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Impaired anticipatory event-related potentials in schizophrenia

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ABSTRACT

Deficits in anticipation are implicated across a variety of cognitive and emotional processes in schizophrenia. Although diminished anticipatory event-related potentials (ERPs) have been detected during tasks requiring motor response preparation in schizophrenia, no prior ERP study has examined non-motor-related anticipatory processes or used motivationally engaging stimuli. Thirty-four schizophrenia outpatients and 36 healthy controls completed a cued, reaction-time contingent picture viewing task to assess two types of anticipatory ERPs, one involving motor response preparation (Contingent Negative Variation [CNV]) and one not involving motor preparation (Stimulus Preceding Negativity [SPN]). The ERP paradigm included emotional and non-emotional pictures, and participants also completed trait anhedonia questionnaires. Patients and controls demonstrated similar patterns of reaction time and self-reported emotional responses to the pictures. However, patients demonstrated generally lower CNV and SPN across pleasant, neutral, and unpleasant picture conditions. Patients also reported lower anticipatory pleasure than controls on a trait questionnaire. Schizophrenia patients demonstrate diminished motor- and non-motor-related anticipatory processing, which may have wide-ranging adverse functional consequences.

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1. Introduction

Anticipation of future events is critical for adaptive functioning across a wide array of activities in daily life, ranging from basic cognitive operations required to efficiently perform simple tasks to complex, future-oriented emotional processes that support motivated behavior. These anticipatory processes enable us to prepare for and consider the potential consequences of forthcoming events rather than respond to such events in a purely reactive manner. The event-related potential (ERP) is a particularly useful tool for investigating early anticipatory processes as the ERP can provide a direct cortical measure of anticipatory processes on the scale of milliseconds to seconds. Distinct aspects of anticipatory processing have been linked to different ERPs, and disturbances in these ERPs are seen in several clinical populations, such as patients with Parkinson's disease or amyotrophic lateral sclerosis (Verleger, 2004; Mattox et al., 2006). Although anticipatory deficits across cognitive and emotional domains have been implicated in schizophrenia, the scope and neural correlates of these deficits remain unclear. The goal of the current investigation is to evaluate distinct anticipatory ERPs in schizophrenia using a paradigm adapted from basic neuroscience research.

1.1. Anticipatory processes and ERPs

Although a variety of terms have been used to describe anticipatory ERPs (see van Boxtel and Bocker, 2004 for a review), a broad distinction can be made between motor and non-motor anticipatory response components. The most extensively studied anticipatory ERP, the Contingent Negative Variation (CNV), is a complex waveform believed to consist of motor as well as non-motor components (van Boxtel and Bocker, 2004). The CNV is typically studied using so-called S1–S2 paradigms involving neutral tones or visual stimuli, in which an S1 "warning" stimulus indicates a forthcoming S2 "imperative" stimulus that signals the participant to perform a speeded button press or some other action. When the interval between S1 and S2 is sufficiently long (e.g., 4000 ms), following an early orienting response (i.e., at around 1000 ms), the late CNV is a slowly-increasing negative potential with a maximal response at fronto-central scalp locations just before S2 is presented. Although the functional significance of the late CNV has been extensively studied and debated, it appears to include at least two components. One component clearly involves motor preparation or readiness prior to making a response to S2. In addition, the late CNV component also involves non-motor anticipatory processes. This is supported by evidence that the amplitude of the CNV is affected by

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non-motor experimental manipulations (van Boxtel and Bocker, 2004).

Enhanced negativity can also be detected in certain S1–S2 tasks even without motor requirements. This Stimulus Preceding Negativity (SPN) is reliably detected in paradigms that involve anticipation of feedback about the correctness of prior performance, stimuli providing an instruction about a future response, or stimuli that are motivationally significant (van Boxtel and Bocker, 2004). Like the CNV, SPN is maximal just prior to the onset of the second stimulus at fronto-central scalp sites, though the amplitude is typically smaller than the CNV.

One factor that impacts the magnitude of both CNV and SPN is the emotional nature of the stimuli used in anticipatory paradigms (for reviews see Bocker et al., 2001; van Boxtel and Bocker, 2004). For example, using variants of a constant foreperiod S1–S2 picture viewing task, Simons and colleagues demonstrated that both CNV and SPN were larger during anticipation of pleasant pictures than neutral pictures, though the effect was most robust under conditions that involved a task relevant motor response (Simons et al., 1979). Similar patterns of CNV and SPN have been reported in other paradigms involving pleasant and unpleasant pictures, threat of unpleasant noise or painful shock, and monetary reward or punishment feedback based on task performance (Klorman and Ryan, 1980; Lutzenberger et al., 1981; Larbig et al., 1982; Kotani et al., 2001; Kotani et al., 2003; Ohgami et al., 2004; Poli et al., 2007). The influence of the emotional quality of the stimuli on these ERPs is thought to reflect engagement of fundamental motivational systems during anticipation of salient stimuli (Bradley and Lang, 2007). Thus, the CNV and SPN are reliable neural markers of anticipatory processes that may be usefully applied to schizophrenia.

1.2. Schizophrenia and anticipation

Disturbances in anticipatory processes have been implicated in schizophrenia across several levels of analysis. For example, anticipatory disturbances have been linked to performance deficits on basic neurocognitive measures, such as anti-saccade, cued reaction time, and choice anticipation tasks (Fuller and Jahanshahi, 1999; Quintana et al., 2004; Avila et al., 2006), as well as to impairments in foresight in daily life (Eack and Keshavan, 2008). Anticipatory processes have also been linked to emotional disturbances in schizophrenia, particularly the negative symptom of anhedonia. Our group recently reported converging evidence of impaired anticipatory pleasure, but normal consummatory or "in-the-moment" pleasure, in schizophrenia across studies using self-report trait questionnaires and the experience sampling method (Gard et al., 2006). These findings are bolstered by a set of fMRI studies (Juckel et al., 2006a; Juckel et al., 2006b) that found patients showed less activation in the ventral striatum than healthy controls during reward anticipation. Further understanding of the scope and neural correlates of anticipatory deficits may help explain several aspects of maladaptive functioning in schizophrenia.

