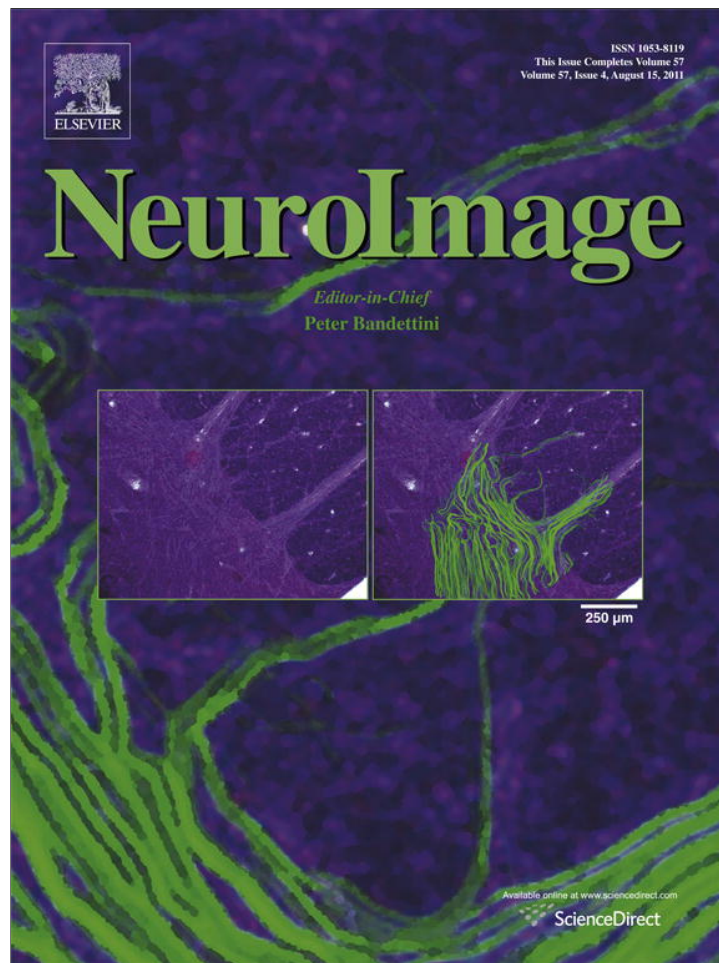


Provided for non-commercial research and education use.
Not for reproduction, distribution or commercial use.



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

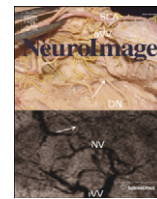
In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>



Contents lists available at ScienceDirect

NeuroImage

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

Ventral striatal and medial prefrontal BOLD activation is correlated with reward-related electrocortical activity: A combined ERP and fMRI study

Joshua M. Carlson^{a,*}, Dan Foti^{b,1}, Lilianne R. Mujica-Parodi^a, Eddie Harmon-Jones^c, Greg Hajcak^b

^a Department of Biomedical Engineering, State University of New York at Stony Brook, Stony Brook, NY, USA

^b Department of Psychology, State University of New York at Stony Brook, Stony Brook, NY, USA

^c Department of Psychology, Texas A&M University, College Station, TX, USA

ARTICLE INFO

Article history:

Received 7 February 2011

Revised 8 April 2011

Accepted 13 May 2011

Available online 23 May 2011

Keywords:

Reward

Striatum

fMRI

Erp

Feedback negativity

Feedback related negativity

ABSTRACT

Functional magnetic resonance imaging (fMRI) research suggests that the ventral striatum (VS)/nucleus accumbens, medial prefrontal cortex (mPFC), and broader mesocorticolimbic dopamine system mediate aspects of reward processing from expectation of reward to pleasantness experienced upon reward attainment. In parallel, research utilizing event-related potentials (ERP) indicates that the feedback negativity (FN) is sensitive to reward vs. non-reward feedback and outcome expectation. The FN has been source localized to the mPFC and dorsal striatum, and converging evidence suggests that the FN reflects reward processing in the mesocorticolimbic system. However, the extent to which ERP and fMRI measures of reward processing are correlated has yet to be explored within the same individuals. The primary aim of the current study was to examine the convergence between fMRI (i.e., VS and mPFC) and ERP (i.e., FN) measures of reward processing in forty-two participants who completed counterbalanced fMRI and ERP sessions while performing the same monetary gambling task. For the *Win>Loss* comparison, fMRI activation in the mesocorticolimbic reward circuit including the VS and mPFC was positively correlated with the FN. Here, we demonstrate that monetary gains activate the VS, mPFC, caudate, amygdala, and orbital frontal cortex, enhance the FN ERP component within 300 ms post feedback, and that these measures are related. Thus, fMRI and ERP measures provide complementary information about mesocorticolimbic activity during reward processing, which may be useful in assessing pathological reward sensitivity.

© 2011 Elsevier Inc. All rights reserved.

Introduction

The mesocorticolimbic dopamine (DA) system, which includes dopaminergic projections from the ventral tegmental area to both the ventral striatum (VS)/nucleus accumbens and dorsal striatum (i.e., caudate and putamen) as well as orbital frontal cortex (OFC), medial prefrontal cortex (mPFC), and amygdala, has long been implicated in reward processing (Nestler and Carlezon, 2006). In functional magnetic resonance imaging (fMRI) studies, the VS responds to drugs (Breiter et al., 1997; Drevets et al., 2001), attractive faces (Senior, 2003), erotic images (Sabatinelli et al., 2007a; Walter et al., 2008), favorable social interactions (Zink et al., 2008), monetary rewards (Knutson and Bossaerts, 2007), and pleasant tastes (O'Doherty et al., 2002). The VS responds in anticipation of reward (Knutson et al., 2001a, 2001b; O'Doherty et al., 2002) and other striatal areas including the caudate

mediate the relationship between action and reward outcome (Tricomi et al., 2004; Zink et al., 2004). Reward attainment (Knutson et al., 2001b; O'Doherty et al., 2002) and outcome monitoring (Kringelbach, 2005) recruit the mPFC. Finally, the subjective feeling of hedonia is associated with OFC activation (Kringelbach, 2005; Kringelbach et al., 2003). Thus, components of the mesocorticolimbic DA system mediate reward processing from seeking to gratification.

Complementary evidence from scalp-recorded event-related potentials (ERPs) has revealed that the “feedback negativity”² (FN; peaking at 300 ms) is sensitive to positive vs. negative outcomes such as monetary rewards (Gehring and Willoughby, 2002; Miltner et al., 1997). Variation in FN amplitude is thought to reflect the early, binary evaluation of outcomes as either better or worse than expected. The FN is larger in response to unexpected outcomes (Hajcak et al., 2007;

² This ERP component is referred to alternately as the feedback error-related negativity, medial frontal negativity, or feedback negativity. These names are derived from the observation of a relative negative deflection in the ERP for unfavorable outcomes. Taking the “loss minus win” difference yields negative values at frontocentral recording sites. Recent evidence, however, suggests that the FN may actually reflect a positivity to favorable outcomes (Foti et al., 2011; Holroyd et al., 2008), although we have opted to use the “loss minus win” convention (as opposed to “win minus loss”) in figures here to be consistent with the existing literature.

* Corresponding author at: Laboratory for the Study of Emotion and Cognition, Department of Biomedical Engineering, Bioengineering Building Room 117, SUNY Stony Brook, Stony Brook, NY 11794.

E-mail address: carlsonjm79@gmail.com (J.M. Carlson).

¹ Authors one and two equally contributed to this manuscript.

