaction ($F1,24) = 9.6$, $P < 0.006$). Mean reaction time for trials with SA loss feedback (528.6 ± 21.3 ms) was significantly longer compared to reaction time for trials with SA gain feedback ($t(24) = 4.7$, $P < 0.001$; 477.3 ± 18.8 ms), EA loss feedback ($t(24) = 2.1$, $P < 0.05$; 504.7 ± 18.1 ms), and EA gain feedback ($t(24) = 2.8$, $P < 0.01$; 503.1 ± 21.9 ms). In addition, reaction time for trials with SA gain feedback was significantly shorter compared to reaction time for trials with EA gain feedback ($t(24) = -2.9$, $P < 0.01$) and EA loss feedback ($t(24) = -2.7$, $P < 0.02$).

Imaging Data

Self-attribution increases BOLD responses to feedback

Main effect: A one-sample *t* test showed greater activity for SA than EA feedback in the right anterior cingulate gyrus, the left insula, the midbrain, the thalamus, the left calcarine sulcus, and the vermis (Table I, Fig. 2A). Mean percent signal change for the vermis and left insula is reported in Figure 2B for illustrative purpose. Simple effects are reported in Table I and in the Supporting Information.

Whole brain search for agency × valence interaction. Does agency attribution modulate BOLD responses to losses and gains differently?

A one-sided whole brain analysis for the contrast (SA losses − EA losses) − (SA gains − EA gains) showed a significant suprathreshold cluster in the right insula and the medial superior frontal/anterior cingulate gyrus (Table II, Fig. 3A). Mean percent signal change for the anterior cingulate gyrus and the right insula is reported in Figure 3B.

At a lower statistical threshold a significant interaction was also found in the midbrain ($P < 0.04_{\text{FDR-corrected}}$ corresponding to a cluster size of 236 voxels at a $P < 0.005$ uncorrected, $t = 4.30$, $x = 6$, $y = -22$, $z = 32$, $x = 0$, $y = -22$, $z = 16$; Fig. 3C). Mean percent signal change for the midbrain is reported in Figure 3D.

In contrast, a significant interaction in the left insula was not found even when a small volume correct analysis

