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Reward Processing in Certain vs. Uncertain Contexts in Schizophrenia: An ERP Study

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Abstract

Disturbances in motivation are prominent in the clinical presentation of people with schizophrenia and might reflect a disturbance in reward processing. Recent advances in affective neuroscience have subdivided reward processing into distinct components, but there are two limitations of the prior work in schizophrenia. First, studies typically focus on only one component rather than on the unfolding of reward processing across multiple stages. Second, studies have not considered the impact of certainty effects, which represent an important contextual factor that impacts processing. We examined whether individuals with schizophrenia show the typical certainty effects across three phases of reward processing: cue evaluation, feedback anticipation, and feedback receipt. Electroencephalography from 74 healthy controls and 92 people with schizophrenia was recorded during a cued gambling task under conditions in which cues indicated forthcoming reward outcomes that were certain or uncertain. Controls demonstrated the expected certainty effects across each stage. Initial cue evaluation (cue P300) was intact in the schizophrenia group, but people with schizophrenia showed diminished certainty effects during feedback anticipation (stimulus-preceding negativity [SPN]) and receipt (feedback reward positivity [fRewP] and feedback P300). During feedback receipt, event-related potentials in people with schizophrenia were similar to controls for the uncertain context, but larger than controls for the certain context. Essentially, people with schizophrenia appeared to process certain feedback as though it were uncertain. These findings show, for the first time, that the fundamental distinction between certain and uncertain contexts is altered in schizophrenia at a neural level.

General Scientific Summary

Distinguishing between certainty and uncertainty is a critical component of reward processing, because predicting the future requires consideration of the probabilities of potential outcomes. This study showed, for the first time across multiple reward-processing stages, that people with

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schizophrenia show a fundamental impairment in distinguishing between certain and uncertain contexts when anticipating and receiving reward feedback. People with schizophrenia appeared to process certain feedback as though it had occurred in an uncertain context.

Keywords

schizophrenia; certainty effects; valence effects; reward processing; event-related potentials (ERPs)

Disturbances in motivation are prominent in the clinical presentation of people with schizophrenia (Green, Horan, Barch, & Gold, 2015; Reddy et al., 2017; Ventura et al., 2015). People with schizophrenia often fail to initiate and persist in goal-directed activities, which manifests in the marked functional impairment and social isolation that characterize this condition (Green, Horan, & Lee, 2015; Green et al., 2018; Horan & Blanchard, 2003; Juckel & Morosini, 2008). Guided by affective neuroscience-based models (Barch & Dowd, 2010; Barch, Pagliaccio, & Luking, 2016; Strauss, Waltz, & Gold, 2014), researchers have begun to investigate whether these motivational difficulties reflect a disturbance in reward processing using measures of neural functioning, such as event-related brain potentials (ERPs). While these investigations have provided new key insights, the current study addresses two issues that limit our understanding of reward processing in schizophrenia. First, reward processing is a complex, multifaceted construct composed of distinct stages, including feedback anticipation associated with cues signaling forthcoming reward and reward outcome. However, ERP research in schizophrenia has typically focused on a single component of reward processing rather than capturing the unfolding dynamics of reward processing as they occur in daily life. Second, reward processing is powerfully moderated by contextual factors. One fundamental factor is whether the reward signaling cues we encounter are certain and fully predict the receipt of rewards or are uncertain and provide only partial information about reward receipt. Although extensive human and non-human animal research indicates that reward processing differs in several fundamental ways between certain versus uncertain contexts, no studies have examined this basic distinction in schizophrenia. The current ERP study was designed to address both of these limitations by comparing schizophrenia and healthy comparison groups on a novel paradigm that evaluated multiple reward processing stages under conditions in which reward predicting cues were either certain or uncertain.

ERPs Corresponding to Reward Processing Stages

Reward processing comprises a dynamic set of component processes that unfold across a series of temporal stages and is often examined during paradigms that manipulate reward/loss contingencies (Barch et al., 2016; O'Doherty, Cockburn, & Pauli, 2017; Wallis, 2007). As displayed in Table 1, the current investigation examined three stages of reward processing during certain and uncertain contexts. *Cue evaluation* refers to the initial responsiveness to whether a predicted outcome is certain or uncertain. *Feedback anticipation* refers to the preparation for and anticipation of a future outcome. *Feedback receipt* refers to the immediate response to a reward or punishment. In uncertain contexts the hedonic value

of an outcome (feedback receipt) informs the responsiveness to cues (cue evaluation), which guides preparation for the future outcomes (feedback anticipation). The majority of research in healthy individuals examines only one stage of reward processing during certain or uncertain contexts, which limits interpretation about the temporal unfolding of reward processing.

Each of the three stages of reward processing is associated with distinct ERP components, which are related to characteristic patterns for certainty effects (i.e., certainty vs. uncertainty) and valence effects (i.e., reward/loss vs. neutral conditions; see Table 1; for review, see Glazer, Kelley, Pornpattananangkul, Mittal, & Nusslock, 2018). For cue evaluation, the cue P300 (cP300) is a centro-medial ERP that is larger following cues indicating upcoming reward than for cues indicating upcoming neutral outcomes (Broyd et al., 2012; Novak, Novak, Lynam, & Foti, 2016; Novak & Foti, 2015), and this cP300 valence effect is intact in schizophrenia (Vignapiano et al., 2016). For feedback anticipation, the stimulus-preceding negativity (SPN) is a right-hemisphere dominant ERP that is associated with the anticipation of feedback (Brunia, Hackley, van Boxtel, Kotani, & Ohgami, 2011; Brunia, van Boxtel, & Böcker, 2011). SPN is larger for reward-related feedback than for neutral feedback (Hughes, Mathan, & Yeung, 2013). For reward anticipation, one study found that patients generally show a reduced SPN while viewing emotional and neutral images (Wynn, Horan, Kring, Simons, & Green, 2010). Notably, other work on the anticipation of reward or pleasure in schizophrenia using self-report and fMRI measures generally evidence impairments (Buck & Lysaker, 2013; Chan et al., 2010; Gard, Kring, Gard, Horan, & Green, 2007; Li et al., 2015). Hence, patients should show deficits in reward-related feedback anticipation.

Two ERPs are commonly associated with feedback receipt: the feedback reward positivity (fRewP) and the feedback P300 (fP300). fRewP is a medial-frontal ERP that is generally largest for reward outcomes, less for neutral outcomes, and even less for loss outcomes (see Proudfit, 2015). Whereas fRewP is generally related to outcome valence, fP300 is a centro-parietal ERP that tends to relate to outcome magnitude and expectancy (Hajcak, Holroyd, Moser, & Simons, 2005; Hajcak, Moser, Holroyd, & Simons, 2007; Pfabigan, Alexopoulos, Bauer, & Sailer, 2011; Wu & Zhou, 2009). Both reward and loss trials yield larger fP300 than neutral trials (Glazer et al., 2018). For feedback receipt in schizophrenia, a recent meta-analysis of fRewP indicates that fRewP appears intact (Martin et al., 2018). To our knowledge, no studies have examined valence effects for fP300 in patients.