A number of studies have reported diminished CNV in schizophrenia using standard cognitive paradigms, including S1–S2 paradigms using simple visual and auditory stimuli, saccadic eye movement tasks, and delayed match-to-sample tasks (Pritchard, 1986; Klein et al., 1997; Klein et al., 2000; Karayanidis et al., 2006). However, the extent to which diminished CNV in these tasks merely reflect impaired motor response preparation is unclear, as motor abnormalities (even those not associated with antipsychotic side effects) are well documented in schizophrenia (Morrens et al., 2007). To the best of our knowledge, only one study has attempted to evaluate both CNV and SPN in schizophrenia. Using a saccadic eye movement task, Reuter et al. (2006) reported that patients demonstrated impaired CNV but intact SPN, which was interpreted as reflecting impaired action readiness in schizophrenia. However, the experimental conditions used to assess CNV and SPN in their paradigm both involved motor response preparation, making it difficult to distinguish between motor and non-motor anticipatory processes. Also relevant is a series of studies by Simons and colleagues (Simons, 1982; Simons et al., 1982) that used their picture viewing paradigm in non-clinical subjects with elevated scores on the Physical Anhedonia Scale (Chapman et al., 1976), a trait associated with schizophrenia (see Horan et al., 2006 for a review). Anhedonic subjects failed to demonstrate greater CNV and SPN negativity during anticipation of pleasant versus neutral pictures, suggesting that anhedonia may be linked to hypo-responsivity during anticipation of pleasant stimuli. Further research using motivationally significant stimuli that clearly distinguishes between motor and non-motor anticipatory responses can help illuminate the nature of anticipatory ERP deficits in schizophrenia.

1.3. The current study

The current study sought to clarify the scope of anticipatory ERP deficits in schizophrenia using a cued, reaction-time contingent picture viewing task adapted from the paradigm developed by Simons and colleagues. The task was designed to assess both CNV and SPN within a single paradigm. The task stimuli consisted of standardized pictures depicting pleasant, neutral, and unpleasant content. Two primary research questions were addressed:

1. Do individuals with schizophrenia demonstrate diminished anticipatory ERPs across intervals involving a cued motor response (CNV) and no motor response (SPN)? Based on prior research, we expected smaller CNV in the patient group. However, the literature did not lead to a clear prediction regarding SPN.
2. Do anticipatory ERPs differ in patients compared to controls as a function of the emotional valence of picture content? Our prior findings from self-report measures led us to predict that patients would demonstrate smaller anticipatory ERPs than controls during anticipation of pleasant as compared to neutral pictures, though we did not have a clear directional hypothesis for negative pictures.

A secondary goal of the study was to examine whether individual differences in self-reported trait anhedonia, anticipatory pleasure, and in clinically rated negative symptoms within the schizophrenia group were related to CNV and SPN.

2. Materials and methods

2.1. Participants

Forty-eight stabilized outpatients with schizophrenia and 41 healthy control subjects participated in the study. Fourteen patients and 5 controls were excluded from the analyses due to not having a sufficient number of acceptable EEG trials (see below). Thus, the final sample consisted of 34 patients and 36 controls. Schizophrenia patients were recruited from outpatient treatment clinics at the Veterans Affairs (VA) Greater Los Angeles Healthcare System and through presentations in the community. Patients met criteria for schizophrenia based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; Frist et al., 1996b). Patients with schizoaffective disorder (i.e., a substantial proportion of their illness involved mood episodes) were not included and none of the patients was in a major depressive episode at the time of testing. Exclusion criteria for patients included: substance abuse or dependence in the last six months; mental retardation; a history of loss of consciousness for more than 1 h; an identifiable neurological disorder; or insufficient fluency in English. Twenty-nine patients were receiving atypical antipsychotic medications, two patients were receiving typical antipsychotic medications, and three were receiving both types of medication. Four patients were prescribed benzodiazepines, and

these patients were asked to refrain from taking these medications on the day of testing (i.e., at least 12 h before assessment).

Healthy controls were recruited through flyers posted in the local community and newspaper advertisements in local newspapers. An initial screening interview excluded potential controls who had any identifiable neurological disorder or head injury, had schizophrenia or other psychotic disorder in a first-degree relative, and were not sufficiently fluent in English. Potential controls were screened with the SCID and excluded for history of schizophrenia or other psychotic disorder, bipolar disorder, recurrent depression, lifetime history of substance dependence, or any substance abuse in the last 6 months. Potential controls were also administered portions of the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II; Frist et al., 1996a) and excluded if they had avoidant, paranoid, schizoid, or schizotypal personality disorder.

All SCID interviewers were trained through the Treatment Unit of the Department of Veterans Affairs VISN 22 Mental Illness Research, Education, and Clinical Center (MIRECC) to a minimum kappa of 0.75 for key psychotic and mood items. All participants had the capacity to give informed consent and provided written informed consent after all procedures were fully explained in accordance with procedures approved by the Institutional Review Boards at UCLA and the VA Greater Los Angeles Healthcare System. The participants in this study also participated in a companion study that examined electrophysiological correlates of consummatory pleasure (Horan et al., 2010).

2.2. Clinical ratings

2.2.1. Brief Psychiatric Rating Scale (BPRS)

For all patients, psychiatric symptoms during the previous month were rated using the expanded 24-item UCLA version of the BPRS (Overall and Gorham, 1962; Lukoff et al., 1986) by a trained rater. From this version of the BPRS, five empirically derived subscales scores were computed (Guy, 1976).

2.2.2. Scale for the Assessment of Negative Symptoms (SANS)

Negative symptoms during the preceding month were evaluated using the SANS (Andreasen, 1984) by a trained rater. Four SANS global scales (not including attention (Blanchard and Cohen, 2006)) were used in the current study: Affective flattening, Alogia, Anhedonia–Asociality, and Avolition–Apathy.