Holroyd et al., 2003; Potts et al., 2006), tracks the relative valence of outcomes within the immediate context (Holroyd et al., 2006, 2004a), and is insensitive to outcome magnitude (Hajcak et al., 2006; Sato et al., 2005; Yeung and Sanfey, 2004). One challenge in using the FN to study reward processing, however, is the issue of component overlap. In particular, the FN overlaps in time with the parietally-maximal P300, a component which is also sensitive to subjective probability and expectation violations (Courchesne et al., 1977; Duncan-Johnson and Donchin, 1977). In principle, apparent variation in FN amplitude could actually reflect variation in the P300. In a prior study, we applied temporospatial principal components analysis (PCA) to parse the ERP waveform and isolate the FN from overlapping responses (Foti et al., 2011). One advantage to this approach is that it improves the accuracy of source localization techniques, allowing for a better estimate of potential neural generators of ERP components (Dien, 2010b). In fact, in our data the PCA-derived FN localized to the dorsal striatum (Foti et al., 2011), whereas in previous work using traditional scoring techniques the FN has primarily been localized to the mPFC (i.e., anterior cingulate cortex Gehring and Willoughby, 2002; Miltner et al., 1997; Potts et al., 2006), although others have localized the FN to the dorsal striatum (Martin et al., 2009).

Together, these lines of evidence suggest that activity in both the mPFC and the striatum (dorsal and ventral) may contribute to the FN, but to date there have been no direct comparisons of fMRI and ERP measures of reward-related activity. Data from fMRI and ERP measures reflect distinct physiological processes—changes in cerebral blood flow associated with neuronal activity and synchronized changes in postsynaptic potentials, respectively. Studies have often found linear relationships between fMRI and ERP measures (Logothetis, 2003; Mathalon et al., 2003; Sabatinelli et al., 2007b), which suggests common neural activity across methods, and yet in principle it is also possible for fMRI and ERP measures to be orthogonal to one another within the same experimental task (Nunez and Silberstein, 2000). Here, we explicitly assess the relationship between fMRI (i.e., mPFC and VS) and ERP (i.e., FN) measures of reward sensitivity. In a counterbalanced order, participants completed fMRI and ERP versions of a simple gambling task in which they could win or lose money on each trial (Foti and Hajcak, 2009; Hajcak et al., 2006). We predicted that the *win*>*loss* contrast would yield activation in VS, mPFC, and additional mesocorticolimbic structures (Knutson et al., 2001b) and an enhanced amplitude of the reward-related FN ERP at frontocentral electrode sites (Hajcak et al., 2006). Critically, given that both measure neural reactivity to reward, we expected that *win*>*loss* differences measured by fMRI (i.e., mPFC and VS) and ERP (i.e., FN) would be positively correlated with each other. Furthermore, based on our previous source localization work summarized above (Foti et al., 2011), we hypothesized that a PCA-derived measure of the FN would better correlate with fMRI activity than scores derived from a window measurement.

Methods

Participants

Forty-five (male = 27) consenting adults between the ages of 19 and 25 ($M = 21.11$, $SD = 1.27$) participated in the study. Forty reported being right-handed and five reported being left-handed. Potential participants were screened for metal. Participants were monetarily compensated for their time. The Institutional Review Board of Stony Brook University approved this study. Participants completed fMRI and ERP testing sessions in a counterbalanced order (23 completed the fMRI session first)³. Two participants had poor

quality EEG data, defined as having fewer than 20 artifact-free trials per condition (Marco-Pallares et al., 2011). Grubbs' (1969) test was performed on key study variables to identify outliers; one participant had significantly deviant fMRI VS data ($z = 5.04$, $p < 0.05$). These three participants were excluded from respective subsequent analyses, leaving 42 (25 male) individuals with both ERP and fMRI measures.

Gambling task (fMRI)

The experiment was programmed and run with E-prime (Psychology Software Tools, Pittsburgh, PA). An MRI-compatible 60 Hz projector with a 1024 × 768 resolution, reflected stimuli onto a mirror attached to the head coil. Each trial began with a white fixation cue presented in the center of a black screen (500 ms). Next, a screen displayed two doors side-by-side for 4000 ms. Participants were instructed that behind one of the doors there was a monetary prize (+\$0.50) while behind the other door there was a loss (−\$0.25). Participants used a MRI-compatible response box to make their choice of door. Note, participants were told that if they did not choose while the doors were on the screen, that the computer would choose a door at random. Then, after another brief fixation cue (500 ms), a feedback screen was displayed (1000 ms) where a green '↑' indicated a correct guess, while a red '↓' indicated an incorrect guess. A blank black screen jittered intertrial interval occurred between each trial ($M = 4000$ ms, $Min. = 1500$ ms, $Max = 14000$ ms). The task was 10 min and 5 s in duration and consisted of 60 trials with 30 predetermined wins and losses presented in a pseudorandom order. That is, unknown to participants, left or right door responses did not influence whether or not a trial was a win or loss. Prior to the collection of functional imaging data participants completed two practice trials containing examples of a win and a loss.

Functional image acquisition and analysis

A 3 Tesla Siemens Trio whole body scanner was used to acquire 242 T2*-weighted whole-brain volumes with an EPI sequence sensitive to BOLD signal using the following parameters: TR = 2500 ms, TE = 22 ms, flip angle = 83°, matrix dimensions = 96 × 96, FOV = 224 × 224 mm, slices = 40, slice thickness = 3.5 mm, and gap = 0. Standard preprocessing procedures were performed in SPM8, including image realignment corrections for head movements, slice timing corrections for acquisition order, normalization to standard 2 × 2 × 2 mm Montreal Neurological Institute space, and spatial smoothing with a Gaussian full-width-at-half-maximum 8 mm filter. First-level single subject SPMs were created from a model, which specified the onset of loss (i.e., ↓) and win cues (i.e., ↑).

Gambling task (ERP)

The ERP version of the gambling task was administered using Presentation software (Neurobehavioral Systems, Inc., Albany, California, USA) to control the presentation and timing of all stimuli. The task was designed to proceed in a similar manner to the fMRI version, with the timing of stimuli within each trial as follows: (i) the graphic of two doors was presented until a response was made, (ii) a fixation mark was presented for 1000 ms, (iii) a feedback arrow was presented for 2000 ms, (iv) a fixation mark was presented for 1500 ms, and (v) 'Click for the next round' was presented until a response was made. To familiarize participants with the task, they first completed five practice trials.

ERP data acquisition and analysis

The continuous EEG was recorded using a custom cap (Cortech Solutions, Wilmington, North Carolina, USA) and the ActiveTwo BioSemi system (BioSemi, Amsterdam, Netherlands). The signal was preamplified at the electrode with a gain of 1; the EEG was digitized at

³ Values for all extracted fMRI activations and PCA scores did not differ between the two testing orders (all p 's ≥ 0.30).

24-bit resolution with a sampling rate of 512 Hz using a low-pass fifth order sinc filter with a half-power cutoff of 102.4 Hz. Recordings were taken from 64 scalp electrodes based on the 10/20 system, as well as two electrodes placed on the left and right mastoids. The electrooculogram was recorded from four facial electrodes: two 1 cm above and below the left eye, one 1 cm to the left of the left eye, and one 1 cm to the right of the right eye. Each electrode was measured online with respect to a common mode sense electrode that formed a monopolar channel. Off-line analysis was performed using Brain Vision Analyzer software (Brain Products, Munich, Germany). All data were re-referenced to the average of all scalp electrodes and band-pass filtered with cutoffs of 0.1 and 30 Hz. The EEG was segmented for each trial, beginning 200 ms before feedback onset and continuous for 1000 ms following feedback onset. Each trial was corrected for blinks and eye movements using the method developed by Gratton et al. (1983). Specific channels were rejected in each trial using a semi-automated procedure, with physiological artifacts identified by the following criteria: a step of more than 50 μV between sample points, a difference of 300 μV within a trial, and a maximum difference of less than 0.5 μV within 100-ms intervals. Additional physiological artifacts were identified using visual inspection (1.62% of total ERP data).