Taken together, the limited data on valence effects of these ERPs suggest impairments in SPN and intact cP300 and fRewP, with no studies of the fP300. However, limitations of these studies of valence effects include examining only a single stage of reward processing and not considering the psychometric properties (e.g., test-retest reliability, internal consistency) of these components.

Reward Processing in Certain vs. Uncertain Contexts

In order to obtain desirable outcomes in our daily lives, we are required to form predictions based on the cues that are available to us. In our complex environment these cues vary in

degree of certainty, either fully predicting the receipt of a reward (i.e., certain) or providing only partial information (i.e., uncertain). Achieving a desired reward requires distinguishing between certain and uncertain cues, and forming predictions based on those cues facilitates adaptive responses and is a critical aspect of daily living. The distinction between certain and uncertain cues is critical, because mistaken certainty or uncertainty can lead to faulty predictions and contribute to poor daily functioning.

Extensive human and non-human animal research indicates that reward processing differs in several fundamental ways between certain versus uncertain contexts. Certainty is widely viewed as inherently desirable whereas uncertainty as inherently aversive and makes greater demands on cognitive control processes (Ladouceur, Gosselin, & Dugas, 2000; Luhmann, Chun, Yi, Lee, & Wang, 2008; Reuman, Jacoby, Fabricant, Herring, & Abramowitz, 2015). Furthermore, different brain networks are involved in reward processing when outcomes are certain versus uncertain. During certain contexts there is greater activity in the ventromedial prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex, whereas during uncertain contexts there is activity in a wider network including posterior parietal cortex, prefrontal cortex, and the striatum. Despite the importance of the certainty/uncertainty distinction for various cognitive processes (Esber & Haselgrove, 2011; Mushtaq, Bland, & Schaefer, 2011; Rushworth & Behrens, 2008), the longstanding scientific interest in uncertainty (Bertelson & Boons, 1960), and the relevance of uncertainty processing for psychopathology (e.g., anxiety and depressive disorders; Grupe & Nitschke, 2013; Hélie, Shamloo, Novak, & Foti, 2017; Lake & Labar, 2011; Zald & Treadway, 2017), no ERP studies have directly examined the impact of certain vs. uncertain reward related cues in schizophrenia.

Most of the reward-related ERPs shows a distinct pattern for certainty effects. For cue evaluation, cP300 is larger during trials when reward is possible than during trials when reward is not possible (Broyd et al., 2012; Novak et al., 2016; Novak & Foti, 2015; Vignapiano et al., 2016). However, cP300 does not appear to show a distinct pattern for certainty effects because studies of the relationship between uncertainty and cP300 are confounded by the impact of reward incentives. During feedback anticipation, SPN appears to index the degree of uncertainty, as it is larger for uncertain than for certain trials (Foti & Hajcak, 2012; Hughes et al., 2013), is greater for improbable than for probable outcomes (Catena et al., 2012), and increases in amplitude as outcomes become more uncertain (Fuentemilla et al., 2013; Megías et al., 2017). For feedback receipt, fRewP is larger for uncertain than for certain outcomes (Eppinger, Kray, Mock, & Mecklinger, 2008; Hewig et al., 2007; Holroyd, Krigolson, Baker, Lee, & Gibson, 2009; Wu & Zhou, 2009), and fP300 shows a similar pattern (Hajcak et al., 2005; Hajcak et al., 2007; Pfabigan et al., 2011; Wu & Zhou, 2009). Although certainty effects are well understood in studies of healthy controls, to our knowledge no study has examined ERPs associated with certainty effects across stages of reward processing in schizophrenia.

People with schizophrenia have difficulty making predictions based on environmental cues (Culbreth, Gold, Cools, & Barch, 2016; Gold, Waltz, Prentice, Morris, & Heerey, 2008; Strauss et al., 2014), and this difficulty may be due in part to an impairment in processing uncertain cues. For example, people with schizophrenia demonstrate cognitive control

deficits (for review, see Barch, Culbreth, & Sheffield, 2018), and cognitive control is needed to resolve uncertainty (for review, see Mushtaq et al., 2011). These cognitive control deficits might also impair the maintenance of the value of a certain or uncertain cue (Strauss et al., 2014). Additionally, uncertainty relates to activity in dorsolateral prefrontal cortex and posterior parietal cortex (for meta-analysis, see White, Engen, Sørensen, Overgaard, & Shergill, 2014), and reduced activity in these brain regions during uncertain contexts has been observed in schizophrenia (Krug et al., 2014). These studies suggest that people with schizophrenia would show impairments in the processing of uncertainty, but it remains unclear whether the processing of certain cues is deficient or whether the ability to distinguish between certainty and uncertainty is impaired.

The Current Study

The primary goal of the present study was to determine whether patients with schizophrenia show an intact distinction between certain and uncertain conditions across three stages of reward processing. We used a novel cued reward paradigm that manipulated both certainty effects (certain and uncertain conditions) and valence effects (reward, loss, and neutral conditions). Regarding the primary research question of certainty effects, we predicted patients would show a diminished ability to distinguish between certain and uncertain conditions across the three stages of processing in light of the large cognitive control impairments seen in schizophrenia. The secondary aim was to determine whether patients show the expected valence-related differences in monetary outcomes: gain, loss, and breaking even (neither gain nor loss). For reward outcome we expected to replicate findings of an intact fRewP in schizophrenia, but the small number of studies for other ERP components did not support clear directional hypotheses.

Method

Participants

Study enrollment included 92 outpatients with schizophrenia and 74 healthy comparison participants (see Table 2). The research was approved by the Institutional Review Board at the VA Greater Los Angeles Healthcare System, and all participants provided written informed consent. These participants were part of a larger research project from which results for other experimental tasks have already been reported (Llerena, Wynn, Hajcak, Green, & Horan, 2016; Reddy, Waltz, Green, Wynn, & Horan, 2016). None of the ERP data presented in this manuscript have been reported elsewhere.

The schizophrenia group, but not the controls, were reassessed on EEG four weeks later to examine test-retest reliability of ERP scores. These data are not directly relevant to the research question addressed in the current paper, but they are included in the supplementary material if the reader is interested in the test-retest reliability of these ERP scores.

Psychiatric diagnoses were assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition (SCID-I/P; First, Spitzer, Gibbon, & Williams, 1996). Interviewers were trained to establish interrater reliability and obtained a minimum kappa of .75 for key psychotic and mood items and a minimum kappa of .85 for diagnostic

accuracy. Training materials included a library of videotaped interviews developed by the Treatment Unit of the Department of Veterans Affairs VISN 22 Mental Illness Research, Education, and Clinical Center. Exclusion criteria for patients included substance dependence in the last six months or abuse in the last month, an identifiable neurological disorder, a current mood episode, loss of consciousness for more than one hour, and limited fluency in English. All patients were clinically stable as indicated by no hospitalizations within three months prior to study participation, no medication changes within six weeks prior to study participation, and no changes in housing status in the two months prior to study participation. With regard to medication status, 84% of participants were using atypical antipsychotics, 7% were using typical antipsychotics, 5% were using both atypical and typical antipsychotics, and 5% were not using antipsychotic medications.