2.3. Trait measures

2.3.1. Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006)

Participants rate 18 items on a 6-point scale (1 = very false to 6 = very true) to describe how much pleasure they experience when anticipating or directly engaging in activities that are typically considered to be pleasurable. The scale is comprised of separate Anticipatory and Consummatory pleasure subscales, which demonstrate good psychometric properties and convergent/discriminant validity (Gard et al., 2006).

2.3.2. Trait anhedonia measures

All participants completed the Social Anhedonia Scale (Eckblad et al., 1982) and the Physical Anhedonia Scale (Chapman et al., 1976). These scales demonstrate good psychometric properties and have been extensively utilized in schizophrenia research (Edell, 1995).

2.4. Procedures

A cued reaction-time-contingent picture viewing task (Simons et al., 1979; Simons et al., 1982) was used to assess ERPs during two types of anticipatory intervals: one preceding a cued motor response (i.e., CNV) and a second preceding the presentation of an expected emotional stimulus without a motor response (i.e., SPN). Of the two ERPs, picture valence-related effects tend to be more robust with the CNV. However, we did not only want to use the CNV due to well-established motor slowing in schizophrenia. Based on piloting of various task parameters (e.g., cue modality and duration of anticipatory intervals), the following procedures were used.

2.4.1. Reaction time task

First, each participant completed a reaction time (RT) task to establish an individually-calibrated cut-off score for "fast" versus "slow" button presses. We elected to use individualized cut-off scores due to the well-documented overall increases in reaction time in schizophrenia (Morrens et al., 2007). This procedure also helped ensure that participants in both groups would be exposed to comparable numbers of "short" versus "long" picture presentations in the SPN portion of each trial (described below). Participants were asked to press the spacebar on a keyboard as fast as possible to the offset of a visual (fixation point) and auditory (1500 Hz tone) cue, simultaneously presented for 3000 ms. Each participant completed twenty trials for determining an optimal RT cut-off. A 3rd quartile cut-off was used to determine each participant's individual RT threshold (i.e., their threshold was set at the 75% slowest trial) to be used in the experimental trials.

2.4.2. Anticipation task stimuli

The stimuli for the task were 20 pleasant, 20 unpleasant, and 20 neutral valence pictures, each presented twice in randomized order, from the International Affective Picture System (IAPS; Lang et al., 1999).[1] Local IRB constraints led us to exclude pictures with extremely graphic scenes involving weapons, violence, physical injuries/deformities, or nudity. Pictures from the three categories differed on mean normative ratings (9-point scales, pleasant high) of valence (pleasant: M = 7.76; neutral: 4.90; unpleasant: 3.15). In addition, the emotional pictures were higher on normative arousal ratings than neutral (pleasant: 4.48; unpleasant: 5.86; neutral: 2.62). Stimuli were presented on a 17 in. CRT monitor positioned 1 m in front of the participant. Stimulus presentation and synchronization was administered through E-Prime v1.1 (PST Technologies, Pittsburgh, PA).

2.4.3. Anticipation task

The EEG recording session began by providing task instructions to participants and administering five practice trials to ensure participant comprehension. An overview of the trial structure is presented in Fig. 1. Each trial began with a 1000 ms fixation point displayed on the screen followed by a 500 ms blank screen. A visual cue and a 1500 Hz tone were then simultaneously presented for 3000 ms. The visual cue consisted of either a "+" sign, a "−" sign, or a "O", indicating whether a subsequently presented picture would be pleasant, unpleasant or neutral picture, respectively. Participants were instructed to press the space bar as fast as possible when the cue ended. This initial portion of the trial closely matches cued-reaction time procedures typically used to assess CNV. Following cue offset, a 4000 ms blank screen was presented. Then, a pleasant, unpleasant, or neutral picture corresponding to the earlier cue was presented (no motor response involved). The length of picture presentation was determined by how quickly the participant responded to the initial cue offset. If the participant responded faster than his/her individual RT threshold, the picture was presented for 5000 ms; if the participant responded slower than threshold, the picture was presented for only 500 ms. We expected participants to demonstrate faster RTs for emotional pictures based on consistent evidence that healthy subjects freely choose to view both pleasant and unpleasant

[1] Unpleasant: 1051, 1300, 1301, 2141, 2276, 2700, 2722, 3230, 3350, 6836, 8485, 9000, 9280, 9290, 9340, 9373, 9480, 9560, 9912, and 9920; Neutral: 2190, 2210, 2215, 2230, 2441, 2570, 2850, 5510, 5531, 6150, 7000, 7006, 7034, 7035, 7050, 7080, 7090, 7130, 7175, and 7235; Pleasant: 1440, 1463, 1610, 2050, 2058, 2080, 2160, 2216, 2311, 2340, 2341,2360, 4623, 4641, 5460, 5480, 7230, 8420, 8501, and 8510.