Stimulus-locked ERPs were averaged separately for non-rewards (i.e., monetary losses) and rewards (i.e., monetary gains), and the activity in the 200-ms window before feedback onset served as the baseline. The FN was scored with temporospatial principal components analysis (Dien and Frishkoff, 2005) using the ERP PCA (EP) Toolkit, version 1.3 (Dien, 2010a). Following recently published sets of guidelines for applying PCA to ERP datasets (Dien, 2010b; Dien et al., 2005, 2007), a temporal PCA was performed on the data first in order to capture variance across time points. Promax rotation was used, and 11 temporal factors were extracted based on the resulting Scree plot (Cattell, 1966). A separate spatial PCA was performed for each of the 12 temporal factors. Infomax rotation was used, and based on the averaged Scree plot for all 11 temporal factors, four spatial factors were extracted, yielding 44 unique factors combinations. Of these, 17 accounted for at least 0.5% of the total variance and were retained for further analysis; three significantly differentiated between wins and losses (Bonferroni correction: $p < .003$), and we focused our analyses on the one most consistent with the FN. The covariance matrix and Kaiser normalization were used for each PCA. The waveforms for each factor were reconstructed (i.e., converted to microvolts) by multiplying the factor pattern matrix with the standard deviations. Factors of interest were scored using the peak values on non-reward and reward trials. Statistical analysis was performed using SPSS (17.0; SPSS, Inc., Chicago, Illinois, USA).

Source analysis was applied to the temporospatial factor corresponding to the FN. This analysis was conducted by specifying a pair of hemispheric dipoles (the second dipole mirroring position but not orientation) in BESA (Verion 5.1, MEGIS Software GmbH, Gräfelfing, Germany) using an elliptical four-shell model. One disadvantage of dipole modeling is the necessity of setting the number of sources to be fit a priori; however, this is ameliorated by the use of two-step PCA, which decomposes the ERP waveform into unique sources of variance. Indeed, recently published simulation data indicates that PCA significantly improves the accuracy of source localization techniques (Dien, 2010b). The entire epoch was selected for the fitting process because the spatial distribution of two-step PCA factors is invariant across time. A residual variance of no more than 10% was used as the criterion for a good quality solution.

Results

fMRI

A second-level whole brain analysis was performed for the *win vs. loss* *t*-test contrast to assess the brain regions involved in reward

processing. Images were thresholded using a family-wise error (FWE) corrected $\alpha = 0.05$ with an extent threshold of 10 continuous voxels. As expected and can be seen in Figs. 1a–c, this analysis revealed subcortical activations bilaterally in the caudate, amygdala, and VS. In addition, cortical areas in the reward circuit such as the mPFC and OFC (see Figs. 2a–b), which included both medial and lateral orbital frontal areas, were activated for this contrast.⁴ The mPFC region was centered on the border of the ventro-rostral ACC and the medial frontal gyrus. Table 1 provides a detailed statistical description of the above-mentioned activations in addition to other areas revealing rewarded-related activations. No areas were significantly greater for losses compared to wins using a FWE corrected $\alpha = 0.05$.

ERP

The grand average ERP waveforms (prior to PCA) are presented in Fig. 3. The FN was maximal approximately 300 ms following feedback onset at frontocentral recording sites, which is consistent with previous research. Based on visual inspection of the PCA waveforms and the associated spatial distributions, Temporal Factor 7/Spatial Factor 1 was identified as being most consistent with the FN (Fig. 4). This factor had a peak temporal loading of 281 ms following feedback onset, was maximal at frontocentral recording sites, and significantly differentiated rewards from non-rewards ($t(41) = 6.84$, $p < 0.001$). Consistent with a previous application of temporospatial PCA, the factor waveforms indicated that this response was a positivity on reward trials that was reduced on non-reward trials (Foti et al., 2011). To be consistent with the existing FN literature, however, the presented difference waves and scalp distributions (Figs. 3–4) indicate the difference between losses and wins, making the FN appear as a relative negativity at frontocentral sites. Also consistent with the aforementioned study, source localization of the *win vs. loss* contrast identified the dorsal striatum as a likely neural generator, with MNI coordinates of (31, –16, 10) and residual variance of 1.39%, indicating a good quality solution.

fMRI and ERP correlations

Caudate, VS, amygdala, OFC, and mPFC fMRI activity elicited by the *win vs. loss* contrast was extracted (using the “eigenvariate” button in SPM8) from voxels (with an uncorrected $p < 0.001$) within a 6 mm sphere centered on the coordinates reported in Table 1. These regional fMRI activations were then compared to individuals' PCA difference for the *win vs. loss* contrast. PCA values were converted to positive numbers, such that larger numbers indicate a larger difference between monetary losses and gains. As displayed in Fig. 1d, Pearson correlations (one-tailed) revealed the strongest correlation between PCA scores and hemodynamic activity in the right VS ($r = 0.52$, $p < 0.001$), but this relationship was also present in the left VS ($r = 0.28$, $p < 0.05$). Additional positive correlations were observed between PCA scores and fMRI activity in the mPFC ($r = 0.26$, $p < 0.05$; see Fig. 2c), left lateral OFC ($r = 0.28$, $p < 0.05$), amygdala (left: $r = 0.42$, $p < 0.01$ and right: $r = 0.36$, $p < 0.01$), and caudate (left: $r = 0.44$, $p < 0.01$ and right: $r = 0.37$, $p < 0.01$). On the other hand, fMRI activation in the medial OFC was not correlated with PCA scores ($r = 0.15$, $p > 0.1$). Furthermore, *win vs. loss* elicited activation in motor (medial: $r = 0.07$, $p > 0.1$ and lateral: $r = 0.18$, $p > 0.1$) and visual cortices ($r = 0.17$, $p > 0.1$) were not correlated with PCA scores. Thus, we found that the PCA-derived FN factor was positively correlated

⁴ Consistent with circuit- or system-level processing, reward related activations in the bilateral VS, caudate, amygdala, mPFC, and left OFC were all correlated with each other (r 's ranging between 0.20 and 0.74). The highest correlation occurred between the right VS and caudate ($r = 0.74$, $p < 0.001$) and the lowest correlation was between the left VS and the mPFC ($r = 0.20$, $p = 0.10$).

