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Anterior cingulate activity to monetary loss and basal ganglia activity to monetary gain uniquely contribute to the feedback negativity

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Abstract

Objective—The feedback negativity (FN) is an event-related potential that differentiates unfavorable versus favorable outcomes. Although thought to reflect error-related activity within the anterior cingulate cortex, recent work indicates the FN may also reflect reward-related activity that has been linked to the basal ganglia. To date, it remains unclear how to reconcile these conflicting perspectives.

Methods—We decomposed the FN by applying time-frequency analysis to isolate activity unique to monetary losses and gains. The FN was recorded from 84 individuals during a laboratory gambling task.

Results—Two signals contributed to the FN elicited by unpredictable outcomes: theta activity (4-7 Hz) was increased following monetary loss, and delta activity (< 3 Hz) was increased following monetary gain. Predictable outcomes elicited delta but not theta activity. Source analysis revealed distinct generators, with loss-related theta localized to the anterior cingulate cortex and gain-related delta to a possible source in the striatum. Symptoms of depression, anxiety, and stress reactivity were specifically associated with blunted gain-related delta.

Conclusions—The FN may be a composite of loss- and gain-related neural activity, reflecting distinct facets of reward processing.

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[3]For comparison, we also correlated the filtered time-domain waveforms used for source analysis with their analogous time-frequency factor scores. The loss vs. gain comparisons were strongly related (delta: r = .47, p<.001; theta: r = .75, p<.001), and related to internalizing symptoms in a similar manner: General psychological distress was inversely related to delta (r =-.25, p<.05) but not theta activity (p=.12).

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Significance—Gain-related delta activity may provide unique information about reward dysfunction in major depression and other internalizing psychopathology.

Keywords

ERP; feedback negativity; reward; ACC; striatum; depression

Introduction

Decision-making is guided by feedback about the consequences of our actions: favorable outcomes suggest a course of action to be pursued, whereas unfavorable outcomes indicate the need for adjustments. Event-related potential (ERP) studies of feedback processing have focused on the feedback negativity (FN), an early component that differentiates unfavorable outcomes (i.e., errors, monetary loss) compared to favorable outcomes (i.e., correct responses, monetary gain) (i.e., correct responses, monetary gain; Gehring and Willoughby, 2002; Miltner et al., 1997). The differentiation in FN amplitude between favorable and unfavorable outcomes peaks at approximately 300 ms and at frontocentral electrodes, and source localization techniques have identified a likely neural generator in the anterior cingulate cortex (ACC; Gehring and Willoughby, 2002; Miltner et al., 1997; Potts et al., 2006; Ruchsow et al., 2002); converging evidence of an ACC source is also found from simultaneous ERP and functional magnetic resonance imaging (fMRI) recordings (Hauser et al., 2014). The FN has been discussed in terms of reinforcement learning, such that variation in FN amplitude reflects phasic changes in mesencephalic dopamine signals to the ACC when outcomes are better or worse than expected (Holroyd and Coles, 2002). Consistent with this perspective, FN amplitude is increased for unpredicted compared to predicted outcomes (Hajcak et al., 2007; Holroyd et al., 2003).

Critically, the FN has often been interpreted as an ERP response specifically elicited by monetary loss and error feedback, thereby reflecting a process which tracks the occurrence of unfavorable outcomes (Heldmann et al., 2008; Holroyd and Coles, 2002; Holroyd et al., 2003). That is, the FN has typically been viewed as a negative deflection in the ERP waveform that is increased for monetary loss and is either reduced or absent for monetary gain. Recent work, however, converges upon the opposite viewpoint: variation in FN amplitude may instead be largely driven by neural activity on gain trials. In particular, it has been suggested that both monetary gain and loss feedback elicit a common N2, and monetary gain feedback also elicits a distinct positive-going deflection (Baker and Holroyd, 2011; Holroyd et al., 2011; Holroyd et al., 2008). Functionally, the N2 is thought to index the conflict associated with unpredicted outcomes rather than valence per se, whereas the reward positivity reflects dopaminergic signals to positive outcomes (Baker and Holroyd, 2011). Because these components typically have extensive temporal and spatial overlap, they both contribute to observed FN amplitude and are difficult to distinguish using traditional time-domain ERP analysis.

Complementing these data, several studies have shown that when the FN is scored using temporospatial principal components analysis (PCA), it is isolated as an absolute positivity that is increased for gains compared to losses (Carlson et al., 2011; Foti and Hajcak, 2009;

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Foti et al., 2011b)—in accordance with the reward positivity identified by Baker and Holroyd (2011). The advantage of applying PCA in this manner is that it maximizes the separation between the FN and other overlapping ERP components, particularly the P300. In contrast to previous work attributing the FN to activity in the ACC, source localization of this PCA-derived reward response has revealed a possible source in the striatum (Foti et al., 2011b), a part of the core neural network involved in reward processing (Liu et al., 2011). In a follow-up study utilizing both ERPs and fMRI recorded in separate sessions, FN amplitude correlated directly with the gain-related hemodynamic response in the striatum, orbitofrontal cortex, and medial prefrontal cortex (Carlson et al., 2011); FN amplitude also correlated with midbrain gray matter volume, an association which was mediated by functional activity in the striatum (Carlson et al., 2014). Further, a recent study using simultaneous ERP and fMRI recordings observed that trial-by-trial variation in FN amplitude was associated with BOLD signal within the striatum, cingulate, and medial prefrontal cortex—and that this association with reward circuit activity was specific to gain trials (Becker et al., 2014).