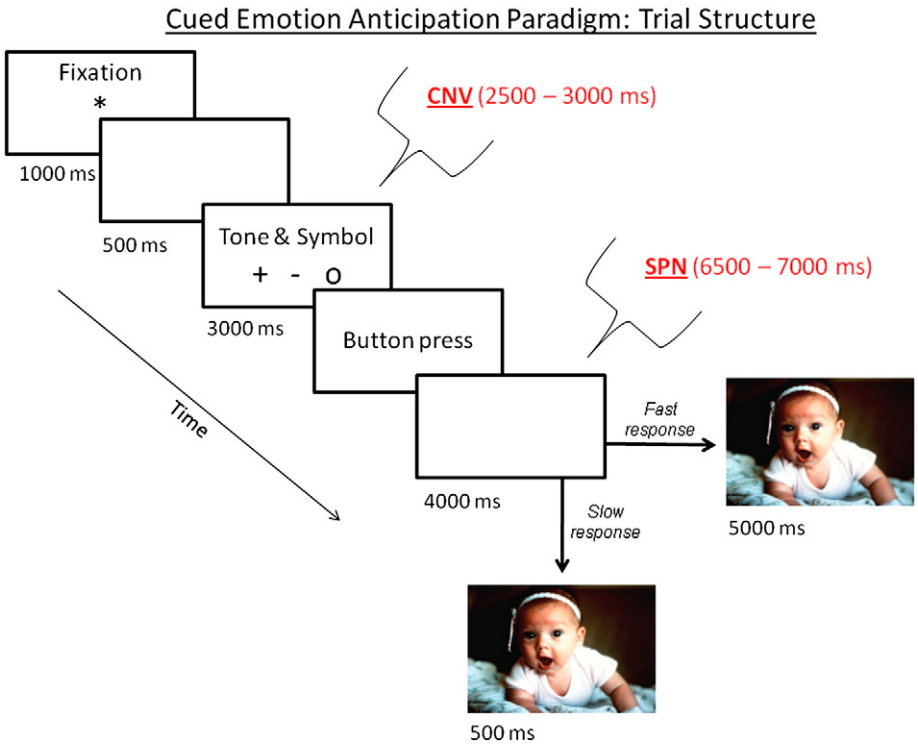

Fig. 1. Schematic of the trial structure for the cued emotion anticipation task. The CNV was measured as activity in the last 500 ms of the cue slide and the SPN as activity in the last 500 ms of the anticipatory period.

pictures longer than neutral pictures when rating their response to IAPS stimuli (Lang et al., 1993; Cuthbert et al., 1996) and evidence that people with and without schizophrenia show more rapid button pressing to extend viewing time of emotional compared to neutral pictures (Heerey and Gold, 2007). The experiment consisted of 40 trials for each picture type, for a total of 120 trials. The entire session lasted approximately 45 min.

After the EEG recording session, participants re-viewed the pictures and reported on their emotional experience (i.e. valence and arousal). Each picture was presented on the screen for a maximum of 10 s. Participants were instructed to view the pictures and press the spacebar on a keyboard when they were ready to make their experience rating; if the participant did not press the spacebar within 10 s the picture ended and the participant was prompted to make their experience rating. Time to pressing the spacebar was computed as picture viewing time. Valence and arousal ratings were collected using a computerized modification of the Self Assessment Manikin (Lang, 1985). Ratings were performed on a 1–9 Likert scale, with scores ranging from very unpleasant/unarousing (a score of 1) to very pleasant/arousing (a score of 9). After the participant made his/her rating, the next picture was presented.

2.4.4. EEG recording

Participants had their EEG activity continuously recorded during the picture viewing task. EEG activity was collected using a 64-channel Neuroscan SynAmps2 amplifier and a Neuroscan 64-channel QuickCap (Compumedics USA, Charlotte, NC). Data were sampled at 500 Hz with filter settings of 0 to 100 Hz in DC acquisition mode. 64 cap-mounted, equidistant sintered Ag–AgCl electrodes were positioned in the QuickCap using the 10–20 international placement system. Additionally, four electrodes were used to measure horizontal electrooculogram (EOG; placed on the outer canthus of the left and right eyes) and vertical EOG (placed above and below the left eye). All electrodes were referenced to a point halfway between electrodes Cz and CPz and a forehead ground was employed. All electrodes were re-referenced offline to the left and right mastoids.

All data were processed offline using Neuroscan Scan 4.3 software. Eyeblinks were removed from the data using established mathematical procedures (Semlitsch et al., 1986). Data were low-pass filtered at 20 Hz and then epoched to 100 ms pre- and 7000 ms post-stimulus. Baseline correction on the 100 ms prior to stimulus presentation was applied. Epochs were then linearly detrended over the entire length of the epoch. Artifact rejection was performed for any trial that exceeded +/−100 μV at electrode sites Fz, FCz, Cz, CPz, and Pz. Visual inspection of trials was then performed to eliminate any remaining abnormal EEG responses. Fourteen patients and five controls with more than 50% of the total trials rejected using these criteria were excluded from the analyses. The relatively large number of excluded patients likely reflected the combination of DC recording and the seven second recording epoch required to record the anticipatory slow-wave activity in this paradigm, which is considerably longer than a typical ERP recording epoch (e.g., 500 ms) and more likely to result in non-trivial DC drift. In addition, several patients had generally poor quality recordings that appeared to reflect excessive movement. There were no significant differences between included and excluded patients on any demographic, trait, or behavioral measure. Excluded patients did, however, have lower BPRS-Anergia and SANS-affective flattening item scores than included patients. For included subjects, a mean (S.D.) of 101.8 (14.3) of trials was accepted for schizophrenia patients and 95.2 (17.7) for normal controls.

ERP waveforms were created by averaging all accepted trials separately for each picture valence. The CNV was determined as the mean activity in the 500 ms prior to the participants' response to the cue offset. The SPN was determined as the mean activity in the 500 ms prior to the presentation of the picture.

2.5. Data analysis

For demographic and trait data, group differences for continuous variables were evaluated with *t*-tests and for categorical variables with chi-square tests. For the anticipation task, separate 2 (group: patients, controls) × 3 (picture type: pleasant, unpleasant, and neutral) ANOVAs

were used to examine viewing time, arousal, and experienced valence ratings to the pictures, as well as reaction times and number of long picture presentations during the ERP recording session. For each ERP component (CNV and SPN) a 2 (group: patients versus controls) × 3 (picture type: pleasant, unpleasant, and neutral) × 5 (electrode: Fz, FCz, Cz, CPz, and Pz) ANOVA was run. In cases of repeated measures with more than one degree of freedom, we used Greenhouse–Geisser correction factors (ε). We report the uncorrected degrees of freedom, the corrected *p*-value, and ε. Finally, Pearson correlation coefficients examined relations among behavioral and ERP variables from the emotion anticipation task, trait anhedonia measures, clinically rated anhedonia/asociality, and global negative symptom ratings. All statistical analyses used a two-tailed significance level of 0.05.

3. Results

3.1. Group characteristics

Demographic and trait information for both groups and symptom ratings for the schizophrenia patients are presented in Table 1. The groups did not significantly differ in sex, marital status, or parental education level. However, the patients were older and had lower education levels than controls. This project prioritized matching subjects on parental education as a way to control for family socio-economic status, as opposed to personal education that can be influenced by the illness itself. On the trait measures, patients scored higher than controls on the Social (d = 1.32) and Physical Anhedonia (d = 1.08) scales. On the TEPS, patients reported significantly lower scores than controls on the Anticipatory subscale (d = .50), but the groups did not significantly differ on the Consummatory subscale (d = .42). Finally, the patients had a typical age of onset, were chronically ill, and showed mild to moderate levels of clinical symptoms at the time of testing.