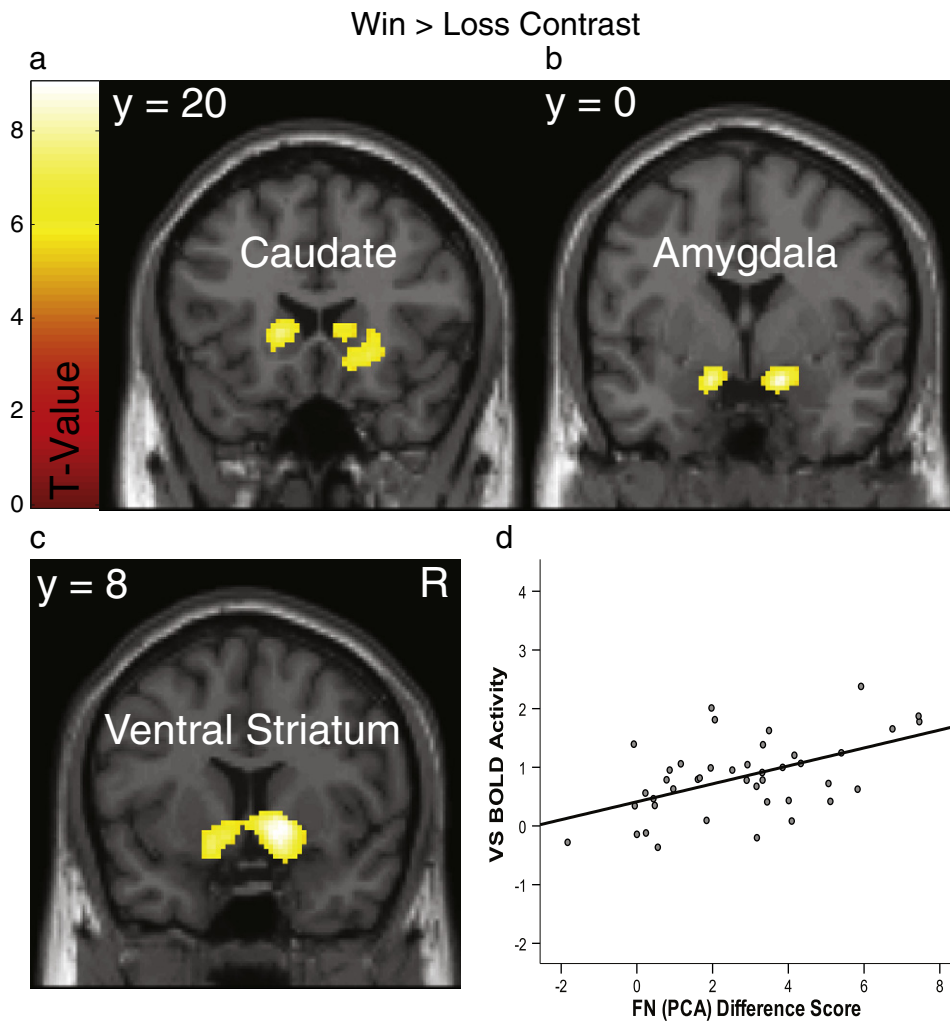


Fig. 1. Greater activation was observed for monetary wins compared to losses bilaterally in the a) caudate (left), b) amygdala (right), and c) ventral striatum. d) Scatterplot depicting the relationship between the FN and BOLD responses in the right ventral striatum. Activation displayed at $p < 0.05$ FWE-corrected.

with fMRI activation across the entire reward circuit, but was not correlated with activation in motor and visual cortical regions.

For comparison, we also scored the FN using a traditional window measurement, rather than PCA, taking the average activity at FCz from

250 to 350 ms. Correlating this window measurement with the same fMRI variables, all of the associations were in the same direction as with the PCA variable, but they were uniformly weaker; with only significant correlations in the right hemisphere VS ($r = 0.34$, $p < 0.05$),

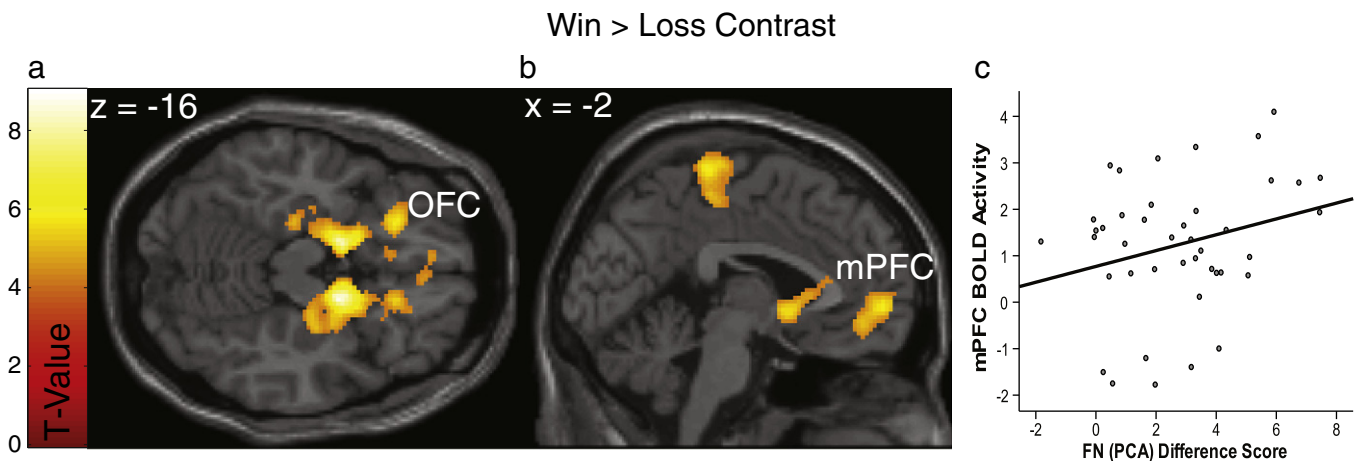


Fig. 2. The a) left orbital frontal cortex and b) medial prefrontal cortex were activated in response to monetary wins compared to losses. c) Scatterplot depicting the relationship between the FN and BOLD responses in the medial prefrontal cortex. Activation displayed at $p < 0.0001$ uncorrected.

Table 1
Reward vs. Loss Related Activations.

Region	Hemisphere	MNI Coordinates			Voxels	t value
		x	y	z		
<i>Subcortical Structures*</i>						
Ventral Striatum	L	-14	10	-8	1386	7.19
	R	10	6	-4	1386	9.01
Caudate (Head)	L	-16	20	2	1386	7.64
	R	12	20	4	1386	6.15
Amygdala	L	-14	0	-16	1386	8.02
	R	16	0	-16	1386	8.52
<i>Frontal Regions</i>						
Orbital Frontal Cortex (lateral)	L	-26	30	-12	32	6.16
OFC (medial)	L-R	2	26	-24	10	6.94
Medial Prefrontal Cortex (ventral)	L	-6	48	-8	18	5.88
mPFC (dorsal)	L	-2	56	0	18	5.80
Superior Frontal Gyrus	L	-18	32	54	81	6.80
	R	26	36	48	26	6.63
Motor Cortex (lateral)	L	50	-8	36	51	6.28
MC (medial)	L-R	16	-22	72	200	6.29
<i>Posterior Regions</i>						
Visual Cortex	L	-42	-56	0	13	6.10

Reported activations were significant at $p < 0.05$ family-wise error corrected.

* A single cluster of activation extended into multiple subcortical regions.

amygdala ($r = 0.30, p < 0.05$), and caudate ($r = 0.28, p < 0.05$). Collectively, these data suggest that PCA-derived factor scores correlate better than traditional scoring approaches with reward-related neural activity measured with fMRI.

Although source analysis applied directly to the PCA waveform identified the dorsal striatum as a likely neural generator, this region did not overlap with the dorsal or ventral striatal regions showing significant BOLD activation. Given that accurate source localization is challenged by the nature of the “inverse problem,” we utilized the fMRI data to solve the “forward problem” to assess how well these localized activations explain the scalp distribution of the FN. In particular we focused on the right VS (the maximally activated region from the fMRI analysis and most strongly correlated with the FN) as a neural generator of the FN. A subsequent source analysis was conducted fixing the dipole locations at the bilateral VS coordinates and leaving the orientations free to vary. The residual variance was 2.32%, indicating a good quality solution. Additional dipoles were then added at the coordinates of the remaining thirteen regions, including those that did and did not show significant associations between BOLD response and FN amplitude. The residual variance with these 15 dipoles was 0.78%. The source waveforms from this analysis provide an indication of the relative contribution of each dipole to the

observed scalp potential; the peak values of these waveforms are presented in Fig. 5. The right VS dipole had the largest single contribution, followed by the dipole in the right caudate. The remaining dipoles had relatively smaller contributions.