Healthy controls were recruited though postings on websites. Exclusion criteria for controls included a neurological disorder, loss of consciousness for more than one hour, a psychotic disorder in a first-degree relative, and limited fluency in English. Healthy controls were also excluded for a history of psychotic disorder, bipolar disorder, recurrent depression, a lifetime history of substance dependence, or substance abuse in the last month as assessed by the SCID-I/P. The Structured Clinical Interview for DSM-IV Axis II Disorders (First, Gibbon, Spitzer, Williams, & Benjamin, 1996) was administered to healthy controls to assess for and exclude those with avoidant, paranoid, schizoid, or schizotypal personality disorders.

Experimental Task

Participants completed a cued reward guessing task in order to examine three different stages of processing: cue evaluation, feedback anticipation, and feedback receipt. A schematic of an example trial can be seen in Figure 1. Each trial began with a 2,000 ms cue, which specified five possible outcomes for a particular trial: a complete green circle indicated a 100% chance of winning money, a half green and half white circle indicated a 50% chance of winning money and a 50% chance of breaking even (i.e., neither winning nor losing money), a whole white circle indicated a 100% chance of breaking even, a half red and half white circle indicated a 50% chance of losing money and a 50% chance of breaking even, and a whole red circle indicated a 100% chance of losing money. A fixation cross was then presented for 500 ms. The fixation cross was then replaced by two doors, and the participant selected one of the doors by pressing a left or right mouse button. Once the participant selected a door, the doors were removed from the screen and followed by a 1,500 ms fixation cross. Following the offset of the fixation cross, feedback was presented for 2,000 ms. The feedback stimulus consisted of one of three different stimuli: a green upward arrow indicated that the participant had won $0.50, a white “0” indicated that the participant had broken even, and a red downward arrow indicated that the participant had lost $0.25. These values were chosen to equate the subjective value of gains and losses (Tversky & Kahneman, 1992). Participants completed 140 trials (20 certain gain, 20 certain loss, 20 certain even, 40 uncertain gain, and 40 uncertain loss). Participants broke even on 50% of uncertain gain trials and on 50% of uncertain loss trials. The order of the trial type and feedback was random. Prior to beginning the task, participants were told that they would be given their cumulative winnings. Because the number of win/loss/even trials was fixed, cumulative earnings amounted to $10 for all participants.

Electrophysiological Data Recording and Reduction

EEG data recording and reduction procedures were identical for Session 1 and Session 2. Continuous EEG was recorded using an ActiveTwo BioSemi amplifier (BioSemi, Amsterdam, Netherlands). EEG signals were pre-amplified at the electrode with a gain of one and were digitized at a sampling rate of 1,024 Hz with a 24-bit analog-to-digital converter (least significant bit: 31.25 nV). EEG was filtered online using a low-pass, fifth-order sinc filter with a half-power cut-off of 204.8 Hz. EEG was recorded from 64 active scalp electrodes placed based on the 10/20 system using a custom cap (Cortech Solutions, Wilmington, North Carolina, USA). Two additional scalp electrodes were placed on the left and right mastoids. Electrooculogram was recorded from four additional sensors placed above and below the left eye and near the outer canthi. Electrodes were referenced online to a common mode sense electrode that formed a monopolar channel.

Data were subsequently filtered offline using ERPLab v6.1.4 (Lopez-Calderon & Luck, 2014). Cue- and feedback-related EEG data (i.e., cP300, fRewP, fP300) were digitally filtered using a sixth-order IIR Butterworth filter with half-amplitude cutoffs at .05 and 20 Hz. Feedback preceding activity (i.e., SPN) was digitally filtered using the same Butterworth filter but with half-amplitude cutoffs of .01 and 5 Hz. EEG data were algebraically rereferenced to averaged mastoids and epoched based on specifications reported below. Ocular artifact (i.e., eye blinks and saccadic eye movement) were then removed from the segmented waveforms using independent components analysis (ICA) implemented in the ERP PCA Toolkit v2.65 (Dien, 2010a). Specifically, any ICA components that correlated at .9 or above with the scalp topography of a blink template and at .8 or above with the scalp topography of vertical and horizontal saccade templates were removed from the data. Following ocular artifact correction, trials that contained more than a 100 μV step within 100 ms intervals or a voltage difference of 300 μV through the duration of the epoch were rejected.

Following artifact correction and rejection, individual-subject ERPs were analyzed, and EEG sites for analysis were chosen based on grand average waveforms and prior studies of cP300 (e.g., Novak & Foti, 2015), SPN (e.g., Brunia, van Boxtel, et al., 2011), fRewP (e.g., Foti, Weinberg, Dien, & Hajcak, 2011), and fP300 (e.g., Kujawa, Smith, Luhmann, & Hajcak, 2013). In order to reduce the biasing effects of background EEG noise on ERP measurements, all ERPs were scored using a mean amplitude approach (Clayson, Baldwin, & Larson, 2013; Luck, 2014).

Following data extraction of ERP measurements, the internal consistency of scores was assessed to ensure that ERP scores met appropriate standards (Clayson & Miller, 2017b; Hajcak, Meyer, & Kotov, 2017; Infantolino, Luking, Sauder, Curtin, & Hajcak, 2018). To this end, participants were excluded if their data did not have an adequate number of trials in a given ERP average to obtain reliability standards. The number of trials needed to achieve a reliability threshold of .70 was calculated. This threshold of .70 was deemed acceptable based on published guidelines for ERP score reliability for paradigms that are in the early stages of development (Clayson & Miller, 2017b), such as the one used in the current study. In addition to internal consistency, test-retest reliability of ERP scores was examined in people with schizophrenia, and these analyses are reported in the supplementary material.

Generalizability theory was used to calculate dependability, which is a measure of internal consistency analogous to Cronbach's alpha from classical test theory (see Baldwin, Larson, & Clayson, 2015; Brennan, 2001; Shavelson & Webb, 1991). ERP score reliability was examined using the ERP Reliability Analysis Toolbox v 0.4.7 (Clayson & Miller, 2017a). See supplementary material for additional information about reliability analyses. Supplementary Tables 1–4 summarize the number of trials needed to obtain a dependability point estimate of .70 for each ERP component and event type for certainty and valence effects. For the primary analyses of interest (i.e., examination of certainty effects), the data for all participants met the necessary trial cutoffs for each ERP, except for SPN (one control and one patient were excluded), and the overall internal consistency of the data was high (controls: $.83 < \phi s < .98$; patients: $.87 < \phi s < .98$).

For secondary analyses (i.e., examination of valence effects), the paradigm did not include enough trials to achieve adequate dependability for all valence effects during certain and uncertain conditions. Thus, trial cutoffs for the event types that were within the number of trials presented during the paradigm were used for determining exclusion criteria. These exclusion criteria resulted in up to one control and four patients be excluded from any given analysis of valence effects. Internal consistency estimates appeared lower for valence effects during certain conditions (controls: $.47 < \phi s < .83$; patients: $.63 < \phi s < .76$) than during uncertain conditions (controls: $.79 < \phi s < .90$; patients: $.77 < \phi s < .92$). Given the low internal consistency estimates for some valence effects for certain conditions, results should be interpreted with caution.