3.2. Preliminary analyses

Preliminary analyses examined potential confounds. First, we examined whether age and personal education significantly correlated with behavioral or ERP variables from the anticipation task within each group and should therefore be accounted for in the primary analyses. There was only one significant correlation in the patients (neutral picture viewing times correlated −.33 with age [$p<.05$]) and one in controls (arousal ratings for unpleasant pictures correlated −.41 with age [$p<.05$]). However, including age, education, or sex as covariates or factors in the analyses did not change any of the main findings. Age, education, and sex were therefore not considered further. Second, because the exclusion criteria for substance dependence history was not directly parallel across groups, we examined whether patients with alcohol ($n=9$) and/or drug ($n=15$) dependence histories differed from patients without substance dependence histories. There were no significant differences between these patient sub-groups on any demographic, trait, behavioral, or ERP measure. Furthermore, the patient versus healthy control group comparisons reported below were essentially unchanged when patients with any alcohol and/or drug dependence history were excluded from the analyses. Substance dependence was therefore not considered further in the analyses.

Table 1
Demographic, trait, and clinical information in patients ($n=34$) and controls ($n=36$).

	Patients	Controls	Statistic
Sex (% male)	78.9	66.7	X^2 (1,70) = 1.34
Age (SD)	44.6 (10.8)	38.6 (10.4)	$t(69) = 2.36^*$
Marital status			
Never married	60.5	75.0	X^2 (2, 70) = 3.29
Currently married	5.3	9.4	
Ever married	34.2	15.6	
Education (SD)	12.8 (1.4)	14.6 (1.5)	$t(69) = 5.46^{**}$
Parental education (SD)	14.8 (3.3)	13.9 (2.8)	$t(69) = 1.23$
Physical Anhedonia Scale (SD)	18.1 (9.2)	9.7 (6.0)	$t(69) = 4.58^{**}$
Social Anhedonia Scale (SD)	17.2 (8.9)	7.6 (5.1)	$t(69) = 5.59^{**}$
TEPS Anticipatory	45.6 (6.7)	48.9 (6.4)	$t(69) = -2.05^*$
TEPS Consummatory	36.4 (7.8)	39.5 (6.9)	$t(69) = -1.77+$
Age of onset (SD)	20.3 (10.2)		
Duration of illness	24.3 (8.4)		
BPRS			
Thought disturbance (SD)	2.8 (1.4)		
Anxiety/depression (SD)	2.5 (0.9)		
Anergia (SD)	2.0 (0.8)		
Hostility (SD)	1.9 (0.8)		
Activation (SD)	1.3 (0.5)		
SANS			
Affective flattening (SD)	2.2 (1.4)		
Alogia (SD)	1.2 (1.2)		
Avolition (SD)	3.2 (1.1)		
Anhedonia (SD)	2.9 (1.4)		

Notes: Means are presented with accompanying SDs. TEPS = Temporal Experience of Pleasure Scale; BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms. $+p<.10$; $^*p<.05$; $^{**}p<.001$.

3.3. Affective experience ratings and viewing time

For valence ratings, there was a significant main effect of picture type, F (2, 136) = 737.05, $p<0.001$, but no significant group or interaction effects. Across groups, there were significant differences between each picture type, with mean [S.E.] ratings highest for pleasant pictures (7.20 [0.12]), followed by neutral (5.17 [0.08]) and unpleasant (2.54 [0.08]) pictures.

For arousal ratings, there were significant effects for picture type, F (2, 136) = 34.32, $p<0.001$, and the group × picture type interaction, F (2,136) = 4.28, $p<.05$, but not for group. The interaction was accounted by the following: for controls, there were significant differences between each picture, with arousal ratings highest for positive (6.67 [.15]), followed by unpleasant (5.78 [.29]), and neutral (4.47 [.17]); for patients, ratings for positive pictures (6.78 [1.19]) were significantly higher than ratings for both unpleasant (5.30 [.37]) and neutral (5.30 [.15]) pictures, which did not differ from each other.

For viewing time, there was a significant picture type effect, F (2, 136) = 12.35, $p<0.001$, but no significant group or interaction effects. Across groups, mean [S.E.] viewing times (in ms) were all significantly different for each picture type, with viewing times longest for unpleasant pictures (3434 [270]) followed by pleasant (3034 [281]) and neutral pictures (2604 [229]).

3.4. Anticipation task

3.4.1. Behavioral data

For reaction time to cue offset, a significant main effect for group revealed the expected longer reaction time in patients (308.13, SE = 13.43) than controls (220.96, SE = 14.25), F (1,69) = 19.82, $p<.001$. Neither the picture type nor the group × picture type interaction was significant.

For the number of "long" picture presentations (i.e. those in which the subject responded within their individually-calibrated cut-off) there were no significant effects for group, picture type, or the interaction of these factors. The mean total number of long picture presentations was nearly identical between groups: 85.3 for patients and 86.6 for controls, suggesting that both groups were comparably engaged in the task.