Discussion

To the best of our knowledge, we provide the first evidence combining fMRI and ERP measures of reward processing indicating that these measures are positively correlated with each other. Consistent with prior work in reward processing, we found that mesocorticolimbic DA structures including the VS, caudate, amygdala, mPFC, and OFC were activated during fMRI acquisition in response to monetary gains compared to losses (Elliott et al., 2003; Knutson et al., 2001a, 2001b; Kringelbach et al., 2003). Consistent with previous ERP research the FN was more positive following gains than losses approximately 250–350 ms post feedback (Gehring and Willoughby, 2002; Miltner et al., 1997) and the single best estimate of this differentiation is in the dorsal striatum (Foti et al., 2011). When fMRI activations were used to guide source estimation, however, a VS source was complemented by additional FN sources, including the caudate and mPFC. Therefore, our results support two parallel lines of

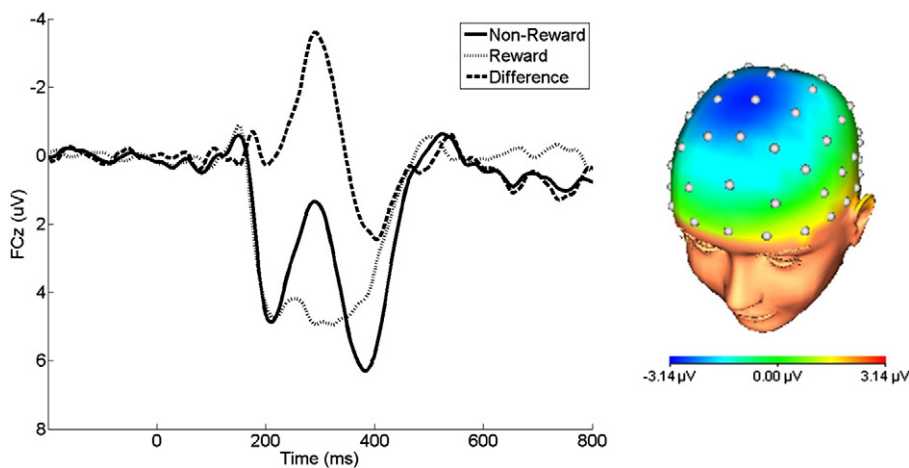


Fig. 3. Left: ERP waveforms at electrode FCz for non-rewards, rewards, and the difference (non-reward minus reward). Right: Scalp distribution of the difference between non-rewards and rewards from 275 to 325 ms.

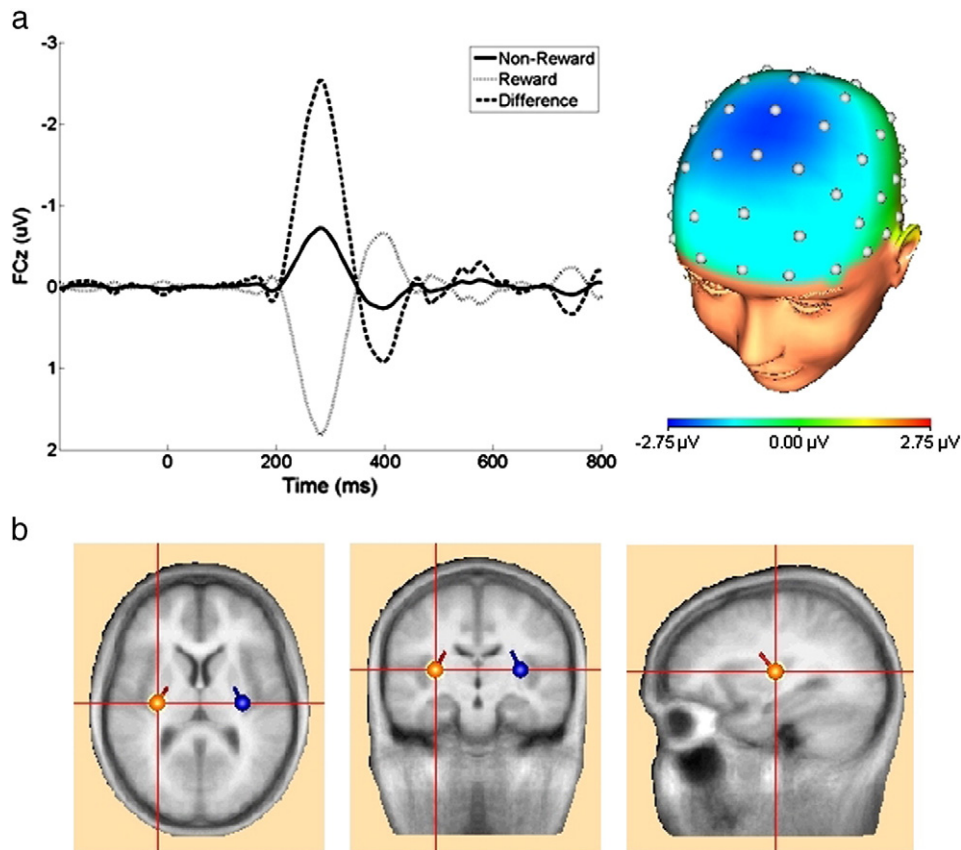


Fig. 4. a) PCA waveforms at electrode FCz for non-rewards, rewards, and the difference (non-reward minus reward). b) Location and orientation of the source solution for temporal factor 7/spatial factor 1.

research on reward processing—and provide an empirical link between these methods by demonstrating across individuals that the FN is correlated with VS, caudate, amygdala, mPFC, and OFC response to rewards.

Linking fMRI and ERP research together is important for the field of human neuroscience because these two methodologies have com-

plementary strengths and weaknesses in terms of spatial and temporal resolution, respectively. Although fMRI (blood oxygen) and ERP (postsynaptic potentials) measure distinct physiological processes with time scales differing on an order of magnitude, our results are suggestive of common underlying neural activity for both fMRI and ERP measures of reward. Initial research (Logothetis, 2003)

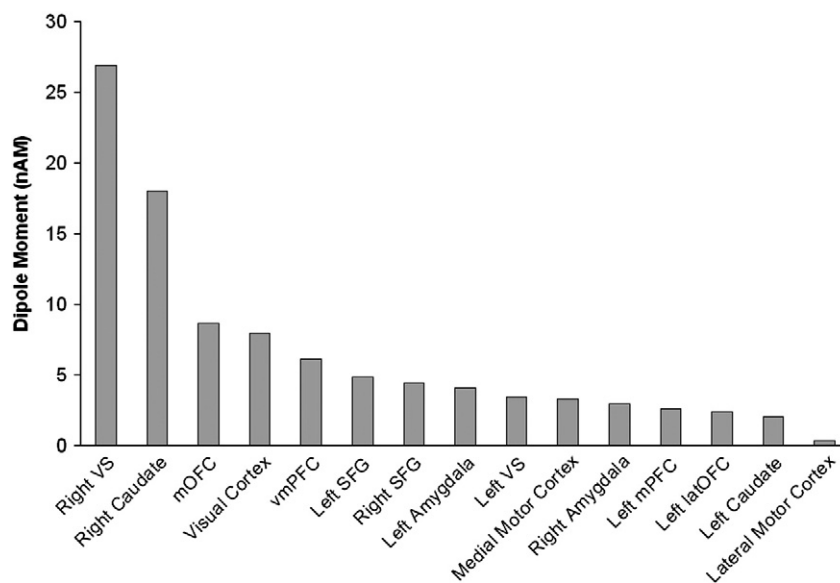


Fig. 5. Peak values of the source waveforms resulting from source analysis fitting fifteen simultaneous dipoles. The dipole locations were fixed at the coordinates of the regions showing significant BOLD activation.

on the mechanisms underlying of the BOLD response has shown a high coherence between neural activity and the BOLD signal (with a 6–12 s lag between neural activation and the peak BOLD response). Importantly, this coherence is strongest for neuronal local field potentials compared to single cell spiking, indicating that, similar to EEG/ERP, BOLD fMRI is primarily reflective of regional neural activity (Logothetis, 2003). In the current study, right VS activity was best correlated with the FN, which suggests that the rapid 280 ms electrocortical response (FN) may be reflective of the actual timescale in which VS neurons are differentially responsive to reward vs. non-reward outcomes. However, further research is necessary to determine this level of specificity. Nevertheless, it appears that common or related neural activity is underlying reward circuit BOLD activity and FN amplitude modulation.