Cue-related activity.—Stimulus-locked epochs were extracted from 200 ms prior to presentation of the cue to 800 ms following cue presentation. The first 200 ms of the epoch served as a prestimulus baseline. Cue-related activity corresponding to cP300 was extracted as the average activity from 400 to 650 ms following cue presentation at Pz.

Feedback-preceding activity.—Stimulus-locked epochs were extracted from 200 ms prior to the offset of the doors to 1,500 ms following the offset of the doors. The first 200 ms of the epoch served as a prestimulus baseline. Feedback-preceding activity corresponding to SPN was extracted as the average activity from 1,000 to 1,500 ms following the offset of the doors. Activity was averaged over six right-frontal sites (FC4, FC6, C4, C6, F4, F6), because SPN is lateralized over the right-hemisphere (for review, see Brunia, van Boxtel, et al., 2011).

Feedback-related activity.—Stimulus-locked epochs were extracted from 200 ms prior to presentation of the feedback stimulus to 800 ms following feedback presentation. The first 200 ms of the epoch served as a prestimulus baseline. Feedback-related activity corresponding to fRewP was extracted as the average activity from 225 to 300 ms following feedback presentation at FCz and Fz. Feedback-related activity corresponding to fP300 was extracted as the average activity from 325 to 500 ms following feedback presentation at Cz.

Certainty effects appeared to broadly impact ERP activity within the fP300 time window (approximately 200 to 800 ms following the presentation of feedback). The robust fP300 response led to concerns of overlap between fP300 and fRewP. We conducted a

temporospatial principal components analysis (PCA) on feedback-related ERP activity, but we were not able to isolate fRewP from fP300 (see supplementary material). Given that fP300 exhibited a robust response and we were unable to isolate fRewP from fP300, we chose to focus solely on feedback-related activity indexed by fP300 throughout the remainder of the manuscript. fRewP findings are presented in the supplementary material.

Clinical Ratings

Symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS; Kay, Opler, & Lindenmayer, 1989). The PANSS is a 30-item structured interview that assessed five symptom dimensions: positive (observed internal consistency: Cronbach's $\alpha = .82$), negative ($\alpha = .84$), disorganized ($\alpha = .70$), excited ($\alpha = .72$), and anxiety/depression ($\alpha = .61$).

Data Analysis

The primary focus was on group differences for certainty processing for cue evaluation, feedback anticipation, and feedback receipt. Separate 2-Group (controls, patients) × 2-Certainty Effect (certain trials, uncertain trials) repeated measures analyses of variance (ANOVAs) were conducted for cP300, SPN, and fP300.

Follow-up secondary analyses were then conducted to examine valence effects within certain and within uncertain conditions. Valence effects within certain and uncertain outcomes were examined separately due to the asymmetry in outcomes across effects. On the one hand, uncertain gain trials could result in gain or breaking even outcomes, but not a loss outcome. On the other hand, uncertain loss trials could result in loss or breaking even outcomes, but not a gain outcome. Hence, the asymmetry in potential outcomes precludes the certainty effects and valence effects from being examined using one ANOVA for each ERP. For cP300 and SPN, separate 2-Group × 3-Valence Effect within Certain Outcomes (certain gain cues, certain loss cues, certain even cues) and 2-Group × 2-Valence Effect within Uncertain Outcomes (uncertain gain cues, uncertain loss cues) ANOVAs were conducted. For fP300, separate 2-Group × 3-Valence Effect within Certain Outcomes and 2-Group × 4-Valence Effect within Uncertain Outcomes (uncertain gain cues, gain outcomes; uncertain gain cues, even outcomes; uncertain loss cues, loss outcomes; uncertain loss cues, even outcomes) were conducted. For all ANOVAS, *partial-eta*^{2} $\left(\eta_p^2\right)$ was reported as a measurement of effect size, and a Huynh-Feldt epsilon adjustment was applied to correct for possible violations of sphericity for factors with more than two levels. Significant effects were followed up with independent samples or paired samples *t* tests. Cohen's *d* was reported as a measurement of effect size for *t* tests.

Results

Sample Characteristics

With regard to demographic characteristics (see Table 2 for summary information and statistical analyses), there was a larger proportion of women in the control group than in the patient group. Controls had higher personal, but not parental, levels of education compared with patients.

Cue-Related Activity

Summary information for cP300 scores are shown in Tables 3 and 4. Grand average waveforms for cP300 are shown in Figures 2 and 3, and voltage maps are shown in supplementary Figure 1. Main effects and interactions for each ANOVA on cP300 amplitude are shown in Table 5 and interpreted below.

cP300.

Certainty Effect.: The Group × Certainty ANOVA on cP300 showed a main effect of certainty. cP300 amplitude was larger for certain trials than for uncertain trials. The main effect of group and Group × Certainty interaction were not significant.

Valence Effect within Certain Trials.: The Group × Valence Effect ANOVA yielded a main effect of valence within certain outcomes. cP300 was larger for certain gain trials than for both certain loss trials and certain even trials, $t(156) = 2.37$, $p = .02$, $d = .19$; $t(156) = 7.59$, $p < .001$, $d = .61$, respectively. cP300 was also larger for certain loss trials than for certain even trials, $t(156) = 5.41$, $p < .001$, $d = .43$. The main effect of group and Group × Valence Effect interaction were not significant.

Valence Effect within Uncertain Trials.: A Group × Valence Effect ANOVA on cP300 amplitudes within uncertain outcomes did not yield any significant main effects or a significant interaction.

Feedback-Preceding Activity

Summary information for SPN amplitudes are shown in Tables 3 and 4. Grand average waveforms are shown in Figures 2 and 3, and voltage maps are shown in supplementary Figure 2. Main effects and interactions for each ANOVA on SPN amplitude are shown in Table 5 and interpreted below.

SPN.

Certainty Effect.: The Group × Certainty ANOVA yielded a main effect of certainty with larger SPN for uncertain trials than for certain trials. The main effect of group was not significant. The Group × Certainty interaction was significant. Only controls showed larger SPN for uncertain than for certain trials, $t(71) = -4.59$, $p < .001$, $d = .51$. None of the remaining comparisons were significant ($|ts| < 1.3$, $ps > .20$, $ds < .21$).

Valence Effect within Certain and Uncertain Trials.: Neither the Group × Valence ANOVA within certain outcomes nor the Group × Valence ANOVA within uncertain outcomes yielded any significant main effects or interactions.

Feedback Receipt Activity

Summary information for fP300 amplitudes are shown in Tables 3 and 6. Grand average waveforms are shown in Figures 2 and 4. Main effects and interactions for each ANOVA on fP300 amplitude are shown in Table 7 and interpreted below.

fP300.

Certainty Effect.: The Group × Certainty ANOVA on fP300 amplitude yielded a main effect of certainty with larger fP300 for uncertain than for certain trials. The main effect of group was not significant. The ANOVA also yielded a significant interaction. Controls and patients showed larger fP300 for uncertain trials than for certain trials, $t(72) = -9.21$, $p < .001$, $d = 1.08$; $t(88) = -6.21$, $p < .001$, $d = .66$, respectively. Patients showed larger fP300 for certain trials than controls, $t(159) = -4.06$, $p < .001$, $d = .64$, and group differences were not observed for uncertain trials, $t(159) = -.34$, $p = .74$, $d = .05$.