3.4.2. ERP data

The overall ERP waves, collapsed across all three types of pictures, are presented for patients (red) and controls (blue) in Fig. 2. The mean values (with standard error bars), collapsed across all three types of pictures, for each group and each electrode analyzed for the CNV and SPN can be seen in Fig. 3. For the CNV, the group main effect was significant, F (1, 68) = 14.35, $p<0.001$. There was also a significant

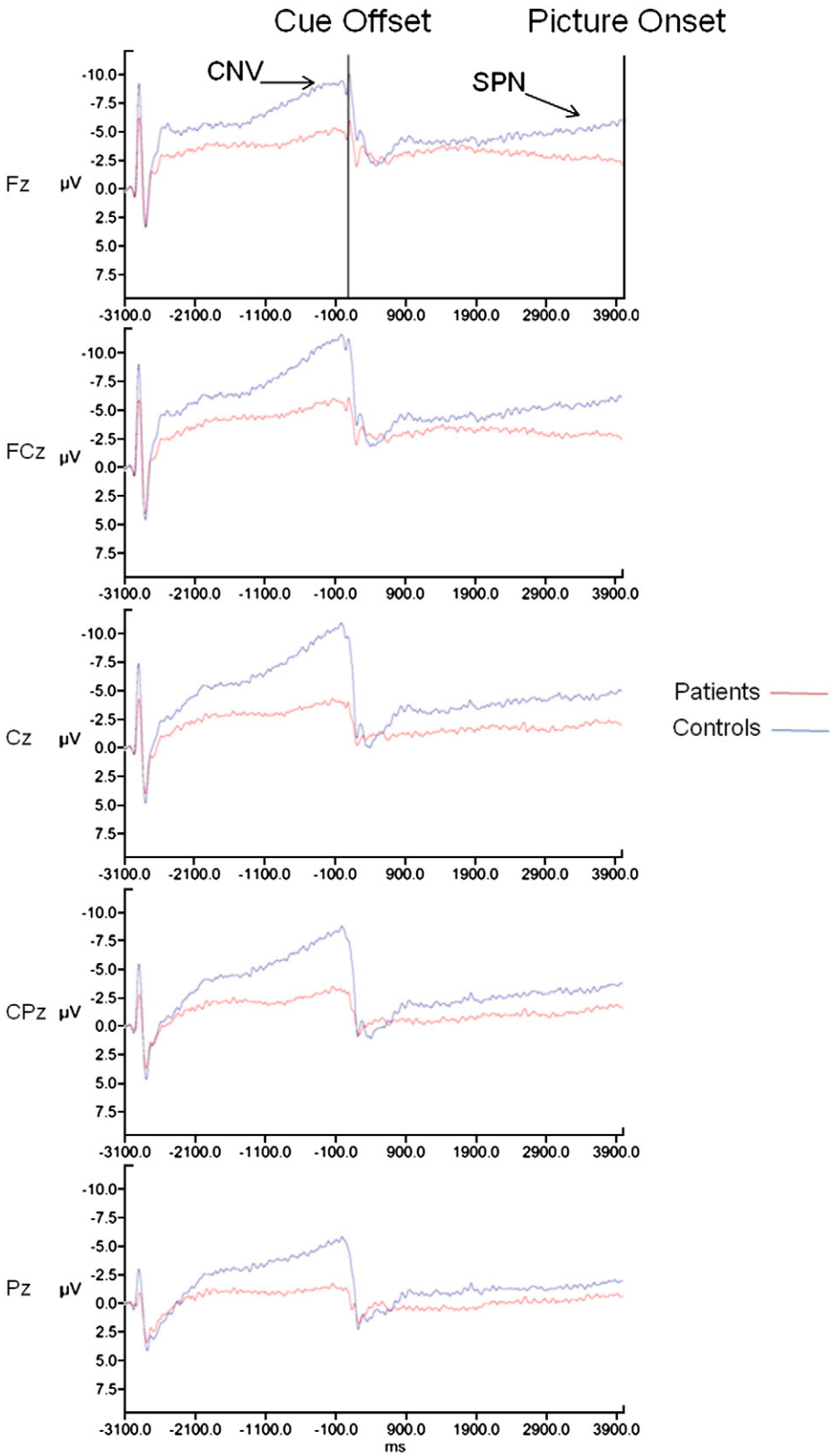

Fig. 2. ERP waveforms (collapsed across picture type) at electrodes Fz, FCz, Cz, CPz, and Pz for schizophrenia patients (red) and healthy controls (blue). For reference, lines appear at cue offset (at 0 ms on the x-axis) and picture onset (at 4000 ms on the x-axis) in the ERP for Fz (top of the figure). Note that negativity is plotted upward on the y-axis.

effect of electrode, F (4, 272) = 36.31, $p<0.001$, $\varepsilon = 0.53$. The picture type main effect, the picture type × group interaction, and the picture type × electrode × group interaction were not significant. The mean (S.E.) CNV for patients was −3.76 (0.89) μV and −8.48 (0.87) μV for controls. To further examine the electrode main effect, we looked at the linear and quadratic trends. The linear and quadratic

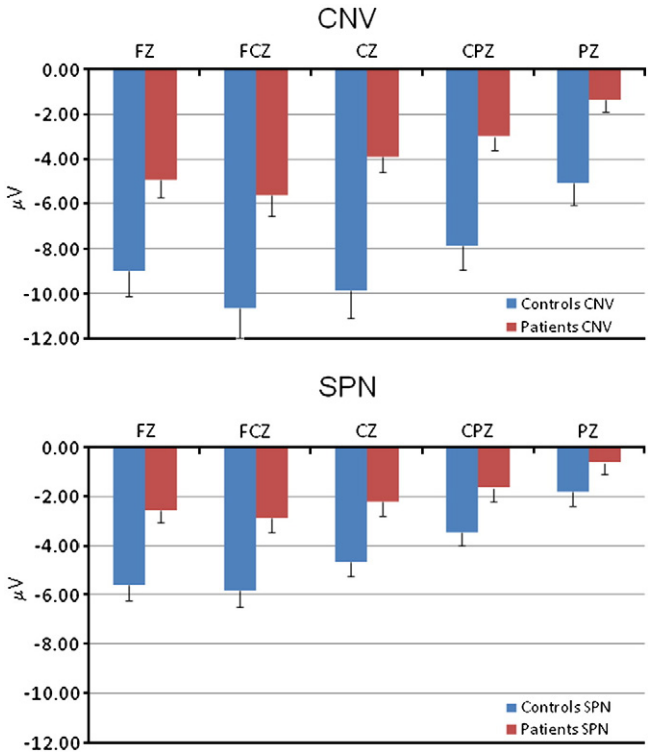

Fig. 3. Mean amplitudes (with standard error bars) for the CNV (top panel) and SPN (bottom panel) at electrodes Fz, FCz, Cz, CPz, and Pz for schizophrenia patients (red columns) and healthy controls (blue columns).

trends were significant (F (1, 68) = 45.23, p<0.001; F (1, 68) = 36.04, p<0.001) accounting for 73% and 24% of the variance across electrode sites respectively, indicating that the CNV was largest at fronto-central sites (Fz, FCz, and Cz) and diminished in amplitude at centro-parietal sites (CPz and Pz), as can be seen in Fig. 3.