Reframing the FN as a response to monetary gain—a neurobiological index of hedonic capacity—makes it well-suited to studying individual differences in reward sensitivity. Indeed, a recent study demonstrated that FN amplitude relates to individual differences in both behavioral and self-report indicators of reward sensitivity (Bress and Hajcak, 2013). As a neural measure of reward sensitivity, the FN has also been applied to the study of abnormal reward processing in relation to psychopathology. FN amplitude on gain trials is increased among problem gamblers, indicating hypersensitivity to reward (Hewig et al., 2010). On the other hand, FN amplitude is blunted among adults and children with current depressive symptoms, indicating reduced reward sensitivity (Bress et al., 2013b; Bress et al., 2012; Foti and Hajcak, 2009; Liu et al., 2014). The FN appears to be an effective tool for capturing trait and state differences in reward processing, and it may potentially be a useful biomarker for quantifying impaired reward sensitivity in relation to psychiatric illness.

A remaining challenge is how best to reconcile these two distinct conceptualizations of the FN as either an error signal elicited by unfavorable outcomes or a reward signal elicited by favorable outcomes. One possibility is that both accounts are accurate, and that both loss- and gain-related neural activity contribute to the scalp-recorded FN. Emerging evidence from time-frequency decompositions of the FN suggests that this may be the case. Unlike traditional time-domain ERP analyses, this approach is capable of isolating neural signals with distinct frequency characteristics, even if the signals have considerable temporal and spatial overlap (Bernat et al., 2005; Harper et al., 2014). When applied to ERPs elicited by monetary feedback, two distinct effects in the time range of the FN are apparent. On the one hand, activity in the theta frequency band (4-7 Hz) is increased for monetary loss; on the other, activity in the delta frequency band (< 3 Hz) is increased for monetary gain (Bernat et al., 2008; Bernat et al., 2011; Cohen et al., 2007; Nelson et al., 2011). In the time-domain ERP waveform, the delta response would manifest as a positive-going peak that is increased (i.e., more positive) on gain trials, and the theta response would manifest as a negative-going peak that is increased (i.e., more negative) on loss trials. When entered as simultaneous predictors of time-domain FN amplitude, both the delta and theta responses yield significant effects, indicating that they reflect relatively independent processes that each contribute to the observed FN (Bernat et al., 2008; Bernat et al., 2011). These findings potentially provide

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a conceptual and empirical bridge between the two opposing viewpoints of the FN, demonstrating how unique sources of loss- and gain-related neural activity may contribute to the ERP response—and how they may be quantified separately using time-frequency analysis.

In the current study, we sought to build upon this preliminary evidence by applying time-frequency analysis to an FN dataset recorded in a relatively large sample during a simple gambling task. The FN in this dataset was previously scored using temporospatial PCA (Foti and Hajcak, 2009) as well as a standard time-window measure (Foti and Hajcak, 2012), but the frequency characteristics were not considered. We focused the current analysis on two key questions: First, we examined the likely neural generators of the theta- and delta-band responses, with the goal of potentially reconciling inconsistent source localization results in the FN literature. Loss-related theta activity has been linked to a source in the ACC (Vaidyanathan et al., 2008), which is consistent with several reports localizing the time-domain FN to the ACC (Gehring and Willoughby, 2002; Miltner et al., 1997; Potts et al., 2006; Ruchsow et al., 2002). Of particular interest here is the possibility that gain-related delta activity may be localized to a source in the striatum (Becker et al., 2014; Carlson et al., 2011; Foti et al., 2011b). To the extent that the FN may represent a composite of anterior cingulate and basal ganglia activity, time-frequency analysis may be an effective technique for isolating activity emanating from these two distinct neural generators.

Second, we considered how time-frequency analysis might shed additional light on our understanding of the link between abnormal FN amplitude and symptoms of internalizing psychopathology. Insofar as theta and delta appear to reflect distinct facets of feedback processing—possibly with distinct neural generators—leveraging time-frequency representations of the FN may yield complementary information not readily apparent in the time-domain ERP waveform, potentially allowing for greater specificity in linking psychiatric symptomology to impaired reward processing (Bernat et al., 2011). In a prior report from this sample, we linked blunted FN amplitude to symptoms of depression and psychological stress (Foti and Hajcak, 2009). These associations were somewhat stronger for gain trials but were only statistically significant for the FN difference score (i.e., loss minus gain); we examined whether this would translate to a reduction in loss-related theta activity, gain-related delta activity, or a combination of both.

A further benefit of revisiting this FN dataset using time-frequency decomposition is that we are able to examine the coherence across multiple data analytic strategies. We considered the convergence across a standard time-window measure, temporospatial PCA, and time-frequency representations of the FN. Both theta- and delta-band activity uniquely account for variance in FN amplitude when the latter is scored as the peak deflection in the ERP waveform (Bernat et al., 2008; Bernat et al., 2011), and we considered whether the time-frequency measures would similarly relate to the temporospatial PCA measure of the FN.

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Methods

Participants

Eighty-eight undergraduate students participated in the study. Four participants were excluded from analysis due to poor quality recordings, leaving 84 participants (46 male, 38 female) in the final sample.[1] All participants received course credit in an introductory psychology class for their participation, as well as $5.00 as their winnings from the gambling task. Written informed consent was obtained from all participants, and this research was formally approved by the Stony Brook University Institutional Review Board.

Measures and Materials

Psychological distress—Past-week symptoms of psychological distress were assessed using the short-form version of the Depression Anxiety Stress Scale (DASS-21; Lovibond and Lovibond, 1995). The DASS-21 was designed to be in accordance with the tripartite model of anxiety and depression (Clark and Watson, 1991), with the depression subscale focusing on low positive affect, the anxiety scale on physiological hyperarousal, and the stress scale on non-specific symptoms of negative affect. The total of the three subscales can be used as a measure of general psychological distress. Excellent reliability and validity have been established in both clinical and non-clinical samples (Antony et al., 1998; Brown et al., 1997; Clara et al., 2001; Crawford and Henry, 2003; Henry and Crawford, 2005; Sinclair et al., 2012; Szabo, 2010). In a prior report from this sample, blunted FN amplitude (loss minus gain) was associated with scores on the depression and stress subscales; the association with anxiety was weaker and nonsignificant (Foti and Hajcak, 2009).