Valence Effect within Certain Trials.: A Group × Valence ANOVA on fP300 amplitude indicated a main effect of group with patients showing larger fP300 than controls. The main effect of valence was also significant. fP300 was larger for certain gain than for both certain loss and certain even trials, $t(160) = 2.37$, $p = .02$, $d = .19$; $t(160) = 10.02$, $p < .001$, $d = .79$, respectively. fP300 for certain loss trials was larger than for certain even trials, $t(160) = -8.37$, $p < .001$, $d = .66$. The Group × Valence interaction was not significant.

Valence Effect within Uncertain Trials.: The main effect of valence was significant, and the follow-up *t* tests are shown in Supplementary Table 5 and summarized here. fP300 was largest when the participant won than when the participant broke even or when it was possible to lose money (regardless of monetary outcome; ts > 6.8, ps < .001, ds > .54). When it was possible to lose money, fP300 was larger when the participant lost money than when the participant broke even (regardless of whether it was possible to win or lose money; ts > 4.0, ps < .001, ds > .31). fP300 amplitudes were similar when the participant broke even and it was possible to win or lose money, $t(160) = -1.10$, $p = .27$, $d = .09$. The main effect of group and Group × Valence interaction were not significant.

Discussion

The primary aim of the study was to determine whether people with schizophrenia demonstrate intact processing across three stages of reward processing under certain vs. uncertain conditions (i.e., certainty effects). To our knowledge this is the first study to examine certainty effects across multiple stages of reward processing in either healthy or schizophrenia samples within a single paradigm. Controls demonstrated the expected certainty effects (see Table 1), showing clear ERP differentiation between certain vs. uncertain conditions across all three stages. Although initial cue evaluation (i.e., cP300) was intact in the schizophrenia group, they showed an atypical pattern of reduced differentiation between certain vs. uncertain conditions during subsequent stages. During feedback anticipation (i.e., SPN), the schizophrenia group showed no distinction between certain and uncertain conditions. During feedback receipt (i.e., fP300), they showed a significant, but diminished, distinction between conditions. During feedback receipt, the schizophrenia group's ERPs were similar to controls for the *uncertain* context but were *larger* than controls for the certain context. In other words, the schizophrenia group appeared to process certain events more similar to uncertain events than controls did. These findings show, for the first time across multiple stages of reward processing, that the fundamental distinction between certain and uncertain reward processing is altered in schizophrenia.

Certainty Effects Across Reward-Processing Stages

Our multi-stage paradigm enabled us to identify how abnormal certainty effects temporally unfold in schizophrenia. During the initial cue evaluation stage, both groups showed a similarly clear cP300 differentiation between the certain versus uncertain conditions. While this finding might appear inconsistent with prior studies showing impaired processing in uncertain conditions in schizophrenia, the other studies used tasks that involved relatively complex learning and risky/implicit decision making processes (e.g., Albrecht, Waltz, Frank, & Gold, 2016; Cheng, Tang, Li, Lau, & Lee, 2012; Fond et al., 2013; Reddy et al., 2013). An important feature of the present paradigm is that participants were informed via explicit cues about the upcoming probability (100% vs. 50%) of reward, punishment or breaking even outcomes, without the added cognitive processing demands like those in prior studies. Thus, the schizophrenia group was able to properly encode the basic distinction between certain and uncertain contexts in response to explicit and simple cues in our paradigm that removed cognitive challenges in understanding for participants.

Despite intact initial encoding, the schizophrenia group showed disturbed certainty effects in the subsequent stages. During feedback anticipation, SPN amplitudes did not differentiate between certain and uncertain conditions in the schizophrenia group. This is consistent with neuroimaging and self-report studies showing impaired anticipation of reward or pleasure in this disorder (Buck & Lysaker, 2013; Li et al., 2015; Radua et al., 2015; Subramaniam et al., 2015). It has been proposed that impairments in reward anticipation might be due to deficits in either cue responsivity or cognitive control (e.g., Culbreth, Moran, & Barch, 2017). Our findings suggest deficits in cognitive control rather than cue responsivity, because cP300 amplitudes were intact in the schizophrenia group. Hence, cognitive control is more likely to contribute to anticipatory disturbances in schizophrenia.

During feedback receipt, the schizophrenia group continued to show a diminished certainty effect. This reflected exaggerated fP300 responses in the certain condition but normal fP300 in the uncertain condition. The schizophrenia group's tendency to process certain events more similar to uncertain events than controls did is maladaptive in light of the widely held view that certainty is inherently desirable, whereas uncertainty is inherently aversive and makes greater demands on cognitive control processes (Ladouceur et al., 2000; Luhmann et al., 2008; Reuman et al., 2015). Furthermore, intolerance of uncertainty (e.g., Grupe & Nitschke, 2013), an aversion of uncertainty that reflects a belief that a negative event will likely occur, is commonly observed in other forms of psychopathology, particularly internalizing disorders such as anxiety disorders and depression (Carleton, 2014; Grupe & Nitschke, 2013; Lake & Labar, 2011; McEvoy & Mahoney, 2012; Tanovic, Gee, & Joormann, 2018). The schizophrenia group, in contrast, showed an atypical response to feedback receipt that could reflect a belief that certainty is improbable. Speculatively, a fundamental disturbance in the ability to distinguish feedback during certain versus uncertain contexts could impact reality testing, and thereby contribute to the onset or maintenance of delusional beliefs or hallucinatory experiences. A bias toward processing feedback as though it is uncertain would also be expected to adversely impact a variety of cognitive control and motivational processes required for adaptive functioning (Esber & Haselgrove, 2011; Mushtaq et al., 2011; Rushworth & Behrens, 2008).

Valence Effects Across Reward-Processing Stages

There were no group differences in valence effects for any stage of reward processing during either certain or uncertain conditions. This finding converges with a few studies showing normal valence-related activity in schizophrenia for cP300 during cue evaluation (Vignapiano et al., 2016) and for fP300 (Houthoofd et al., 2013) during feedback receipt. These findings are also broadly consistent with ERP studies of the late positive potential that showed intact valence-related effects for responses to emotional images in schizophrenia (e.g., Horan, Foti, Hajcak, Wynn, & Green, 2012; Horan, Wynn, Kring, Simons, & Green, 2010). However, nonsignificant group differences for valence effects should be interpreted in the context of lower internal consistency for valence effects than for certainty effects, particularly for valence types within certain trials. In this novel paradigm there were fewer trials for each valence type, and future work should include more trials per valence type to ensure adequate internal consistency.