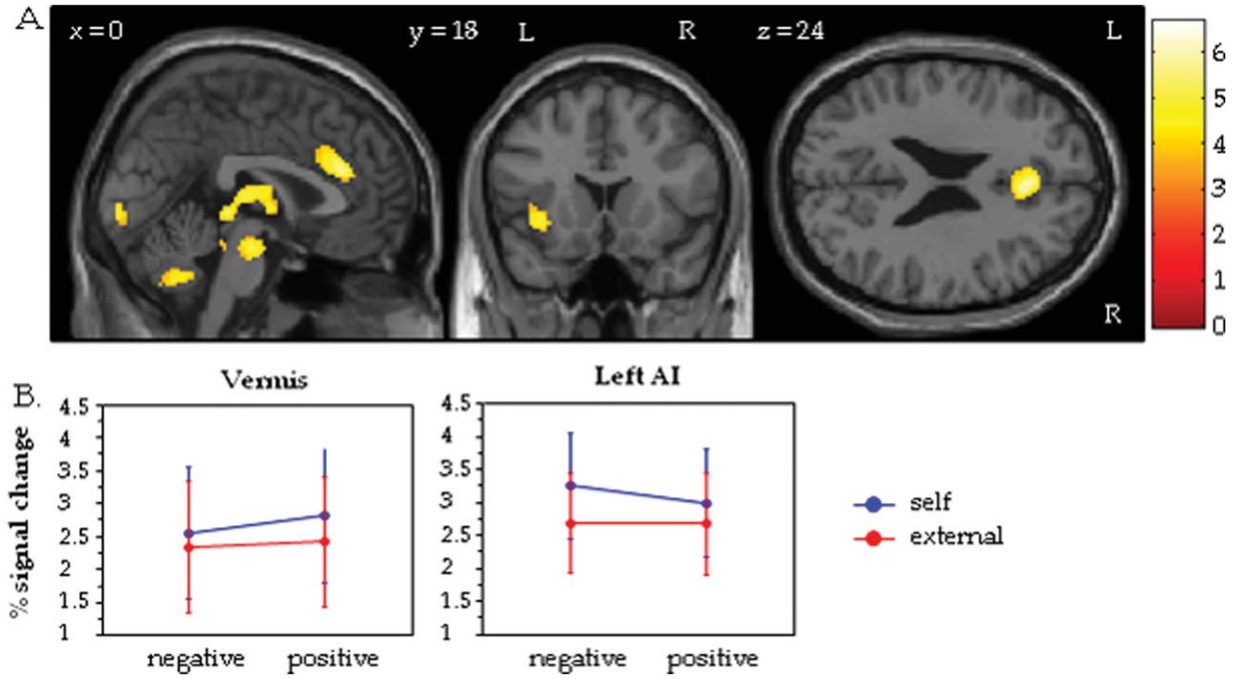

Figure 2.

(**A**) Increased BOLD signal for SA feedback in the posterior cerebellar vermis, the midbrain, the thalamus, the dorsal anterior cingulate cortex and the left anterior insula. R = right hemisphere, L = left hemisphere. (**B**) Mean percent signal change in the posterior vermis and the left anterior insula (AI).

was conducted using the structurally defined mask of the left insula from the wfupickatlas of the SPM toolbox. To assess if activation of the insula was different between hemispheres, we extracted the mean percent signal of the right insula (from the functional cluster reported in the interaction analysis, Fig. 3B) and the left insula (from the functional cluster reported in the main effect analysis, Fig. 2B) and conducted a three-way RM-ANOVA with hemisphere (left/right), attribution (SA/EA) and valence (negative/positive) as independent factors. We found a significant hemisphere × attribution × valence interaction ($F1,24) = 14.2$, $P < 0.001$). When SA feedback was analyzed separately, we found a main effect of valence ($F1,24) = 28.4$, $P < 0.001$) and also a tendency for a hemisphere × valence interaction ($F1,24) = 3.9$, $P < 0.06$). In the right AI, activity was significantly higher for SA losses compared to SA gains ($t = 4.1$, $P < 0.0005$), while in the left AI this difference was only marginal ($t = 2.0$, $P < 0.06$).

Conversely, the other tail of this whole brain analysis—i.e., the contrast (SA gains − EA gains) − (SA losses − EA losses)—showed a significant suprathreshold cluster in the right ventral putamen (Table II, Fig. 3A). Mean percent signal change for the ventral putamen is reported in Fig. 3B.

TABLE II. Brain activity associated with valence × agency attribution

Cluster (voxels)	*T* (peak)	*P* (cluster-level)	Region	*x*	*y*	*z*	Hem
(SA vs. EA losses) > (SA vs. EA gains)							
284	5.82	$0.002_{\text{-FWE-corrected}}$	Superior Frontal G (Medial)	0	32	24	R/L
			Anterior Cingulate G	6	30	24	R
			Anterior Cingulate G	−8	28	26	L
161	5.52	$<0.04_{\text{-FWE-corrected}}$	Insula	40	16	−6	R
			Insula	30	22	−20	R
			Insula	28	24	−10	R
(SA vs. EA gains) > (SA vs. EA losses)							
204	6.64	$<0.02_{\text{-FWE-corrected}}$	Putamen	20	12	−14	R

FWE = family-wise error, G = gyrus, Hem = hemisphere, L = left, R = right.