To the best of our knowledge, only one previous reward processing study has collected both ERP and fMRI data within a single sample (Martin et al., 2009). This prior work utilized reward-related fMRI activations in the ACC to drive ERP source localization, but did not directly compare these measures. Here we expand on this prior work by demonstrating positive correlations between the FN and a number of regions in the reward circuit including the VS, caudate, amygdala, mPFC/ACC, OFC. By directly relating these two measures, the current data demonstrates the presence of a linear relationship between reward-related neural activity across neuroimaging methods, and that this relationship is more apparent when the ERP waveform is parsed using temporospatial PCA than traditional scoring methods (e.g., average activity in a time window). Thus, the current data suggests that ERP and fMRI measures of reward processing are positively correlated across the reward circuit and that temporospatial PCA improves this association relative to traditional difference scores.

The observed association between fMRI activation in the mesocorticolimbic DA circuit and the FN ERP component builds upon indirect evidence provided by prior research. In particular, source localization techniques have identified either the mPFC/ACC (Gehring and Willoughby, 2002; Miltner et al., 1997; Potts et al., 2006) or the dorsal striatum (Foti et al., 2011; Martin et al., 2009) as likely neural generators of the FN. It has been suggested that FN amplitude is related to phasic changes in dopaminergic signals in the ACC (Holroyd and Coles, 2002; Holroyd et al., 2004b). From this perspective, outcomes that are worse than expected elicit phasic decreases in dopaminergic input from the ventral tegmental area that disinhibit ACC neurons—that is, greater neural activity to monetary losses than gains. Functional MRI data, however, suggests the opposite pattern for the mPFC/ACC, which are more active in response to gains compared to losses (Fujiwara et al., 2009; Rogers et al., 2004) and to pleasant compared to unpleasant images (Sabatinelli et al., 2007a). While the current data are consistent with the possibility that mPFC activation contributes to the scalp-recorded FN, they suggest that the directionality of the effect may be in the opposite direction, reflecting increased activity to rewards. In addition, the current data are consistent with a previous report in which we applied source localization techniques in conjunction with temporospatial PCA and localized the FN to the dorsal striatum, suggesting that reward-related activity in the dorsal striatum may also contribute directly to the observed scalp potential (Foti et al., 2011). This latter finding is noteworthy in light of neuroimaging evidence that, like modulation of the FN, striatal activation is sensitive to outcome valence, but not magnitude (Elliott et al., 2003), and that it is sensitive to violations of reward predictions (McClure et al., 2004; O'Doherty et al., 2003). Traditionally, subcortical regions have not been considered as likely generators of scalp-recorded ERPs, although this perspective has been challenged (Rektor, 2002; Sander et al., 2010). In particular, a recent simulation study using a whole-brain anatomical model concluded that activity in subcortical regions, including the

striatum, creates distinct field potentials at the scalp that can be detected and differentiated from cortical activity with relatively few experimental trials (Attal et al., 2009). Linking these two perspectives on the FN, the current study indicates that *both* striatal (ventral and dorsal) and mPFC activation may contribute to the scalp-recorded FN and are more active in response to rewards.

As mentioned in the Introduction, the structures of the mesocorticolimbic reward circuit are thought to mediate different aspects of reward processing such as reward anticipation (VS; Knutson et al., 2001a) and hedonic feeling states (OFC; Kringelbach et al., 2003). Here we used a simple active (response-based) gambling task with unpredictable win and loss outcomes to elicit brain activations generally associated with reward processing (Foti and Hajcak, 2009; Hajcak et al., 2006). An earlier passive (no response) reward prediction study compared ERP and fMRI measures and revealed mPFC/ACC activation to reward (Martin et al., 2009), while we identified a more distributed reward network including the mPFC/ACC, VS, caudate, OFC, and amygdala in addition to areas of motor cortex. A passive reward prediction task was also used in a recent ERP study that quantified the FN using two-step PCA and found effects of both outcome valence and expectation (Potts et al., 2011). They identified a reward-related positivity at central sites, similar to the PCA factor identified here, as well as a concurrent frontal response and an earlier posterior response that were sensitive to unpredicted losses. These differences in neural reactivity may be due to differences in experimental design (i.e., active and unpredictable vs. passive and predictable). It will be important for future research to further implement tasks specifically and systematically designed to assess the unique subcomponents of reward processing to better understand how fMRI and ERP measures of these processes are related. For example, studies have disassociated neural activation that is specific to reward anticipation in the VS from the neural activation elicited upon reward attainment in the mPFC (Knutson et al., 2001b). Furthermore, VS activation during expected monetary gain predicts future “risky” financial decisions, whereas insula activation in anticipation of aversion is associated with future “safe” decisions (Knutson and Bossaerts, 2007) and tracks one's general feeling state of worry (Carlson et al., 2011). Further combined fMRI and ERP research is needed to more fully understand the anatomical and temporal characteristics of this complex process and how these characteristics are associated with future behavior(s) and subjective feeling states.

Understanding the characteristics of mesocorticolimbic reward circuit is not only important for determining its role in affective and mood processing within the healthy population, but also for understanding abnormalities associated with a number of psychopathologies including addiction (see Nestler, 2005 for review), schizophrenia (e.g., Juckel et al., 2006; Simon et al., 2010; Wacker et al., 2009), and depression (reviewed by Fitzgerald et al., 2008; Martin-Soelch, 2009; Nestler and Carlezon, 2006). In the case of depression, behavioral findings (Pizzagalli et al., 2008), fMRI VS activation in adults (Epstein et al., 2006; Fitzgerald et al., 2008; Pizzagalli et al., 2009; but see Knutson et al., 2008 for alternative results) and children (Forbes et al., 2009, 2010), and FN ERP work (Foti and Hajcak, 2009, 2010) support the notion that depression is associated with reduced sensitivity to reward. In particular, a blunted VS response in depression is specifically correlated with anhedonia (Keedwell et al., 2005; Wacker et al., 2009) and deep brain stimulation of the VS attenuates anhedonic symptoms (Schlaepfer et al., 2008). Given that the FN is correlated with VS activation and the relatively inexpensive costs associated with ERP acquisition, it may be possible to use the FN to objectively quantify reward circuit sensitivity, which could be a useful screening measure for psychopathologies associated with abnormal reward processing. However, further research is needed to determine the

clinical efficacy of the FN as a potential marker for reward-related psychopathologies.

In conclusion, our results support prior fMRI research implicating the VS, caudate, amygdala, mPFC, and OFC amygdala in reward processing (Elliott et al., 2003; Knutson et al., 2001a, 2001b; Kringelbach et al., 2003) and link this activity to ERP work on the FN, a relative positivity in the ERP following gain compared to loss feedback (Gehring and Willoughby, 2002; Miltner et al., 1997). Importantly, we found that fMRI and ERP measures of monetary reward processing were positively correlated with each other in a single sample, which suggests that these two neuroimaging methods are measuring shared underlying neural reactivity to reward. Given that various psychopathologies have been associated with abnormal reward processing, the FN may potentially be used as a relatively inexpensive measure to assess pathological reward processing. However, future clinical research is needed to assess the potential of the FN as a screening measure and further basic research is needed to link fMRI and ERP measures for more specific aspects of reward processing, such as reward expectation vs. attainment and associated hedonic feeling states.

Acknowledgments

This research was supported by National Science Foundation grants BCS 0643348 and BCS 0921565 awarded to Eddie Harmon-Jones and Office of Naval Research grant #N0014-04-1-005 awarded to Lilianne Mujica-Parodi.