Similarly, for the SPN the group main effect was significant, F (1, 68) = 10.73, p<0.01. There was also a significant main effect of electrode, F (4, 272) = 32.92, p<0.001, ε = 0.51, and a significant group × electrode interaction, F (4, 272) = 3.06, p<0.05, ε = 0.51. The main effect of picture type, the picture type × group interaction, and the picture type × electrode × group interaction was not significant. The mean (S.E.) SPN for patients was −2.00 (0.50) μV and −4.27 (0.48) μV for controls. The electrode × group interaction was followed up with between group t-tests. Patients and controls showed significant differences at all electrodes except Pz, with all ts (df = 68) > 2.38, ps<0.05. Again, similar to the CNV, the SPN was characterized by significant linear (F (1, 68) = 44.94, p<0.001) and quadratic (F (1, 68) = 20.98, p<0.001) trends across the five midline electrode sites with the linear and quadratic trends accounting for 87% and 11% of the variance respectively, indicating that the SPN was largest at frontal-central sites (Fz, FCz, and Cz) and diminished in amplitude at centro-parietal sites (CPz and Pz), as can be seen in Fig. 3.

In summary, the patients showed generally diminished CNV and SPN, though the topography of the ERPs was similar across groups with maximal responses seen at electrodes Fz, FCz and Cz, as confirmed by the trend analyses.

3.5. Correlational analyses

Table 2 shows the correlations among the behavioral and ERP variables from the Anticipation task, the four trait anhedonia measures, and interview-rated negative symptoms within the schizophrenia group. Our primary interest was in correlations between the trait measures and variables from the experimental task. Higher TEPS Consummatory scores correlated with higher valence ratings to pleasant pictures, as well as lower scores on the Physical and Social Anhedonia scales and on SANS total. None of the trait measures significantly correlated with the ERP variables, though higher Physical and Social Anhedonia were related at a trend-level to lower overall SPN. Unexpectedly, higher (i.e., more pleasant) ratings of neutral pictures correlated with lower overall CNV and SPN.

Within the control group, the trait measures were not significantly related to the ERP variables and demonstrated only few significant correlations with the picture ratings. Higher TEPS Consummatory scores were related to higher (i.e., more positive) ratings for pleasant (r = .33, p<.05) and neutral (r = .37, p<.05) pictures, as well as lower Physical Anhedonia (r = −.54, p<.001). Higher TEPS Anticipatory scores showed a trend-level relation to higher ratings of pleasant pictures (r = .32, p<.10). Finally, higher Physical Anhedonia correlated with lower (i.e., less positive) ratings of neutral pictures (−.34, p<.05).

4. Discussion

A task was developed to assess two different anticipatory ERPs (CNV and SPN) within a single paradigm in people with schizophrenia and healthy controls. Despite similar patterns of reaction time and self-reported experience ratings to the picture stimuli across groups, patients demonstrated generally smaller CNV and SPN than controls across all types of pictures, reflecting impairment across motor and non-motor related anticipatory processes. In addition, patients reported lower trait anticipatory pleasure than controls on the TEPS. Overall, these results suggest that schizophrenia is characterized by broad anticipatory disturbances, which could contribute to maladaptive functioning across a variety of domains.

Table 2
Correlations among valence ratings, erps, trait anhedonia measures, and negative symptom ratings within the schizophrenia group (n = 34).

	1	2	3	4	5	6	7	8	9	10
1. Valence rating — pleasant	–									
2. Valence rating — unpleasant	−.01	–								
3. Valence rating — neutral	.43*	.15	–							
4. CNV — overall	−.02	−.04	−.37*	–						
5. SPN — overall	.01	−.16	−.39*	.76***	–					
6. TEPS — Anticipatory	.24	−.32†	.06	−.04	.12	–				
7. TEPS — Consummatory	.33*	−.30†	.21	−.01	−.03	.58***	–			
8. Physical Anhedonia Scale	−.27	.04	−.28	.11	.32†	.03	−.47**	–		
9. Social Anhedonia Scale	−.23	.06	.04	.28	.31†	−.28	−.40*	.55***	–	
10. SANS — anhedonia/asociality	−.28	.13	−.15	.03	−.07	−.25	−.23	.29†	.37*	–
11. SANS — total	−.29†	.20	−.02	−.19	−.30†	−.30†	−.36*	.21	.10	.70***

Notes: CNV = Contingent Negative Variation; SPN = Stimulus Preceding Negativity; TEPS = Temporal Experience of Pleasure Scale; SANS = Scale for the Assessment of Negative Symptoms. †p<0.10; *p<0.05; **p<0.005; ***p<0.001.

The paradigm developed for this study was designed to measure separately motor and non-motor related anticipatory ERPs, and we found clear CNV and SPN waveforms in healthy controls during the two anticipatory intervals that were maximal in the fronto-central region. Previous reports of diminished CNV in schizophrenia left open the question of whether the patient–control differences were due to motor involvement. The current study helps address this ambiguity in that patients also demonstrated diminished SPN, which does not involve any motor response. Although our results are at odds with Reuter et al.'s (2006) report of impaired CNV but normal SPN in schizophrenia, there are key methodological differences between the paradigms. In that study, CNV was assessed with standard pro- and anti-saccade conditions, whereas SPN was assessed with a delayed condition in which subjects had to wait for 1000 ms until a tone instructed them to execute a pro- and anti-saccadic response. Because the SPN condition involved both motor preparation and response inhibition, it is difficult to distinguish motor from non-motor anticipatory and inhibitory processes in this paradigm. The current paradigm, which was designed to cleanly distinguish between CNV and SPN, indicated that the patients' impairment extended to non-motor aspects of anticipation.