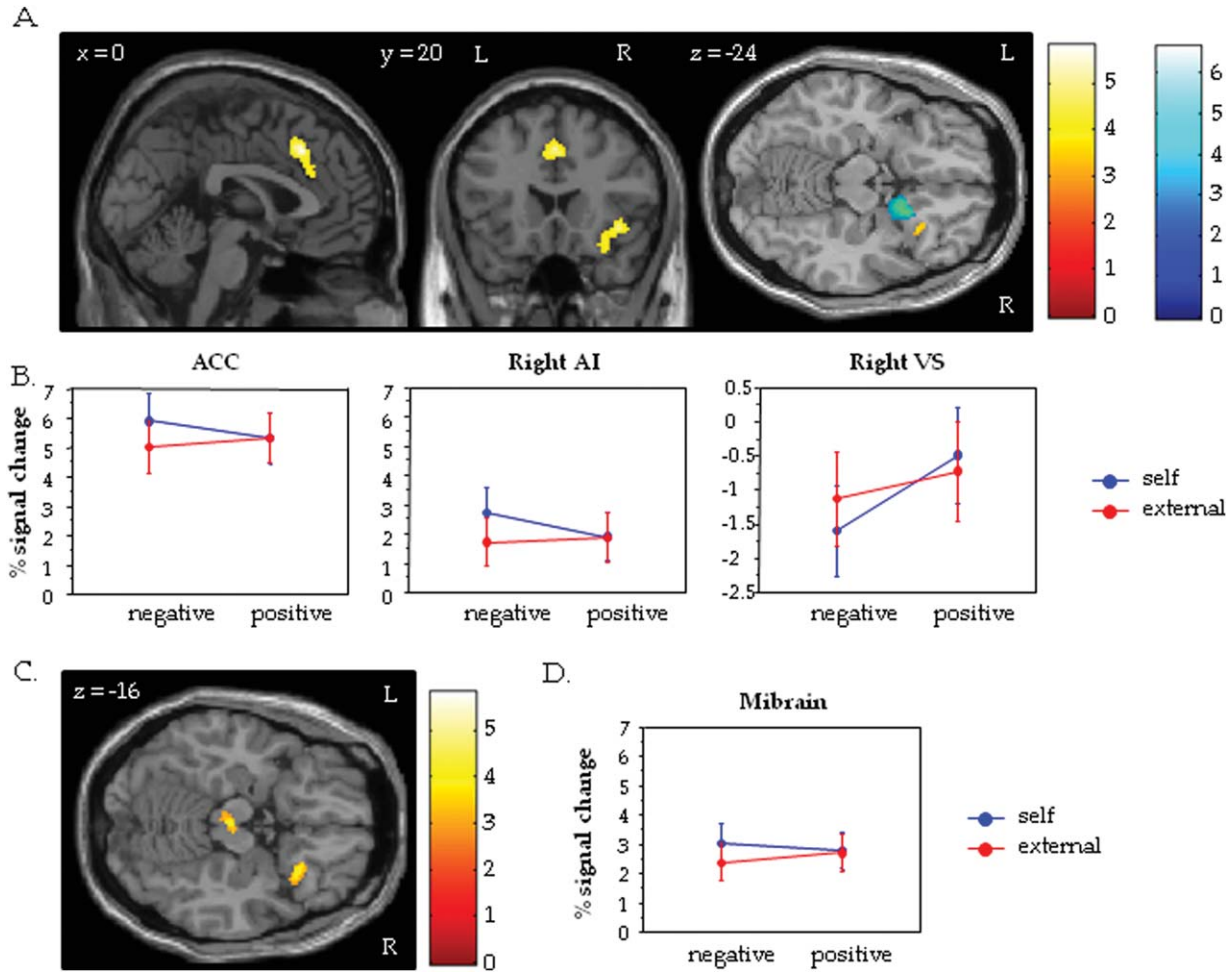

Figure 3.

BOLD signal change associated with the agency x valence interaction. (**A**) The contrast (SA losses − EA losses) − (SA gains − EA gains) is presented in hot colors and the contrast (SA gains − EA gains) − (SA losses − EA losses) in cold colors. (**B**) Mean percent signal change in the dorsal anterior cingulate cortex (ACC) and the right anterior insula (AI) and the right VS. (**C**) At a lower statistical threshold, a significant interaction for the contrast (SA losses − EA losses) − (SA gains − EA gains) was also found in the midbrain. (**D**) Mean percent signal change in the midbrain. R = right hemisphere, L = left hemisphere.

Simple effects are reported in Table I and in the Supporting Information. The results of main effect for the contrast EA - SA feedback are also found in the Supporting Information.

External-attribution increases BOLD responses to feedback

The results and related discussion are reported in the Supporting Information.