References

- Attal, Y., Bhattacharjee, M., Yelnik, J., Cottareau, B., Lefevre, J., Okada, Y., Bardinet, E., Chupin, M., Baillet, S., 2009. Modelling and detecting deep brain activity with MEG and EEG. *Irmb* 30, 133–138.
- Breiter, H.C., Gollub, R.L., Weisskoff, R.M., Kennedy, D.N., Makris, N., Berke, J.D., Goodman, J.M., Kantor, H.L., Gastfriend, D.R., Riorden, J.P., Mathew, R.T., Rosen, B.R., Hyman, S.E., 1997. Acute effects of cocaine on human brain activity and emotion. *Neuron* 19, 591–611.
- Carlson, J.M., Greenberg, T., Rubin, D., Mujica-Parodi, L.R., 2011. Feeling anxious: anticipatory amygdala-insular response predicts the feeling of anxious anticipation. *Soc. Cogn. Affect. Neurosci.* 6, 74–81.
- Cattell, R.B., 1966. The scree test for the number of factors. *Multivar. Behav. Res.* 1, 245–276.
- Courchesne, E., Hillyard, S.A., Courchesne, R.Y., 1977. P3 waves to the discrimination of targets in homogeneous and heterogeneous stimulus sequences. *Psychophysiology* 14, 590–597.
- Dien, J., 2010a. Evaluating two-step PCA of ERP data with Geomin, Infomax, Oblimin, Promax, and Varimax rotations. *Psychophysiology* 47, 170–183.
- Dien, J., 2010b. The ERP PCA Toolkit: an open source program for advanced statistical analysis of event-related potential data. *J. Neurosci. Methods* 187, 138–145.
- Dien, J., Frishkoff, G., 2005. Principal components analysis of event-related potential datasets. In: Handy, T.C. (Ed.), *Event-related Potentials: A Methods Handbook*. The MIT Press, Cambridge, MA, pp. 189–208.
- Dien, J., Beal, D.J., Berg, P., 2005. Optimizing principal components analysis of event-related potentials: matrix type, factor loading weighting, extraction, and rotations. *Clin. Neurophysiol.* 116, 1808–1825.
- Dien, J., Kloe, W., Mangun, G.R., 2007. Evaluation of PCA and ICA of simulated ERPs: Promax vs. Infomax rotations. *Hum. Brain Mapp.* 28, 742–763.
- Drevets, W.C., Gautier, C., Price, J.C., Kupfer, D.J., Kinahan, P.E., Grace, A.A., Price, J.L., Mathis, C.A., 2001. Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biol. Psychiatry* 49, 81–96.
- Duncan-Johnson, C.C., Donchin, E., 1977. On quantifying surprise: the variation of event-related potentials with subjective probability. *Psychophysiology* 14, 456–467.
- Elliott, R., Newman, J.L., Longe, O.A., Deakin, J.F., 2003. Differential response patterns in the striatum and orbitofrontal cortex to financial reward in humans: a parametric functional magnetic resonance imaging study. *J. Neurosci.* 23, 303–307.
- Epstein, J., Pan, H., Kocsis, J.H., Yang, Y., Butler, T., Chusid, J., Hochberg, H., Murrough, J., Strohmayer, E., Stern, E., Silbersweig, D.A., 2006. Lack of ventral striatal response to positive stimuli in depressed versus normal subjects. *Am. J. Psychiatry* 163, 1784–1790.
- Fitzgerald, P.B., Laird, A.R., Maller, J., Daskalakis, Z.J., 2008. A meta-analytic study of changes in brain activation in depression. *Hum. Brain Mapp.* 29, 683–695.
- Forbes, E.E., Hariri, A.R., Martin, S.L., Silk, J.S., Moyses, D.L., Fisher, P.M., Brown, S.M., Ryan, N.D., Birmaher, B., Axelson, D.A., Dahl, R.E., 2009. Altered striatal activation predicting real-world positive affect in adolescent major depressive disorder. *Am. J. Psychiatry* 166, 64–73.
- Forbes, E.E., Olino, T.M., Ryan, N.D., Birmaher, B., Axelson, D., Moyses, D.L., Dahl, R.E., 2010. Reward-related brain function as a predictor of treatment response in adolescents with major depressive disorder. *Cogn. Affect. Behav. Neurosci.* 10, 107–118.
- Foti, D., Hajcak, G., 2009. Depression and reduced sensitivity to non-rewards versus rewards: evidence from event-related potentials. *Biol. Psychol.* 81, 1–8.
- Foti, D., Hajcak, G., 2010. State sadness reduces neural sensitivity to nonrewards versus rewards. *Neuroreport* 21, 143–147.
- Foti, D., Weinberg, A., Dien, J., Hajcak, G., 2011. Event-related potential activity in the basal ganglia differentiates rewards from non-rewards: temporospatial principal components analysis and source localization of the Feedback Negativity. *Human Brain Mapping* doi:10.1002/hbm.21182.
- Fujiwara, J., Tobler, P.N., Taira, M., Iijima, T., Tsutsui, K., 2009. Segregated and integrated coding of reward and punishment in the cingulate cortex. *J. Neurophysiol.* 101, 3284–3293.
- Gehring, W.J., Willoughby, A.R., 2002. The medial frontal cortex and the rapid processing of monetary gains and losses. *Science* 295, 2279–2282.
- Gratton, G., Coles, M.G., Donchin, E., 1983. A new method for off-line removal of ocular artifact. *Electroencephalogr. Clin. Neurophysiol.* 55, 468–484.
- Grubbs, F., 1969. Procedures for detecting outlying observations in samples. *Technometrics* 11, 1–21.
- Hajcak, G., Moser, J.S., Holroyd, C.B., Simons, R.F., 2006. The feedback-related negativity reflects the binary evaluation of good versus bad outcomes. *Biol. Psychol.* 71, 148–154.
- Hajcak, G., Moser, J.S., Holroyd, C.B., Simons, R.F., 2007. It's worse than you thought: the feedback negativity and violations of reward prediction in gambling tasks. *Psychophysiology* 44, 905–912.
- Holroyd, C.B., Coles, M.G., 2002. The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychol. Rev.* 109, 679–709.
- Holroyd, C.B., Nieuwenhuis, S., Yeung, N., Cohen, J.D., 2003. Errors in reward prediction are reflected in the event-related brain potential. *Neuroreport* 14, 2481–2484.
- Holroyd, C.B., Larsen, J.T., Cohen, J.D., 2004a. Context dependence of the event-related brain potential associated with reward and punishment. *Psychophysiology* 41, 245–253.
- Holroyd, C.B., Nieuwenhuis, S., Yeung, N., Nystrom, L., Mars, R.B., Coles, M.G., Cohen, J.D., 2004b. Dorsal anterior cingulate cortex shows fMRI response to internal and external error signals. *Nat. Neurosci.* 7, 497–498.
- Holroyd, C.B., Hajcak, G., Larsen, J.T., 2006. The good, the bad and the neutral: electrophysiological responses to feedback stimuli. *Brain Res.* 1105, 93–101.
- Holroyd, C.B., Pakzad-Vaezi, K.L., Krigolson, O.E., 2008. The feedback correct-related positivity: sensitivity of event-related brain potential to unexpected positive feedback. *Psychophysiology* 45, 688–697.
- Juckel, G., Schlagenhauf, F., Koslowski, M., Wustenberg, T., Villringer, A., Knutson, B., Wrase, J., Heinz, A., 2006. Dysfunction of ventral striatal reward prediction in schizophrenia. *Neuroimage* 29, 409–416.
- Keedwell, P.A., Andrew, C., Williams, S.C., Brammer, M.J., Phillips, M.L., 2005. The neural correlates of anhedonia in major depressive disorder. *Biol. Psychiatry* 58, 843–853.
- Knutson, B., Bossaerts, P., 2007. Neural antecedents of financial decisions. *J. Neurosci.* 27, 8174–8177.
- Knutson, B., Fong, G.W., Adams, C.M., Varner, J.L., Hommer, D., 2001a. Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport* 12, 3683–3687.
- Knutson, B., Adams, C.M., Fong, G.W., Hommer, D., 2001b. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J. Neurosci.* 21, RC159.
- Knutson, B., Bhanji, J.P., Cooney, R.E., Atlas, L.Y., Gotlib, I.H., 2008. Neural responses to monetary incentives in major depression. *Biol. Psychiatry* 63, 686–692.
- Kringelbach, M.L., 2005. The human orbitofrontal cortex: linking reward to hedonic experience. *Nat. Rev. Neurosci.* 6, 691–702.
- Kringelbach, M.L., O'Doherty, J., Rolls, E.T., Andrews, C., 2003. Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. *Cereb. Cortex* 13, 1064–1071.
- Logothetis, N.K., 2003. The underpinnings of the BOLD functional magnetic resonance imaging signal. *J. Neurosci.* 23, 3963–3971.
- Marco-Pallares, J., Cudeirell, D., Munte, T.F., Strien, N., Rodriguez-Fornells, A., 2011. On the number of trials needed for a stable feedback-related negativity. *Psychophysiology* 48, 852–860.
- Martin, L.E., Potts, G.F., Burton, P.C., Montague, P.R., 2009. Electrophysiological and hemodynamic responses to reward prediction violation. *Neuroreport* 20, 1140–1143.
- Martin-Soelch, C., 2009. Is depression associated with dysfunction of the central reward system? *Biochem. Soc. Trans.* 37, 313–317.
- Mathalon, D.H., Whitfield, S.L., Ford, J.M., 2003. Anatomy of an error: ERP and fMRI. *Biol. Psychol.* 64, 119–141.
- McClure, S.M., York, M.K., Montague, P.R., 2004. The neural substrates of reward processing in humans: the modern role of fMRI. *Neuroscientist* 10, 260–268.
- Miltner, W.H.R., Braun, C.H., Coles, M.G.H., 1997. Event-related brain potentials following incorrect feedback in a time-estimation task: evidence for a generic neural system for error detection. *J. Cogn. Neurosci.* 9, 788–798.
- Nestler, E.J., 2005. Is there a common molecular pathway for addiction? *Nat. Neurosci.* 8, 1445–1449.
- Nestler, E.J., Carlezon Jr., W.A., 2006. The mesolimbic dopamine reward circuit in depression. *Biol. Psychiatry* 59, 1151–1159.
- Nunez, P.L., Silberstein, R.B., 2000. On the relationship of synaptic activity to macroscopic measurements: does co-registration of EEG with fMRI make sense? *Brain Topogr.* 13, 79–96.
- O'Doherty, J.P., Deichmann, R., Critchley, H.D., Dolan, R.J., 2002. Neural responses during anticipation of a primary taste reward. *Neuron* 33, 815–826.