Gambling task—The task was administered on a Pentium D class computer, using Presentation software (Neurobehavioral Systems, Inc., Albany, CA, USA) to control the presentation and timing of all stimuli. On each trial, participants were shown a graphic displaying two horizontally adjacent doors (occupying 6° of the visual field vertically and 8° horizontally) and were asked to choose which door they wanted to open using the left or right mouse button. Following each choice, a feedback stimulus appeared on the screen informing participants of the outcome, with a green '↑' indicating a correct guess and a gain of $.20, and a red '↓' indicating an incorrect guess and a loss of $.10. The magnitude of gains was double that of losses in order to approximately equate subjective value, as indicated by research on loss aversion (Tversky and Kahneman, 1992). Prior to each trial, a white '0', '1', or '2' cue was presented to inform participants how many doors would contain a prize on that trial, thereby indicating a reward probability of 0, .5, or 1, respectively. ERP responses to the 0- and 2-cues within a subsample have been previously reported (Dunning and Hajcak, 2007). Responses to both certain (i.e., 0% or 100% chance of monetary gain) and uncertain (i.e., 50% chance of monetary gain) feedback are reported here. All cues and feedback were presented against a black background and occupied approximately 3° of the visual field vertically and 1° horizontally. The order and timing of

[1]One participant excluded here was included in a recent report from this sample (Foti and Hajcak, 2012). Preprocessing this participant's data for time-frequency decomposition resulted in 99.6% of available trials being excluded as artifacts, and their data was not considered further. See the "Data Reduction and Analysis, Time-Frequency Domain" section for further details on the preprocessing routine.

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all stimuli were as follows: (i) cues were presented for 2000 s; (ii) a fixation mark was presented for 500 ms; (iii) the two doors were presented until a response was made; (iv) a fixation mark was presented for 1000 ms; (v) feedback was presented for 2000 ms, (vi) a fixation mark was presented for 1500 ms; and (vii) the instruction 'Click for next round' was presented until a response was made. To familiarize participants with the task, they first completed a practice block containing five trials. The actual experiment consisted of 100 trials (25 0-cue, 50 1-cue, and 25 2-cue trials). Positive feedback was presented on exactly 50% of the 1-cue trials (i.e., 25 gains and 25 losses), 100% of the 2-cue trials, and 0% of the 0-cue trials, such that all participants earned a total of $5.00. The order of feedback and trial type was randomized across participants. Every 20 trials, a running total of money earned was presented on the screen.

Data Reduction and Analysis

Psychophysiological recording—The continuous EEG was recorded using a custom cap (Cortech Solutions, Wilmington, NC, USA) and the ActiveTwo BioSemi system (BioSemi, Amsterdam, Netherlands). The EEG signal was digitized at 24-bit resolution with a least significant bit value of 31.25 nV and a sampling rate of 512 Hz, using a low-pass fifth-order sinc filter with a -3 db cutoff of 102.4 Hz. Recordings were taken from 64 scalp electrodes based on the 10/10 system, as well as two electrodes placed on the left and right mastoids. The electrooculogram was recorded from two electrodes 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.

Time-domain analysis—Off-line analysis of time-domain ERP activity was performed using Brain Vision Analyzer software (Brain Products, Munich, Germany). All data were re-referenced to the average of the two mastoid electrodes and band-pass filtered with cutoffs of 0.1 and 30 Hz. The EEG was segmented in epochs beginning 200 ms before feedback onset and continued for 800 ms afterward. Each trial was corrected for blinks and eye movements using the method developed by Gratton and colleagues (Gratton et al., 1983). Specific channels in each trial were rejected 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 artifacts were identified using visual inspection. Stimulus-locked ERPs were averaged separately for each feedback condition (uncertain gain, uncertain loss, certain gain, certain loss), and the activity in the 200-ms window before feedback onset served as the baseline. The FN was scored using a window measure based on the maximum of the loss minus gain difference wave (275-325 ms for uncertain outcomes; 250-300 ms for certain outcomes) at a pooling of frontocentral sites (FCz/1/2, Cz/1/2). This is the same time window and electrode pooling that was used to score the FN in a recent report from this sample (Foti and Hajcak, 2012).

In addition to the window measure, the time-domain FN elicited by uncertain outcomes was also scored using temporospatial PCA (for a detailed description, see Foti and Hajcak, 2009; 2012). This technique is effective at parsing the ERP waveform into unique portions of

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neural activity, thereby isolating the FN from the P300 and other overlapping components (Foti et al., 2011b). The PCA was conducted using the ERP PCA Toolkit, version 1.3 (Dien, 2010a). Following published guidelines for applying PCA to ERP data (Dien, 2010b), we first analyzed temporal variance in the averaged ERP waveforms using temporal PCA and Infomax rotation. This first step captured variance across time points, using electrodes, conditions, and participants as observations. Based on the resulting Scree plot (Cattell, 1966), eight temporal factors were retained for rotation. The spatial distributions of these factor scores were then analyzed using spatial PCA and Infomax rotation; a separate spatial PCA was performed for each temporal factor. This second step captured variance across electrodes, using conditions and participants as observations. Based on the averaged Scree plot, three spatial factors were retained for each temporal factor, yielding 24 unique factor combinations. The covariance matrix and Kaiser normalization were used for each PCA. Temporal Factor 3/Spatial Factor 1 was most consistent with the morphology of the FN (Figure 1a-b) and was selected for statistical analysis. This PCA yielded scores for each condition (gain, loss) and each participant, representing the amount of activity in the original data captured by that factor.