DISCUSSION

We investigated the neural correlates of SA and EA feedback using a modified DAMP task. This task involved feedback both contingent and non-contingent on performance while keeping reward probability and uncertainty ('risk') constant. Our results show that when the feedback was contingent on performance, greater BOLD response was found in the left AI, the ACC, the midbrain, the thalamus, and the cerebellar vermis. Importantly, a valence × attribution interaction was found in the right AI, the ACC, the midbrain, and right ventral putamen. The right AI, ACC, and midbrain showed specifically greater activity for SA losses, while greater negative BOLD signal for SA losses was found in the right ventral putamen. Our results show that the AI is important in SA feedback processing and suggest a functional dissociation of the left and right AI.

Dopaminergic neurons in the ventral striatum (VS) are considered to signal reward prediction error the mismatch between actual and predicted outcome (Niv and Schoenbaum, 2008). Previous neuroimaging studies have shown negative BOLD responses when expected rewards were omitted and positive responses when unexpected rewards were obtained (McClure et al., 2003; Morris et al., 2012). In addition, activity in the VS has been shown to be modulated by the valence and by the agent of the outcome. VS response has been reported to be greater when winning was contingent to performance (Zink et al., 2004), and to increase with task difficulty (Satterthwaite et al., 2012). In our task, outcome uncertainty was high across all feedback conditions, and participants were unaware that task's difficulty was manipulated to maintain an approximately 60% correct response performance rate. Since behavioral data show that healthy subjects tend to overestimate their ability to be in control of the outcome (Alloy and Abramson, 1979; Lewinsohn et al., 1980), it is possible that participants had a higher expectation of winning when the feedback was SA. This bias would lead to a greater negative BOLD signal for SA losses but a smaller change for SA gains (reward prediction error should be zero when expectations are met).

The pattern of increased BOLD signal for SA losses found in the midbrain, ACC, and right AI is consistent with a role of these regions in processing salient events. The ACC and the bilateral AI are key components of the *salience network* (Menon and Uddin, 2010) and joint activation of the AI and the ACC is found across a variety of emotional and cognitive tasks, supporting the role of these brain regions in attentional processes (Medford and Critchley, 2010). Moreover, the midbrain, ACC, and AI are part of functionally connected network involved in error processing that shows considerable anatomical overlap with brain regions involved in the processing novel/salient events (Ide et al., 2013; Seeley et al., 2007; Wessel et al., 2012). This is not a surprise considering that with error processing tasks (e.g., Go/No-Go task) errors are often infrequent events and/or signal the need for a behavioral change. In our task, the frequency of SA losses was around 40% and we did not find significantly slower reaction times on trials immediately following SA loss feedback (see Supporting Information). Despite these differences, our ventral putamen results indicate that SA losses induced the highest mismatch between reward expectation and outcome; suggesting that SA losses were more salient events than other feedback conditions.

These results are also consistent with evidence that indicates dopaminergic neurons in the midbrain play an important role in signaling aversive/negative information (Brooks and Berns, 2013). Electrophysiological data in nonhuman primates show that some dopamine neurons in the midbrain encode reward prediction error signals, whereas others are excited by salient events (rewarding and aversive) but do not respond when salient events are omitted (Matsumoto and Hikosaka, 2009), encoding what is considered to be a salience prediction error signal (Bromberg-Martin et al., 2010). Although the differential role of the midbrain, ACC and right AI in processing of salient events is not fully understood, salient prediction error responses have been reported in the bilateral AI and ACC (Metereau and Dreher, 2013). In addition, both regions receive strong dopaminergic innervations (Gaspar et al., 1989) and thus have the potential to be functionally influenced by dopaminergic signals from the midbrain.