Prior studies of CNV in schizophrenia have used relatively neutral stimuli that may have not been very motivating. In contrast, the current study extends the prior research through use of realistic, emotional picture stimuli that would be expected to enhance task engagement and anticipatory ERPs (van Boxtel and Bocker, 2004). Although we cannot definitively rule out the possibility that diminished CNV and SPN in the patient group reflect a deficit in attention or motivation that led to insufficient engagement of anticipatory processes (rather than from an intrinsic abnormality in anticipatory mechanisms), the comparable patterns of reaction time-dependent long versus short picture presentations across groups suggests that the patients were well-engaged in the task.

It is noteworthy that people with schizophrenia do not show globally diminished ERPs across all types of tasks that involve complex emotional picture stimuli. In a companion study that used similar IAPS stimuli in the context of a passive picture viewing task (Horan et al., 2010), patients and controls demonstrated similar valence-specific patterns on early- to mid-latency ERPs (i.e., P1, P2, and P3), with group differences found only for Late Positive Potentials (500−1000 ms post-picture onset) while viewing pleasant pictures. The anticipatory disturbances seen in the current study, therefore, do not merely reflect a global deficit across all aspects of electrophysiological responding to complex socioemotional stimuli in schizophrenia.

Because anticipation is essential for effective functioning in daily life, the early anticipatory disturbances shown by the schizophrenia patients across both motor and non-motor processes may well have wide-ranging functional consequences. Diminished CNV in schizophrenia has already been linked to poorer performance on laboratory motor tasks, including occulo-motor, cued reaction time, and delayed matching to sample tasks (Avila et al., 2006). In addition, one can speculate that an abnormality in preparatory motor responses would render patients more prone to responding reactively to stimuli in the physical environment, rather than benefiting from proactive preparation of more carefully planned action.

SPN is believed to be primarily sensitive to the expectation of motivationally relevant stimuli, presumably reflecting the engagement of appetitive and defensive motivational systems of the brain (see review in Van Boxtel and Bocker, 2004). For example, SPN does not reflect general attentional or cognitive demands for tasks that do not have motivational value (Kotani and Aihara, 1999; Hillman et al., 2000) or general responsivity to feedback that does not have task-significance (Damen and Brunia, 1994; Kotani and Aihara, 1999; Kotani et al., 2003). Furthermore, neuroimaging and dipole modeling EEG studies suggest that the generators of SPN include brain structures involved in emotional responding, particularly insular cortex (van Boxtel and Bocker, 2004; Kotoani et al., 2009). Diminished anticipation of motivationally relevant stimuli could adversely impact basic feedback-based learning and decision-making processes. For example, many models of decision making depend on the comparison of expected versus actual outcomes (Hajcak et al., 2005; Hajcak et al., 2007). Such comparisons would be altered if someone did not effectively make predictions of expected outcomes, possibly leading to socioemotional disturbances in approaching or avoiding potential rewards or threats.

The current study provides some initial evidence for linkages between disturbances in anticipation and emotional traits in schizophrenia. Using the TEPS, patients report lower anticipatory pleasure than controls while group differences for consummatory are non-significant, a pattern resembling previous research with this scale (Gard et al., 2007). The more comparable level of consummatory pleasure across groups was mirrored by their comparable self-reported emotional experience to the IAPS pictures, a frequently replicated finding in schizophrenia (Kring and Moran, 2008; Cohen and Minor, 2010). The TEPS subscales did not significantly correlate with ERPs, although higher scores on the traditional social and physical anhedonia trait questionnaires did show some trend-level correlations with smaller CNV and SPN. The absence of a relationship between anticipatory ERPs and the TEPS could reflect the multifaceted nature of anticipatory pleasure itself. Indeed, the TEPS only assesses pleasure in anticipation of physical events (e.g., tastes, sights, and touches). The ERPs assessed in the current study tapped anticipation of emotion experiences derived from viewing the emotionally evocative pictures.

Unexpectedly, healthy controls did not show larger anticipatory ERPs for emotional compared to neutral picture conditions. This may reflect some methodological factors. First, most prior studies separately examined either CNV or SPN, and either unpleasant versus neutral or pleasant versus neutral stimuli (see Poli et al., 2007). The combination of these factors within a single paradigm might influence the CNV and SPN in unexpected ways. For example, one unusual feature that results from combining all three valences in a single study is that participants were asked to respond as quickly as possible to all types of pictures (i.e., both pleasant and unpleasant), and this may have had an unexpected effect of obscuring differences in anticipatory ERPs. Second, prior studies typically used highly arousing stimuli, such as erotic pictures, violent/mutilation scenes, or highly fearful images (Howard et al., 1992; Klorman and Ryan, 1980; Simons et al., 1979), or monetary feedback on prior task performance (Kotani et al., 2001; Kotani et al., 2003; Ohgami et al., 2004). Local IRB constraints prohibited us from using the most arousing types of stimuli from the IAPS in the present study. Although the emotional pictures were sufficiently evocative to elicit differences in self-reported emotions, as well as ERPs during passive picture viewing in our companion study (Horan et al., 2010), more arousing stimuli or monetary reward/punishment contingencies may be required to elicit valence-sensitive SPN and CNV.

The study had some limitations common to studies of schizophrenia. Patients were taking various antipsychotic medications at clinically determined dosages and their effects on anticipatory responding are uncertain (Juckel et al., 2006b; Schlagenhauf et al., 2008). Studies of samples that are early in the course of illness, unmedicated, or randomly assigned to receive different types of antipsychotic medications will be required to directly address medication effects. Second, this study did not control for nicotine use, which is common in schizophrenia (de Leon and Diaz, 2005) and could impact ERPs (Pritchard et al., 2004). Third, patients were older than controls, though accounting for age in the analyses did not alter the main study findings. Participants were also predominantly male, which precluded a meaningful examination of potential sex differences. Finally, patients who were excluded due to ERP artifact tended

to have lower levels of negative symptoms related to the outward expression of emotion, potentially limiting the generalizability of the results. Despite these limitations, the current results encourage continued research into the scope, neural correlates, and functional consequences of anticipatory disturbances in schizophrenia.

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