Limitations and Conclusion

The following limitations should be considered. First, individuals with schizophrenia were mostly male, and sex differences have been observed for some of the present ERPs, such as SPN (Greimel et al., 2018). However, follow-up analyses indicated that none of the main effects of sex or interactions with sex were significant $\left(Fs < 3.7, ps > .05, \eta_p^2 s < .03\right)$, but these nonsignificant effects might be due to low statistical power for examining sex as a factor. It is also possible that a history of substance abuse/dependence or major depressive episodes contributed to the present findings in the patient sample (see Supplementary Table 15; Baskin-Sommers & Foti, 2015). Follow-up analyses separately added history of substance abuse/dependence and history of major depressive episodes to the ERP ANOVAs, and these ANOVAs did not yield any significant main effects or interactions associated with either additional factor $\left(Fs < 4.0, ps > .05, \eta_p^2 s < .04\right)$. Second, individuals with schizophrenia were also chronically ill, and it is unclear whether present findings would generalize to individuals in the early course of the illness. Third, individuals with schizophrenia were receiving antipsychotic medications and other types of medication at clinically determined dosages, which might have impacted ERP findings. For example, a study of P300 to performance-related feedback indicated that P300 amplitude in schizophrenia was comparable to healthy controls only after individuals with schizophrenia were treated with antipsychotic medications (Houthoofd et al., 2013). Additional research is needed in determine the impact of medication treatment on ERPs associated with reward processing. Fourth, it is possible that people with schizophrenia were unable to distinguish between certain and uncertain contexts, because they failed to understand or remember the meaning of the cues. Although we did not directly test whether patients understood the meaning of each cue, group differences were not observed in cP300 amplitudes for certainty effects or valence effects, which suggests that initial cue evaluation was intact.

The present paradigm was designed to examine the impact of certainty effects and valence effects across three reward processing stages. However, the manipulation of both certainty and valence limited the interpretation of some ERP effects. For example, cP300 differentiation between certain and uncertain outcomes was impacted by valence effects

within certain trials, such that certain gain and certain loss trials were related to larger cP300 than certain even trials, but cP300 did not significantly differentiate between valence effects with uncertain trials. During feedback receipt, we were unable to examine fRewP activity due to the robust, overlapping fP300 response elicited by uncertainty (see supplementary material). Future research might consider whether certainty effects can be fully disentangled from valence effects during each stage of reward processing using alternative paradigms.

Despite these limitations, the present study highlights a fundamental impairment in distinguishing between certainty and uncertainty in people with schizophrenia. Distinguishing between certainty and uncertainty is a vital process, because predicting the future requires consideration of the probabilities of potential outcomes. The prediction of rewards based on information in the environment is essential for independent living. Although valence effects have received considerable attention in schizophrenia, future research should also consider certainty effects in schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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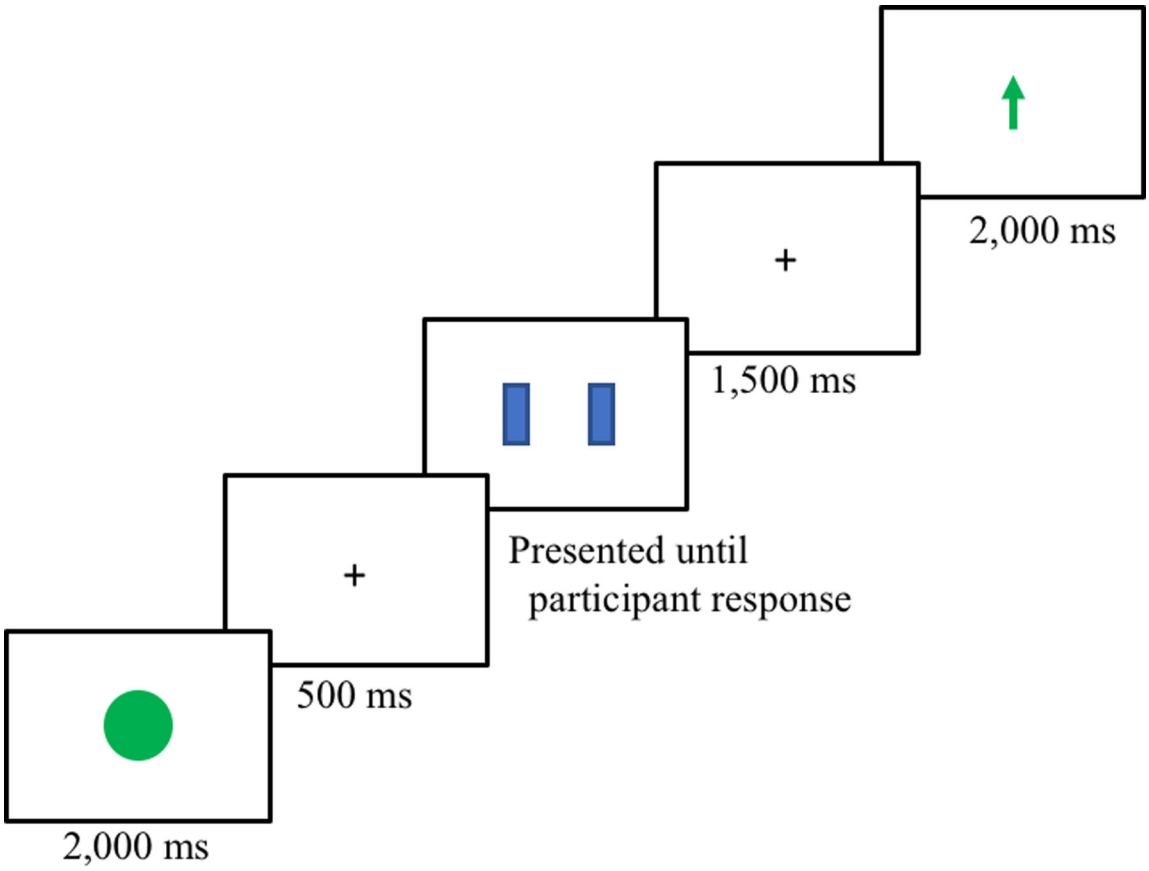

Figure 1.
An example schematic of a certain gain trial.

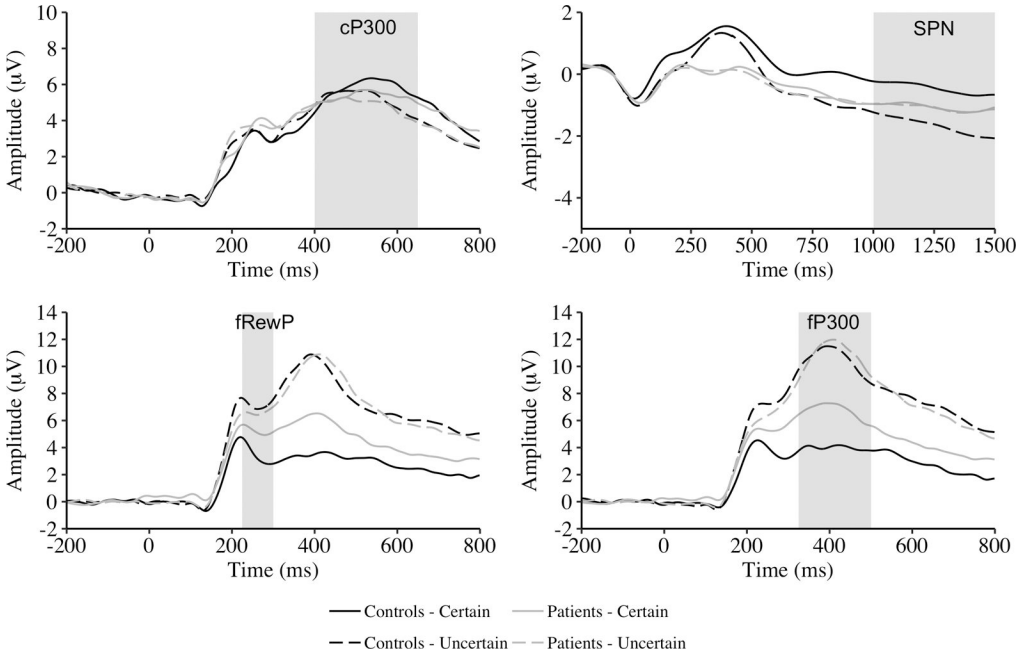

Figure 2.