In contrast to the right AI, the left AI showed an increased BOLD response for SA gains and SA losses. The lack of a significant interaction suggests a functional lateralization of the insula, which is supported by recent neuroimaging data. Ham et al. (2013) used dynamic casual modeling to investigate effective connectivity between the ACC and left and right AI during error processing. Participants performed a Simon task that lead to two types of errors, congruent and incongruent, with incongruent trials leading to post-error slowing. The results showed that the right AI was the only region with intrinsic connectivity to the other two regions for both types of errors, in line with the proposed role of the right AI as the 'integral hub' of the salience network (Menon and Uddin, 2010; Sridharan et al., 2008) and with evidence of a right hemisphere lateralization in visuo-spatial attentional processes (Thiebaut de Schotten et al., 2011). During incongruent errors, however, the ACC modulated the connectivity with the left AI and changes in this effective connectivity correlated with post-error slowing (Ham et al., 2013a). These results suggest that, although the ACC is important to trigger post-error behavioral adaptations (Danielmeier and Ullsperger, 2011), its interaction with the left AI may be 'important for moment-to-moment adjustments in behavioral control' (Ham et al., 2013a). Consistent with these findings, a previous neuroimaging study comparing the neural correlates of aware and unaware errors showed that activity in left AI was greater for aware errors, the only error trial associated with post-error slowing. In addition, although activity in the ACC did not differentiate between aware and unaware errors, it correlated with post-error slowing (Klein et al., 2007). In our task, longer reaction times were found for trials following SA feedback (see Supporting Information Table I), suggesting that when participants were reminded that their performance affected the outcome they were more 'cautious' about their response in the following trial. This form of 'behavioral adjustment' after SA feedback may explain why activity in the left AI was similar across SA losses and SA gains. It may also explain why we were able to detect a functional lateralization of the AI. Based on these findings, it is possible that activation in left AI reflected outcome evaluation, signaling the need for a behavioral change—that in our task was not unique to error trials. Although there was no correlation between reaction time for post-SA trials and activity in the left AI or the ACC (data not shown), participants were not

incentivized to respond as quickly as possible, and post-SA slowing was unlikely to have a strong influence on performance due to the long interval between trials. Therefore, the longer reaction time after SA trials cannot be compared to the post-error slowing reported in fast reaction time tasks (Danielmeier and Ullsperger, 2011).

This functional AI differentiation is further supported by different patterns of functional connectivity of the right and left AI both at rest and during the task [(Cauda et al., 2011, 2012) but see also (Nelson et al., 2010)], and by recent evidence demonstrating a right functional lateralization of the brain for visuospatial and attentional processing and a left lateralization for language and fine motor coordination (Gotts et al., 2013). These findings are consistent with the results of Zhang and Li (2012), who used independent component analysis to identify the neural networks engaged during a Stop Signal task. The authors identified, among others, a right fronto-parietal network (comprising the right AI) involved in attentional monitoring and a left fronto-parietal network (comprising the left AI) important for response inhibition (Zhang and Li, 2012). Since only correct response inhibition trials are associated with a change in the motor response (withholding to press), these results provide further evidence for a functional lateralization of the networks involved in behavioral adjustment and attention processing. A functional asymmetry, however, does not imply that the right and left AI are part of two functionally independent networks. In fact, both AI are functionally connected at rest to the contralateral insula and the ACC (Taylor et al., 2009), a region widely implicated in both post-error adjustments and salience processing (Hickey et al., 2010; Metereau and Dreher, 2013; Wessel et al., 2012). In addition, the left AI has been identified as one of the common nodes of functional connectivity between the salience network and the executive control network (Seeley et al., 2007). Therefore, the left AI is strategically positioned to utilize salient information to implement the necessary behavioral adaptations.

Comparing SA and EA feedback, we also found increased BOLD activity in the thalamus and the cerebellar vermis. Traditionally the cerebellum has been considered important for the acquistion and control of motor skills. However, in our fMRI task the motor output was the same for each trial condition, thus activation in the posterior vermis cannot be explained by its role in motor-related functions. A potential role of the vermis in feedback processing is supported by findings of vermis activation in anticipation of potential monetary gains (Bjork and Hommer, 2007; Knutson et al., 2001, 2003). More importantly, using a stop signal task, Ide and Li (2011) showed that post-error slowing was associated with increased BOLD response in the right ventrolateral PFC (extending to the AI) during post-error trials. To identify brain regions that significantly influenced the ventrolateral PFC time series, they used Granger causality mapping and found a network of bilateral connectivity between the posterior vermis/tonsil and the right thalamus as well as between the thalamus and the SMA, and of unilateral projection from the thalamus and the SMA to the right ventrolateral PFC (Ide and Li, 2011a). As suggested by the authors, these results highlight the potential role of a cerebello-thalamo-cortical pathway that includes the vermis in cognitive control processes.