Time-frequency decomposition—To isolate power in the delta and theta frequency bands, the EEG signal was preprocessed separately within Matlab (Mathworks, Inc., Natick, MA, USA). This processing stream was similar to the original one described above; here, the extracted time windows were wider to allow for the discarding of edge effects, and the artifact rejection procedure was fully automated and somewhat more conservative. All data were re-referenced to the average of the two mastoid electrodes and segmented into epochs beginning 1000 ms before feedback onset and continuing for 2000 ms afterward. Each trial was corrected for blinks and eye movements using the method developed by Gratton and colleagues (Gratton et al., 1983). The data were downsampled to 32 Hz to reduce the file size of the energy distributions, while retaining an adequate sample rate to fully characterize the frequency bands of interest. Specific channels in each trial were rejected where activity exceeded ± 100 μV in either the pre- (-1000 to -1 ms) or post-stimulus (1 to 2000 ms) time regions; An average of 6.38% of individual channel data was rejected due to artifacts (Range: 0.24-40.72%).[2] Stimulus-locked ERP activity was averaged separately for certain and uncertain gains and losses, and the activity in the 100-ms window before feedback onset served as the baseline.

Time-frequency decomposition of the averaged ERP activity was then conducted following published guidelines (Bernat et al., 2011), using scripts provided by Bernat and colleagues (2005). In light of prior work demonstrating that activity in the delta and theta activity each uniquely contribute to the time-domain FN (Bernat et al., 2008; Bernat et al., 2011; Nelson et al., 2011), we structured our time-frequency decomposition to specifically target these frequency bands of interest. To ensure that theta- and delta-band activity received equal weight within the PCA of the time-frequency transform, the ERP waveform was first filtered with two distinct 3rd order Butterworth filters: A 2 Hz high-pass filter was used to isolate

[2]As this was a fully-automated procedure, more conservative criteria for identifying physiological artifacts were used than in the time-domain processing stream. Area measures of the FN (loss minus gain) derived from the two processing streams were highly correlated with one another ($r = .97$, $p<.001$), indicating strong convergence.

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theta-band activity, and a 4 Hz low-pass filter was used to isolate delta-band activity. This pre-filtering step is beneficial because higher-frequency activity (i.e., theta) is smaller in amplitude compared to lower-frequency activity (i.e., delta), such that the PCA solution will otherwise be dominated by delta-band activity. Filtering the waveform maximizes the initial separation between delta and theta, allowing for a more precise characterization of neural activity within these frequency bands occurring within the time range of the FN.

These filtered signals were then transformed into time-frequency energy distributions using the binomial reduced interference distribution (RID) variant of Cohen's class of time-frequency transforms. The use of RID transforms here was chosen over wavelets, another common time-frequency decomposition technique, because RID transforms provide uniform resolution across the time-frequency surface. Wavelets can be 'tuned' to match the signal of interest, but are limited to an extent by the inherent trade-off between time and frequency resolution. RID transforms, on the other hand, have the ability to precisely characterize the frequency characteristics of the surface at high frequency bands, as well as the temporal characteristics at low frequency bands (Bernat et al., 2005). While both RID and wavelet approaches have been effectively used to quantify the spectral characteristics of EEG data, the RID transform is particularly well-suited to isolate delta activity in the time range of the FN—a primary goal of the current study—by maximally separating this from later delta activity in the time range of the P300/Slow Wave.

RID transforms were calculated separately for uncertain and certain outcomes. A time-frequency PCA was then applied separately to each set of transforms, within the area bounded by the 0-750 ms time range and the 0-12 Hz frequency range. This step is distinct from the PCA performed on the time-domain ERP data that is described above. While the ultimate goal of both PCAs is to isolate unique sources of neural activity, in the former case PCA was applied to the ERP waveform and here the PCA was applied to the time-frequency energy surfaces resulting from the RID transform. Based on visual inspection of the resulting Scree plots (Cattell, 1966), the following factor solutions were chosen: four factors for the delta distribution on uncertain trials, six for theta on uncertain trials, eight for delta on certain trials, and eight for theta on certain trials. Subsequent analysis was restricted to time-frequency factors corresponding to the FN, based on the time course and spatial distribution of activity. For uncertain trials, this yielded two factors of interest: FN-Delta and FN-Theta. For certain trials, only an FN-Delta factor was apparent. These factors were scored at poolings of electrodes where the loss versus gain contrast was maximal (FN-Delta: FCz, Cz/1/2, CPz; FN-Theta: Fz, FCz/1/2, Cz). The remaining delta and theta factors either peaked outside the time range of the FN (< 200 ms or > 400 ms) or did not load on frontocentral electrodes, making them unlikely to contribute to the time-domain FN.

Source localization—To compare the likely neural generators of the theta and delta factors corresponding to the FN, the original time-domain ERP waveforms were filtered based on the energy distributions obtained from the time-frequency analysis. Theta activity was isolated using a 4.5-6 Hz bandpass filter and delta activity using a 1-2.5 Hz filter (Figure 2a-b). These filtered waveforms were then re-referenced to the average of all scalp electrodes, and time windows surrounding the peak of the difference wave were selected for source analysis: 200-300ms for the FN-Delta, and 250-350 ms for the FN-Theta. Two

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complementary localization approaches were employed: First, discrete source analysis was conducted using BESA (Version 5.3, MEGIS Software GmbH, Gräfelfing, Germany). A symmetric pair of hemispheric dipoles was specified within an elliptical four-shell model, and residual spatial variance of no more than 10% was accepted as evidence of a good quality solution. Second, distributed source analysis was conducted using standardized low resolution brain electromagnetic tomography (sLORETA; Fuchs et al., 2002; Jurcak et al., 2007; Pascual-Marqui, 2002), implemented within Brainstorm software (Tadel et al., 2011). An unconstrained solution was applied to a three-shell spherical model, and source regions were bounded to those areas with amplitudes of at least 95% of the global maximum.

Statistical analysis—Scores from the time-windowed FN measure, temporospatial PCA factors, and time-frequency factors were evaluated statistically using ISB SPSS Statistics (Version 21). Effects of monetary outcome (loss vs. gain) were analyzed using paired *t*-tests. Associations between ERP variables and DASS-21 scores were examined using bivariate correlation and multiple linear regression.