- O'Doherty, J.P., Dayan, P., Friston, K., Critchley, H., Dolan, R.J., 2003. Temporal difference models and reward-related learning in the human brain. *Neuron* 38, 329–337.
- Pizzagalli, D.A., Iosifescu, D., Hallett, L.A., Ratner, K.G., Fava, M., 2008. Reduced hedonic capacity in major depressive disorder: evidence from a probabilistic reward task. *J. Psychiatr. Res.* 43, 76–87.
- Pizzagalli, D.A., Holmes, A.J., Dillon, D.G., Goetz, E.L., Birk, J.L., Bogdan, R., Dougherty, D.D., Iosifescu, D.V., Rauch, S.L., Fava, M., 2009. Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *Am. J. Psychiatry* 166, 702–710.
- Potts, G.F., Martin, L.E., Burton, P., Montague, P.R., 2006. When things are better or worse than expected: the medial frontal cortex and the allocation of processing resources. *J. Cogn. Neurosci.* 18, 1112–1119.
- Potts, G.F., Martin, L.E., Kamp, S.M., Donchin, E., 2011. Neural response to action and reward prediction errors: comparing the error-related negativity to behavioral errors and the feedback-related negativity to reward prediction violations. *Psychophysiology* 48, 218–228.
- Rektor, I., 2002. Scalp-recorded Bereitschaftspotential is the result of the activity of cortical and subcortical generators—a hypothesis. *Clin. Neurophysiol.* 113, 1998–2005.
- Rogers, R.D., Ramnani, N., Mackay, C., Wilson, J.L., Jezzard, P., Carter, C.S., Smith, S.M., 2004. Distinct portions of anterior cingulate cortex and medial prefrontal cortex are activated by reward processing in separable phases of decision-making cognition. *Biol. Psychiatry* 55, 594–602.
- Sabatinelli, D., Bradley, M.M., Lang, P.J., Costa, V.D., Versace, F., 2007a. Pleasure rather than salience activates human nucleus accumbens and medial prefrontal cortex. *J. Neurophysiol.* 98, 1374–1379.
- Sabatinelli, D., Lang, P.J., Keil, A., Bradley, M.M., 2007b. Emotional perception: correlation of functional MRI and event-related potentials. *Cereb. Cortex* 17, 1085–1091.
- Sander, T.H., Knosche, T.R., Schlogl, A., Kohl, F., Wolters, C.H., Haueisen, J., Trahms, L., 2010. Recent advances in modeling and analysis of bioelectric and biomagnetic sources. *Biomed. Tech. (Berl)* 55, 65–76.
- Sato, A., Yasuda, A., Ohira, H., Miyawaki, K., Nishikawa, M., Kumano, H., Kuboki, T., 2005. Effects of value and reward magnitude on feedback negativity and P300. *Neuroreport* 16, 407–411.
- Schlaepfer, T.E., Cohen, M.X., Frick, C., Kosel, M., Brodessa, D., Axmacher, N., Joe, A.Y., Kreft, M., Lenartz, D., Sturm, V., 2008. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology* 33, 368–377.
- Senior, C., 2003. Beauty in the brain of the beholder. *Neuron* 38, 525–528.
- Simon, J.J., Biller, A., Walther, S., Roesch-Ely, D., Stippich, C., Weisbrod, M., Kaiser, S., 2010. Neural correlates of reward processing in schizophrenia—relationship to apathy and depression. *Schizophr. Res.* 118, 154–161.
- Tricomi, E.M., Delgado, M.R., Fiez, J.A., 2004. Modulation of caudate activity by action contingency. *Neuron* 41, 281–292.
- Wacker, J., Dillon, D.G., Pizzagalli, D.A., 2009. The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. *Neuroimage* 46, 327–337.
- Walter, M., Bempohl, F., Mouras, H., Schiltz, K., Tempelmann, C., Rotte, M., Heinze, H.J., Bogerts, B., Northoff, G., 2008. Distinguishing specific sexual and general emotional effects in fMRI-subcortical and cortical arousal during erotic picture viewing. *Neuroimage* 40, 1482–1494.
- Yeung, N., Sanfey, A.G., 2004. Independent coding of reward magnitude and valence in the human brain. *J. Neurosci.* 24, 6258–6264.
- Zink, C.F., Pagnoni, G., Martin-Skurski, M.E., Chappelow, J.C., Berns, G.S., 2004. Human striatal responses to monetary reward depend on saliency. *Neuron* 42, 509–517.
- Zink, C.F., Tong, Y., Chen, Q., Bassett, D.S., Stein, J.L., Meyer-Lindenberg, A., 2008. Know your place: neural processing of social hierarchy in humans. *Neuron* 58, 273–283.