Grand average waveforms for cue-related activity (i.e., cue P300 [cP300]), feedback-preceding activity (i.e., stimulus-preceding negativity [SPN]) and feedback receipt (i.e., feedback P300 [fP300]) for certain and uncertain trials as a function of group. Note different amplitude scales.

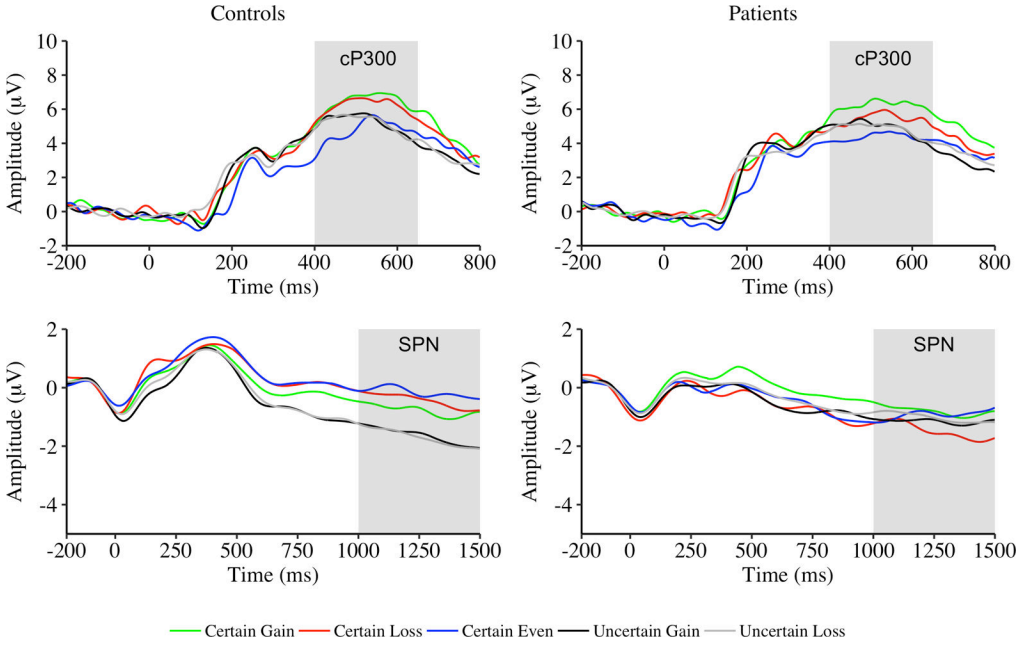

Figure 3.

Grand average waveforms for cue-related activity (i.e., cue P300 [cP300]) and feedback-preceding activity (i.e., stimulus-preceding negativity [SPN]) for certain and uncertain trials as a function of valence effect and group. Note different amplitude scales.

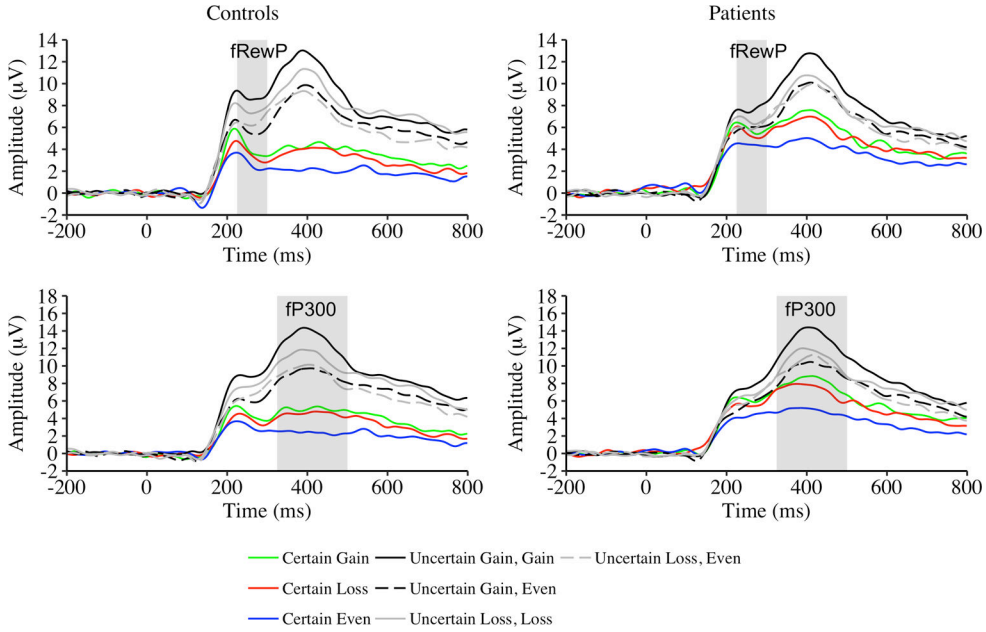

Figure 4.

Grand average waveforms for feedback receipt (i.e., feedback P300 [fP300]) for certain and uncertain trials as a function of valence effect and group.

Table 1

Event-Related Potential Components Associated with Reward Processing Across Three Stages: Cue Evaluation, Reward Anticipation, and Feedback Receipt

	Cue Evaluation	Feedback Anticipation	Feedback Receipt	
	cP300	**SPN**	**fRewP**	**fP300**
Certain vs Uncertain	-	Uncertain > Certain	Uncertain > Certain	Uncertain > Certain
Valence Effect	Reward and Loss > Neutral	Reward and Loss > Neutral	Reward > Neutral > Loss	Reward and Loss > Neutral

Note: Certain > uncertain indicates that ERPs are larger for certain events than for uncertain events. The impact of certainty on cP300 has not been studied independently of valence effects. The valence effect describes the pattern of findings for reward, loss, and neutral outcomes. For a recent review, see Glazer et al. (2018). cP300 = cue P300; SPN = stimulus-preceding negativity; fRewP = feedback reward positivity; fP300 = feedback P300

Table 2

Summary of Demographics and Clinical Symptoms

Characteristic	Controls		Patients			
	***n* = 74**		***n* = 92**			
	n		***n***			
Female/Male	34/40		22/70		$X^2 = 7.95$, $p < .01$	
	Mean	***SD***	***Mean***	***SD***	***t***	***P***
Age (yrs)	47.8	8.3	49.9	10.3	−1.46	.15
Education (yrs.)	14.6	1.8	13.1	1.8	5.03	< .01
Parental Education (yrs.)[1]	14.3	3.0	13.8	3.3	1.01	.32
Symptoms						
PANSS - Negative Symptoms	-	-	15.2	6.5		
PANSS - Positive Symptoms	-	-	18.0	7.2		
PANSS - Disorganized Symptoms	-	-	12.1	3.9		
PANSS - Excited	-	-	5.6	2.4		
PANSS - Depression/Anxiety	-	-	7.1	2.7		

Note:

[1] Information is missing for one control and three patients.