Interestingly, in the context of our findings, the midbrain (ventral tegmental area and substantia nigra) shows strong functional connectivity, at rest, with the bilateral AI and the vermis (Tomasi and Volkow, 2012). Considering that it also sends dopaminergic projections through the ventral striatum to the dorsal ACC, and that the ventral striatum receives cortical inputs from the ACC and the agranular (anterior inferior) insula cortex (Chikama et al., 1997; Haber and Knutson, 2010; Williams and Goldman-Rakic, 1998), the midbrain is in the position to influence the activity of all the brain regions involved in SA feedback processing in our study. We can speculate that, through the VS, ACC, and right AI, this signal affects attentional processes (e.g., reorienting), and through a cerebello-thalamo-cortical pathway that include the ACC and the left insula it modulates cognitive control processes (e.g., post-error slowing) (Boehler et al., 2011; Ide and Li, 2011a). However, it is important to mention that activity in the ACC may be important for error detection, independent from post-error adaptations (e.g., Miltner et al., 1997), and that various networks may be involved in different forms of error processing, as suggested by recent findings showing that some type of errors can be processed independently of the ACC and the AI and still induce post-error behavioral adaptations (Ham et al., 2013b).

Several limitations need to be mentioned. With the present task, longer reaction times were found for trials after a SA feedback rather than specifically after a SA loss (see Supporting Information Table II). This 'behavioral adjustment' after SA feedback may explain why activity in the left AI was similar for SA gains and SA losses. However, there was no correlation between reaction time for post-SA trials and activity in the left AI or ACC (data not shown). As a result, we can only speculate about the functional significance of our findings based on previous studies. Moreover, reaction times for incorrect trials were longer than for correct trials, suggesting that participants had higher uncertainty about their responses, and consequently the outcome, during SA losses. Although reaction time was included as a parametric modulator and *risk* was kept high across all feedback conditions, we cannot exclude the possibility that increased activity reported in the ACC, right AI and midbrain for SA losses may reflect higher *uncertainty* associated with a choice during these trials. Increased uncertainty, however, is usually associated with lower expectancy of reward and thus a reduced prediction error signal in the VS [see also (Ullsperger and von Cramon, 2003)], whereas in our study the strongest negative BOLD signal in the VS was found for SA losses not for EA feedback. In addition, recent electrophysiological evidence in rodents

shows that neurons in the orbitofrontal cortex, a region involved in decision making under risk, code not only reward uncertainty but also salience (Ogawa et al., 2013), indicating that the neural correlates of uncertainty and salience may rely on similar neural networks. Moreover, studies investigating the neural correlates of choice under risk support a functional differentiation of the left and right AI (Huettel et al., 2005; Mohr et al., 2010; Studer et al., 2012). Alternatively, higher activation in the midbrain, ACC and right AI reflected the higher *informational value* of the feedback, since only SA losses provided a valid feedback to improve performance. Previous neuroimaging studies have shown increased activity in the dorsal ACC and AI for informative feedback compared to non-informative feedback (Mies et al., 2011; Ozyurt et al., 2012). However, feedback with higher *informational value* is also likely to be more salient (Nieuwenhuis et al., 2004). In addition, the midbrain and the AI and are considered part of the functionally connected network, in which the habenula acts as a critical modulator between the forebrain structures and the midbrain during error processing (Ide and Li, 2011b). Although activation of the habenula, specific to error feedback, has been previously demonstrated using the DAMP task (Ullsperger and von Cramon, 2003), we were unable to specifically differentiate the signal of the habenular complex from the rest of the thalamus (see Supporting Information). Finally, our interpretation of the findings is based on our ability to disentangle motor responses and feedback-related processes with the current design. Although each trial's feedback attribution was revealed to the participants after the motor response, reaction time for incorrect trials was longer compared to correct trials, thus confounds related to the motor response activity could still be present in the analysis associated with valence. However, because motor responses were performed equally with right and left hands, these potential confounds are unlikely to explain the functional dissociation reported for the left and right AI.

In conclusion, our findings suggest a functional lateralization of the AI. While the right AI, together with the midbrain and the dorsal ACC, may be involved in processing outcome salience, the left AI may have a more prominent role in evaluating the need to implement subsequent behavioral adaptations. Future studies are warranted to confirm these findings.

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