Results

Uncertain Monetary Outcomes

Time domain—The FN elicited by uncertain outcomes was evident as a relative negativity to monetary loss and a relative positivity to monetary gain (Figure 1a). The loss minus gain difference peaked at approximately 300 ms and was maximal at frontocentral electrodes. Following temporospatial PCA, the FN was isolated as an *absolute* positivity which was increased for gains compared to losses (Figure 1b). Like the time domain FN, this temporospatial PCA factor peaked at approximately 300 ms and the loss minus gain difference was maximal at frontocentral electrodes (for a more detailed account, also see Foti and Hajcak, 2009; 2012). The loss versus gain comparison was statistically significant for both the time window measure and the temporospatial PCA measure (Table 1, top), and both effect sizes were large (Cohen's *d*'s >.80).

Time-frequency domain—Two effects were observed within the time range of the FN: delta power was increased for gains compared to losses (FN-Delta; Figure 1c), whereas theta power was increased for losses compared to gains (FN-theta; Figure 1d). The loss versus gain comparison was statistically significant for both delta and theta activity (Table 1, top) and both effect sizes were large (*d*'s >.80). FN-Delta and FN-Theta power were also significantly correlated with one another, indicating an association across frequency bands (Table 1, bottom). Reward-related FN-Delta power was maximal between 1-2.5 Hz and at central electrodes, and the loss minus gain difference peaked at approximately 270 ms. Loss-related FN-Theta power was maximal from 4.5-6 Hz, peaked somewhat later at approximately 330 ms, and had a more frontally-maximal spatial distribution.

Convergence across measures—To examine the consistency between the area, temporospatial PCA, and time-frequency measures, we calculated bivariate correlations (Table 1, bottom). Difference scores were used, and these were all converted to positive numbers so that larger numerical values indicate greater differentiation between loss and

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gain. All of the correlations between FN measures were statistically significant, indicating convergence across the data analytic approaches employed.

Given that the FN-Delta and FN-Theta measures were each related to the time domain FN measures, we then examined unique effects by entering them as simultaneous predictors in a multiple linear regression. When predicting the time window FN (loss minus gain), unique effects were found for both FN-Delta (β=.52, p<.001) and FN-Theta (β=.30, p<.001); an identical pattern was found predicting the temporospatial PCA measure of the FN (FN-Delta: β=.51, p<.001; FN-Theta: β=.26, p<.01). As with the bivariate correlation coefficients, these regression coefficients are all positive because the loss minus gain difference was converted to a positive number for each measure. These results demonstrate that reward-related delta activity and loss-related theta activity uniquely contribute to the observed FN in the time domain—regardless of whether the FN is quantified using a time window average or temporospatial PCA measure.

Source analysis—Both discrete and distributed source analyses of the FN-Delta and FN-Theta elicited by uncertain monetary outcomes indicated distinct neural generators for these two time-frequency measures (Figure 2). Fitting a pair of hemispheric dipoles to the FN-Delta yielded a source in the putamen, a region of the dorsal striatum (Talairach: ±27.8, 8.7, -2.0); residual variance was 5.94%, indicating a good quality solution. Dipole analysis of FN-theta, meanwhile, yielded a source in the ACC (±3.8, 3.9, 32.0) with residual variance of 8.43%, again indicating a good quality solution. No evidence was found for the converse scenario: The source in the ACC yielded a poor fit for delta activity and the source in the striatum yielded a poor fit for theta activity, with both residual variances greater than 15%. Distributed source analysis using sLORETA indicated a similar pattern: FN-Delta was localized to a region centered at (-2.0, 7.5, 5.1) and spanning the dorsal and ventral striatum; FN-theta was localized to a non-overlapping region within the ACC, centered at (-1, 2.2, 34.0). These solutions are consistent with past studies, with the ACC (Gehring and Willoughby, 2002; Miltner et al., 1997) and the striatum (Carlson et al., 2011; Foti et al., 2011b) both identified as possible neural generators of the time-domain FN.

Associations with symptomatology—Descriptive statistics for the three symptom subscales of the DASS-21 were as follows: Depression (M = 5.36, SD = 6.87, Range = 0-32), Anxiety (M = 8.55, SD = 8.50, Range = 0-32), Stress (M = 5.05, SD = 6.49, Range = 0-34). In a previous report from this sample, blunted FN amplitude (loss minus gain) was associated with depressive symptom severity and stress reactivity; the association with anxiety was in the same direction but was weaker and non-significant (Foti and Hajcak, 2009). Here, we examined the association between symptoms and time-frequency measures by taking the loss versus gain difference and converting it to a positive number; negative correlation coefficients indicate that symptom severity is associated with reduced differentiation between losses and gains. Symptoms were uniquely associated with blunted FN-Delta activity, with a significant correlation observed for all three DASS-21 subscales (Depression: r = -.25, p<.05; Anxiety: r = -.26, p<.05; and Stress: r = -.34, p<.01). Entering the three symptom scores as simultaneous predictors of delta activity, the overall regression model was significant (R^2=.11, F(3,83)=3.50, p<.05) but none of the individual scales

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yielded a unique effect (all *p*'s>.05). No significant associations were observed between symptom severity and the FN-Theta (all *p*'s >.15). Taking the sum of all three subscales as a general index of psychological distress and entering FN-Delta and FN-Theta as simultaneous predictors, we observed a significant unique effect of FN-Delta (β= -.32, *p*<.01) but not FN-Theta (β= -.01, *p*=.99).