PANNS = Positive and Negative Syndrome Scale

Table 3

Summary of ERP Amplitudes (μV) for Certain and Uncertain Trials for Controls (n = 73) and Patients (n = 89)

Component	Group	Certain	Uncertain
		M (SD)	***M (SD)***
cP300	Controls	5.8 (4.5)	5.2 (4.1)
	Patients	5.2 (3.9)	4.8 (3.6)
SPN	Controls	−.1 (0.8)	−.4 (0.8)
	Patients	−.2 (0.9)	−.2 (1.0)
fP300	Controls	4.1 (3.7)	10.6 (6.8)
	Patients	6.8 (4.8)	10.9 (7.0)

Note. cP300 = cue P300; SPN = stimulus-preceding negativity; fP300 = feedback P300

Table 4

Summary of cP300 and SPN Amplitudes (μV) as a Function of Certain/Uncertain Outcome and Group

Component	Group		Certain Gain	Certain Loss	Certain Even	Uncertain Gain	Uncertain Loss
		n	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***
cP300	Controls	72	6.4 (5.1)	6.2 (4.5)	4.7 (5.1)	5.2 (4.3)	5.2 (4.4)
	Patients	85	6.2 (4.3)	5.4 (4.1)	4.4 (4.3)	4.9 (4.0)	4.8 (3.6)
SPN	Controls	71	−.1 (10)	−.1 (10)	−1 (0.9)	−.4 (0.9)	−.4 (0.9)
	Patients	85	−.2 (1.0)	−.3 (1.0)	−.2 (0.9)	−.3 (1.0)	−.3 (1.0)

Note. cP300 = cue P300; SPN = stimulus-preceding negativity

Table 5

Analyses of Variance (ANOVAs) for cue P300 (cP300) and Stimulus Preceding Negativity (SPN) Amplitudes

ERP	ANOVA	Effect	
cP300	Group × Certainty Effect	Group	$F(1, 160) = 0.69$, $p = .41$, $\eta_p^2 = .004$ CI[.00, .05]
		Certainty	$F(1, 160) = 13.12$, $p < .001$, $\eta_p^2 = .08$ CI[.02, .16]
		Interaction	$F(1, 160) = 0.57$, $p = .45$, $\eta_p^2 = .004$ CI[.00, .04]
	Group × Valence Effect within Certain Condition	Group	$F(1, 155) = 0.46$, $p = .50$, $\eta_p^2 = .003$ CI[.00, .04]
		Certain Outcome	$F(2, 310) = 31.24$, $p < .001$, $\eta_p^2 = .17$ CI[.10, .24]
		Interaction	$F(2, 310) = 0.79$, $p = .46$, $\eta_p^2 = .005$ CI[.00, .03]
	Group × Valence Effect within Uncertain Condition	Group	$F(1, 155) = 0.27$, $p = .61$, $\eta_p^2 = .002$ CI[.00, .04]
		Uncertain Outcome	$F(1, 155) = 0.03$, $p = .87$, $\eta_p^2 < .001$ CI[.00, .02]
		Interaction	$F(1, 155) = 0.002$, $p = .97$, $\eta_p^2 < .001$ CI[.00, .004]
SPN	Group × Certainty Effect	Group	$F(1, 158) < 0.01$, $p = .96$, $\eta_p^2 < .001$ CI[.00, .009]
		Certainty	$F(1, 158) = 15.74$, $p < .001$, $\eta_p^2 = .09$ CI[.02, .18]
		Interaction	$F(1, 158) = 12.65$, $p < .001$, $\eta_p^2 = .07$ CI[.01, .16]
	Group × Valence Effect within Certain Condition	Group	$F(1, 154) = 1.58$, $p = .21$, $\eta_p^2 = .01$ CI[.00, .06]
		Certain Outcome	$F(2, 308) = 1.14$, $p = .32$, $\eta_p^2 = .01$ CI[.00, .03]
		Interaction	$F(2, 308) = 0.33$, $p = .72$, $\eta_p^2 = .002$ CI[.00, .02]
	Group × Valence Effect within Uncertain Condition	Group	$F(1, 154) = 0.70$, $p = .41$, $\eta_p^2 = .005$ CI[.00, .05]
		Uncertain Outcome	$F(1, 154) = 0.12$, $p = .73$, $\eta_p^2 = .001$ CI[.00, .03]
		Interaction	$F(1, 154) = 0.43$, $p = .52$, $\eta_p^2 = .003$ CI[.00, .04]

Note. Significant main effects and interactions (*ps* < .05) are bolded for ease of identification. Significant analyses are interpreted in the cP300 and SPN sections of the Results. CI = 95% confidence interval for η_p^2.

Table 6

Summary of fP300 Amplitudes (μV) as a Function of Certain/Uncertain Outcome and Group

Component	Group		Certain Gain	Certain Loss	Certain Even	Uncertain Gain, Gain	Uncertain Gain, Even	Uncertain Loss, Loss	Uncertain Loss, Even
		n	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***
fP300	Controls	72	5.0 (4.5)	4.5 (4.2)	2.4 (3.6)	13.0 (7.9)	9.1 (7.2)	10.9 (7.3)	9.2 (6.6)
	Patients	89	8.1 (5.6)	7.3 (5.4)	4.9 (4.8)	13.0 (8.1)	9.6 (6.5)	10.9 (7.5)	10.1 (7.4)

Note. fP300 = feedback P300

Table 7

Analyses of Variance (ANOVAs) for feedback P300 (fP300) Amplitudes

ERP	ANOVA	Effect	
fP300	Group × Certainty Effect	Group	$F(1, 160) = 3.59$, $p = .06$, $\eta_p^2 = .02$ CI[.00, .08]
		Certainty	$F(1, 160) = 119.21$, $p < .001$, $\eta_p^2 = .43$ CI[.31, .52]
		Interaction	$F(1, 160) = 5.85$, $p = .02$, $\eta_p^2 = .04$ CI[.001, .11]
	Group × Valence Effect within Certain Condition	**Group**	$F(1, 159) = 16.47$, $p < .001$, $\eta_p^2 = 09$ CI[.03, .19]
		Certain Outcome	$F(2, 318) = 58.19$, $p < .001$, $\eta_p^2 = .27$ CI[.19, .34]
		Interaction	$F(2, 318) = 0.48$, $p = .62$, $\eta_p^2 = .003$ CI[.00, .02]
	Group × Valence Effect within Uncertain Condition	Group	$F(1, 159) = 0.11$, $p = .74$, $\eta_p^2 = .001$ CI[.00, .03]
		Uncertain Outcome	$F(3, 477) = 56.35$, $p < .001$, $\eta_p^2 = .26$ CI[.19, .32]
		Interaction	$F(3, 477) = 0.92$, $p = .43$, $\eta_p^2 = .006$ CI[.00, .02]

Note. Significant main effects and interactions (*ps* < .05) are bolded for ease of identification. Significant analyses are interpreted in the fP300 section of the Results. CI = 95% confidence interval for η_p^2.