Certain Monetary Outcomes

Monetary outcomes that were fully predictable elicited FN-like activity within the time domain (Figure 3a). Certain outcomes elicited a positive-going deflection in the waveform that was increased for monetary gains compared to losses ($t(83) = 3.17$, $p<.01$). While this loss versus gain contrast was statistically significant, it was a small effect ($d = .35$) and substantially smaller than the loss-gain difference on uncertain trials ($t(83) = 5.94$, $p<.001$). Time-frequency analysis of this response indicated that it was driven primarily by increased delta activity to monetary gains (Figure 3b; $t(83) = 2.04$, $p<.05$, $d = .22$); no significant modulation of theta-band activity was apparent (all *p*'s>.10). Similar to the FN-Delta elicited by uncertain outcomes, this delta activity elicited by certain outcomes was maximal at approximately 240 ms, from 1.5-2.5 Hz, and at frontocentral sites. Unlike the FN-Delta elicited by uncertain outcomes, however, no associations were observed with any of the DASS-21 subscales (all *p*'s>.15); the FN-Delta responses to certain and uncertain outcomes were also uncorrelated with one another ($p = .52$).

Discussion

Consistent with previous work (Bernat et al., 2008; Bernat et al., 2011), the time-domain FN was decomposed in the frequency domain as a combination of two dissociable effects, with activity in the theta band increased in response to monetary loss and activity in the delta band increased for monetary gain. We found clear evidence of convergence across scoring techniques, with both gain-related FN-Delta and loss-related FN-theta uniquely predicting time-domain FN amplitude, regardless of whether the latter was scored using a traditional area measure or using temporospatial PCA. Recent studies have concluded that variation in FN amplitude may be driven by a reward-related positivity (Baker and Holroyd, 2011; Carlson et al., 2011; Foti et al., 2011b; Holroyd et al., 2011; Holroyd et al., 2008), and in the time-frequency domain this is evident as increased activity in the delta frequency band in response to monetary gain. Thus, the PCA decomposition of the FN as a reward-related positivity corresponds closely to the time-frequency representation of reward-related delta activity. The current study also sheds new light on the FN in two key ways. First, source localization of loss-related theta and gain-related delta suggest the possibility of distinct generators in the ACC and basal ganglia, respectively; these data offer a potential explanation for conflicting source localization results in past work. Second, we found that internalizing symptomatology was linked specifically with blunted FN-Delta amplitude in response to uncertain outcomes; symptom severity was not related to FN-Theta amplitude, or to FN-Delta elicited by certain outcomes. Together, these results indicate that the FN represents a composite measure of theta- and delta-band activity, two relatively independent processes that may relate to distinct facets of reward- and loss-processing—and are differentially impacted by internalizing psychopathology.

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The source localization findings are notable in that they potentially resolve an outstanding inconsistency in the FN literature, bridging previous work localizing the FN to either loss-related activity of the ACC (Gehring and Willoughby, 2002; Potts et al., 2006) or reward-related activity of the basal ganglia (Becker et al., 2014; Carlson et al., 2011; Foti et al., 2011b). According to the current results, both of these reported source solutions may be accurate, with each source capturing a distinct portion of the neural activity comprising the observed scalp-recorded FN—a pattern which was observed using both discrete and distributed source analysis. The ACC and a second potential source in the basal ganglia appear to contribute to the FN in distinct ways, such that the former is associated with increased activity to monetary loss and the latter with increased activity to monetary gain; this interpretation is also consistent with the extant neuroimaging literature (Liu et al., 2011). As with any application of source analysis to ERP data, however, this result should be interpreted with some caution (Cohen et al., 2011a; Foti et al., 2011c) and further substantiated with complementary evidence from depth electrodes and lesion studies. For example, gain-related delta may reflect coordinated frontostriatal activation to rewards rather than a direct contribution of the striatum to the scalp-recorded signal per se. Here, converging source localization results were observed using both dipole analysis and sLORETA, techniques which complement one another. Dipole analysis is particularly effective when localizing discrete neural signals that have been maximally separated from overlapping activity, such as PCA-derived responses (Dien, 2010b), but suffers in accuracy when modeling multiple simultaneous sources; sLORETA, conversely, is more effective when localizing more widespread sources of activity (Pizzagalli, 2007). Across both approaches, the current results indicate that gain-related delta activity and loss-related theta activity do not share the same neural generator, and that FN-Delta and FN-Theta represent distinct sources of neural activity.

To the extent that the FN represents a composite of loss- and gain-related activity, the contribution of different neural generators to FN amplitude will depend on the experimental context. For example, two recent studies using simultaneous ERP-fMRI recordings yielded different patterns: In one study using a time estimation task, FN amplitude was associated activity in the striatum, midcingulate, and prefrontal cortex on reward trials only (Becker et al., 2014); in a separate study using a reversal learning task—in which error feedback may have been more salient—FN amplitude was associated only with activity in the dorsal ACC (Hauser et al., 2014). In light of the current findings, time-frequency analysis appears to be an effective tool for dissociating unique gain- and loss-related signals, each of which contribute to the FN.

The time-frequency analysis presented here also provides further insight into the link between blunted FN amplitude and internalizing symptomatology, complementing prior results from time-domain ERP analyses. The FN in this sample was previously linked to symptoms of depression and stress reactivity, an effect which was significant only with the loss minus gain difference wave; while the association with symptoms was stronger for gain trials than loss trials, neither effect was significant alone (Foti and Hajcak, 2009). Building on this finding, the current results demonstrate that symptoms of psychological distress load specifically on FN-Delta activity, with increasing symptom severity associated with a reduction in the gain-related neural response; loss-related FN-Theta was unaffected. This

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confirms that the previously-observed reduction in FN amplitude among symptomatic individuals is driven primarily by a reduced response to gains and not losses.

We note here that delta activity was broadly related to general psychological distress, with significant associations found for all three subscales of depression, anxiety, and stress reactivity. Indeed, a blunted FN has previously been related to trait anxiety (Gu et al., 2010) and laboratory stress manipulations (Bogdan et al., 2011), underscoring that negative affect may be broadly associated with reduced neural sensitivity to rewards in non-clinical populations. There is also substantial evidence, however, that a blunted FN may be particularly relevant to depression: Blunted FN amplitude is specifically associated with symptoms of depression and not anxiety in children (Bress et al., 2013b; Bress et al., 2012), is related to familial history of major depression (Foti et al., 2011a), prospectively predicts the onset of a first major depressive episode (Bress et al., 2013a), and is correlated with subjective anhedonia severity among adults with major depressive disorder (Liu et al., 2014). In light of the current time-frequency and source localization results, one possibility is that blunted FN amplitude in depressed populations is driven primarily by reduced reward-related activity within the striatum, rather than in the ACC. This perspective is in line with fMRI studies linking depression to reduced activation to rewards throughout the striatum, including the caudate (Forbes et al., 2006; Forbes et al., 2009; Olino et al., 2011; Smoski et al., 2009), putamen (Knutson et al., 2008), and ventral striatum (Pizzagalli et al., 2009; Steele et al., 2007). Conversely, other research has shown that deep brain stimulation of the striatum is effective for treating refractory depression (Schlaepfer et al., 2008). Together, this body of research demonstrates that depression may be specifically characterized by striatal dysfunction to reward, and it is possible that delta-band activity contributing to the FN may provide unique information regarding this neurobiological deficit.

While the bulk of our analyses focused on the FN elicited by uncertain outcomes in which there was a 50% chance of reward, we also observed an FN-like ERP response to certain outcomes in which the monetary gain or loss was fully predicted by a preceding cue. Certain wins elicited an increased reward positivity compared to certain losses, albeit substantially smaller in amplitude compared to the FN on uncertain outcomes. A similar ERP has previously been observed in response to cue itself, both in this sample (Dunning and Hajcak, 2007) and in a separate study (Holroyd et al., 2011). However, the novel time-frequency analysis revealed that this response to certain outcomes is composed primarily of reward-related delta activity—but not theta activity—in the time range of the FN. Whereas even fully predicted rewards appear to elicit delta-band activity, theta-activity is unique to uncertain outcomes. This result is in line with the perspective that the FN to unpredictable outcomes reflects a composite of a conflict-related N2 and a reward-related positivity (Baker and Holroyd, 2011) which, in the time-frequency domain, appear to map onto theta- and delta-band activity, respectively.

In the current study, time-frequency decomposition was applied to the averaged ERP waveforms in order to parse distinct sources of stimulus-locked neural activity contributing to the time-domain FN, with the ultimate goal of reconciling conflicting findings in the FN literature. This approach isolates frequency-based activity that relates directly to the

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observed FN, thereby advancing our understanding of this established ERP component by providing unique information that would not be readily available with traditional, time-domain analysis. An alternative, complementary approach is to apply time-frequency decomposition to trial-level data, prior to averaging. This latter analytic strategy allows for the analysis of neural activity that is both in and out of phase with the stimulus, thereby providing information about activity which may not be apparent in the averaged, time-domain ERP waveform (Cunillera et al., 2012; Donamayor et al., 2011; HajiHosseini et al., 2012; Marco-Pallares et al., 2008). By preserving phase information of frequency activity, trial-level analysis also allows for the quantification of phase synchrony and can reveal the coordination of activity across multiple brain regions involved in reward processing (Cohen et al., 2009a; b; Cohen et al., 2012; Cohen et al., 2011b). Applying time-frequency decomposition to individual trial data in this manner is a promising method for investigating activity across the mesocorticolimbic reward circuit, and it can be used in conjunction with either frequency analysis of averaged ERP data or traditional time-domain analysis. The appropriate analytic strategy will depend on the primary research question at hand, and the nature of the neural signal that is of primary interest.

Overall, the current time-frequency analysis supports the possibility that the FN may represent the summation of two distinct neural signals: ACC activity elicited by monetary loss, as well as basal ganglia activity elicited by monetary gain. As such, framing the FN purely as a loss or reward signal may be an incomplete conceptualization—both monetary loss and gain appear to contribute to the observed FN, and in distinct ways. Only the FN-Delta signal to reward, however, appears to be impacted by internalizing psychopathology. Theta- and delta-band activity comprising the FN are unique and dissociable processes, such that individual differences may influence one response and not the other, patterns which might be difficult to discern when analyzing time-domain ERPs alone. In this way, time-frequency decomposition is an effective analytic approach that complements time-domain analyses; when used in concert, information from frequency- and time-based measures of the FN can be synthesized to allow for a more comprehensive understanding of neural activity involved in reward processing.

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Highlights

- The feedback negativity is a composite of two signals: loss-related theta activity in the anterior cingulate cortex, and gain-related delta activity with a potential source in the striatum.
- Symptoms of internalizing psychopathology relate specifically to reduced gain-related delta activity and not loss-related theta activity.
- Gain-related delta activity may specifically be effective for quantifying impaired reward sensitivity and basal ganglia dysfunction in clinical populations.

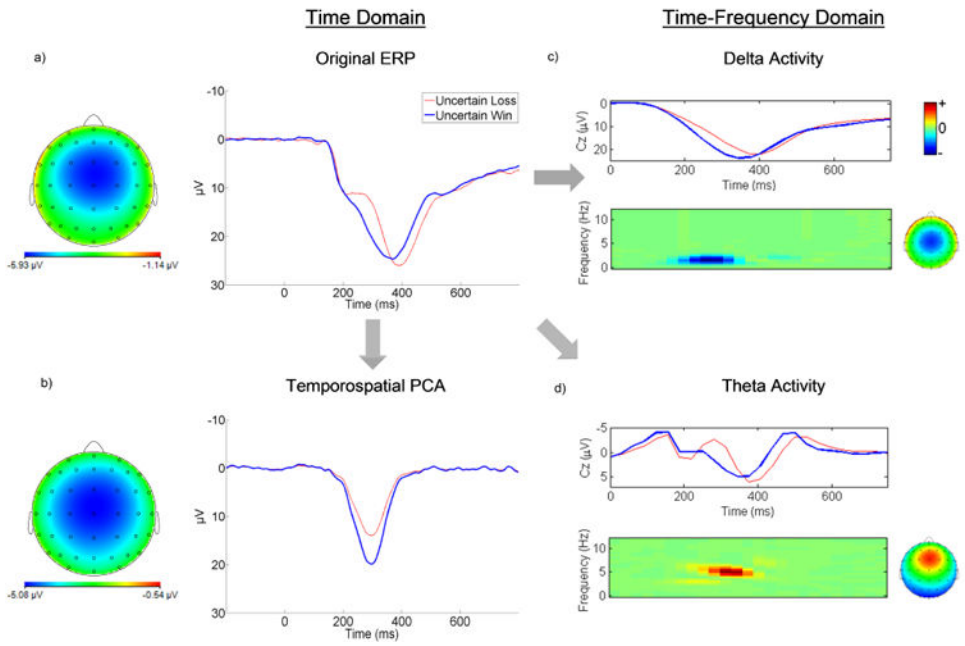

Figure 1.

Event-related potentials elicited by uncertain monetary outcomes. (a) The original waveforms in the time domain at a pooling of FCz/1/2 and Cz/1/2, prior to principal components or time-frequency analyses. (b) The feedback negativity (FN) isolated using temporospatial principal components analysis. (c) Time-frequency representations of the FN within the delta frequency band (< 3 Hz). (d) Time-frequency representations of the FN within the theta frequency band (4-7 Hz). All headmaps represent the loss minus win difference; for the time-frequency headmaps, red indicates increased power for losses (loss>win) and blue indicates increased power for wins (win>loss).

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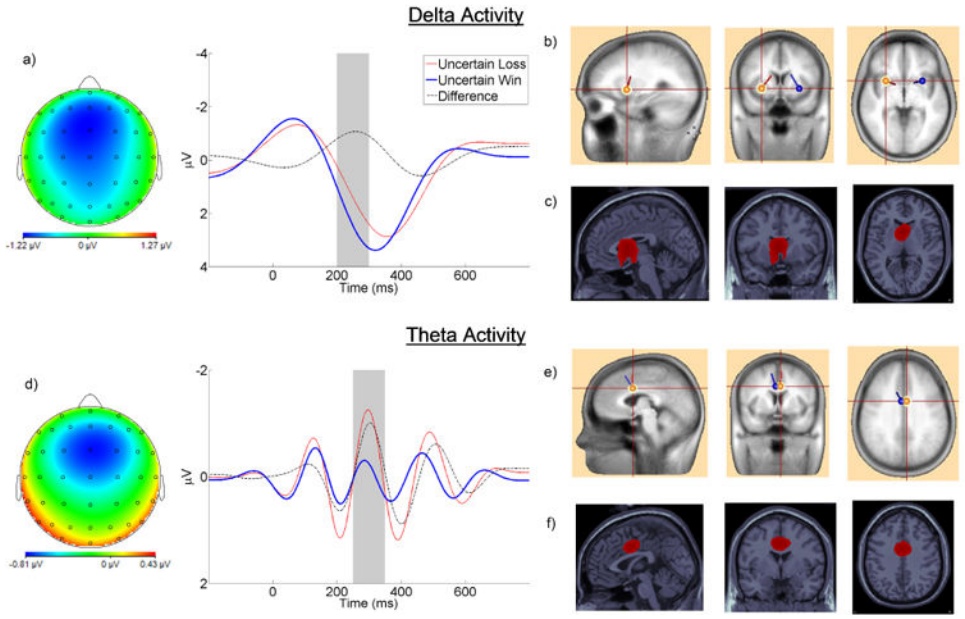

Figure 2.

Source localization of gain-related delta activity (a, b, c) and loss-related theta activity (d, e, f) elicited by uncertain monetary outcomes in the time range of the FN. (a, d) Filtered waveforms and the time window (shaded regions) used for source localization. Headmaps represent the loss minus win difference. (b, e) Location and orientation of fitted hemispheric dipoles. (c, f) Location of distributed sources identified using sLORETA.

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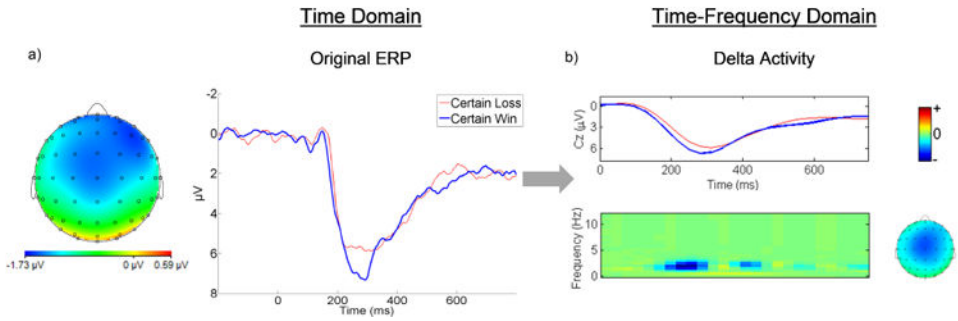

Figure 3.

Event-related potentials elicited by certain monetary outcomes. (a) The original waveforms in the time domain at a pooling of FCz/1/2 and Cz/1/2, prior to time-frequency analysis. (b) Time-frequency representations of the FN within the delta frequency band (< 3 Hz). All headmaps represent the loss minus win difference.

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Table 1

Convergence across scoring methods

Within-Subjects Comparisons	Loss vs. Gain, *t*(83)	Cohen's *d*
Time Domain		
Time Window	10.34***	1.14
Temporospatial PCA	8.60***	.95
Time-Frequency Domain		
Delta	8.55***	1.03
Theta	6.59***	.82

Correlations

	Time Window	Temporospatial PCA	Delta	Theta
Time Window	—			
Temporospatial PCA	.95***	—		
Delta	.66***	.63***	—	
Theta	.54***	.49***	.46***	—

Note: All measures are for uncertain outcome trials only. Correlations reflect the relationship between difference scores (monetary gain vs. loss) and were converted to positive numerical values, such that positive correlation coefficients indicate a direct association.

*** $p<.001$