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Social aversive conditioning in youth at clinical high risk for psychosis and with psychosis: An ERP study

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ABSTRACT

Background: Social cognition and emotion processing are compromised in schizophrenia. Disruptions in these domains may also be present during the psychosis-risk state. Aversive conditioning is an established translational research paradigm to investigate affective reactivity and learning. Using an aversive conditioning ERP paradigm with social cues, we examined whether psychosis patients and at-risk youths differentially respond to aversively conditioned faces.

Methods: Participants (ages 10–30) were enrolled into three demographically-matched groups: clinical risk for psychosis (CR, n = 32), psychosis (PS, n = 26), and healthy control (HC, n = 33). EEGs were recorded during a delay aversive conditioning task in which three neutral faces were paired with an aversive tone at 100%, 50% and 0% contingencies. Analysis focused on group differences in ERP peaks representing visual processing (occipital P120), emotional valence (frontal VPP), and directed attention (parietal-occipital P300), for dimensions of aversiveness (100% vs. 0%) and unpredictability (50% vs. 100% + 0%).

Results: HC, but not CR or PS, showed increased P300 amplitude to aversive vs. non-aversive conditioned stimuli. CR, but not PS or HC, showed increased VPP amplitude to unpredictable vs. predictable stimuli.

Conclusions: PS and CR both fail to allocate appropriate salience to social cues that are predictably aversive. CR, but not PS exhibit heightened emotional reactivity to social cues that are of uncertain salience. Clinical risk for schizophrenia may involve neural abnormalities distinct from both healthy and fully-established disease states.

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1. Introduction

Impaired social-emotional functioning contributes strongly to long term psychosocial dysfunction in schizophrenia (Kurtz et al., 2005; Milev et al., 2005; Rabinowitz et al., 2012), and relates to both negative and positive symptom severity (Buchanan, 2007; Pinkham et al., 2016). In youths at risk for psychosis (Demjaha et al., 2012; Gur et al., 2015; Nelson et al., 2013; Velthorst et al., 2009) impairments in social functioning, including social anxiety and withdrawal, characterize those who convert to psychosis (Cornblatt et al., 2012; Johnstone et al., 2005; Nieman et al., 2013). Notably, impaired facial emotion processing is predictive of conversion to schizophrenia (Corcoran et al., 2015). There is thus a strong rationale to better understand socio-emotional processing deficits in psychosis risk, both to enhance their utility as markers and to elucidate their underlying mechanisms.

Aversive conditioning is an established paradigm for studying social learning of affectively significant information (Sehlmeyer et al., 2009) across human and animal studies. Aversive, or fear, conditioning is a form of associative learning where an initially neutral event (the conditioned stimulus, CS) is temporally paired with a biologically aversive event (the unconditioned stimulus, US). Following repeated pairings, the CS assumes salience and elicits a fear-related response in the absence of the US (Davis and Whalen, 2001; Ledoux, 2000). In discriminant conditioning, one CS is paired with the US and a second CS is not, therefore signaling the absence of the aversive stimulus. A qualitatively different kind of noxious outcome, or stress, results when a CS is unreliably paired with the US, i.e. when the outcome is unpredictable (Mineka and Kihlstrom, 1978). The amygdala has a key role in reactivity to emotionally-relevant stimuli and learning affective associations within the amygdala-striatal-prefrontal cortical pathway (Büchel and Dolan, 2000; Pizzagalli et al., 2003).

Learning associations between facial cues and positive and negative social outcomes is required in everyday life. Deficits in acquiring these associations could lead to impaired social functioning and communication. In schizophrenia, deficits in processing facial expressions (Edwards et al., 2002; Evangeli and Broks, 2000; Gur et al., 2006; Kohler et al., 2010) are associated with severity of negative symptoms (Gur et al., 2006), positive symptoms (Pinkham et al., 2016), and impaired

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amygdala activation (Li et al., 2010). However, little is known about impairments in acquiring associations between social stimuli and salient emotions.

Given its reliance on the amygdala-striatal-cortical pathway, an aversive social learning paradigm should be a sensitive probe of neural substrates underlying impaired social functioning and negative symptoms. There are few studies of aversive conditioning in schizophrenia, none of which have examined conditioning to socially relevant stimuli or studied at-risk youth. One study observed abnormally low amygdala activity, in patients, to aversively conditioned colors (Romaniuk et al., 2010). A second, which focused on the ventral striatum, reported abnormally increased activation to *neutrally* conditioned shapes in patients (Jensen et al., 2008). Although not a formal conditioning experiment, Satterthwaite et al. (2010) examined fMRI activity to neutral faces that had been observed previously depicting either threatening or non-threatening expressions. While controls activated amygdala and orbitofrontal cortex (OFC) more to faces previously seen as threatening, patients activated these regions equally to both previously threatening and non-threatening faces, suggesting reduced differential learning of emotionally salient cues.

The current study was designed to extend our knowledge of social processing abnormalities in psychosis (PS) and in clinical risk for psychosis (CR). We utilized a standard delayed discrimination learning paradigm, with three neutral facial expressions as CS and loud white noise bursts as US. We measured neural responses to aversively conditioned (100%) unconditioned (0%), and unpredictably reinforced (50%) faces using event-related potentials (ERPs), as well as the explicit ability to predict an aversive outcome. We hypothesized that CR and PS would show reduced differential learning of aversive vs. non-aversive faces, reflected in reduced differential ERPs, but that these clinical groups would show exaggerated ERP responsiveness to faces of unpredictable outcome. We anticipated that deficits in acquired emotional responses would be evident in ERPs most strongly reflecting conscious-evaluative stages of stimulus processing.

2. Methods and materials

2.1. Participants

Participants were recruited from the greater Philadelphia area including some from the Philadelphia Neurodevelopmental Cohort (Calkins et al., 2015). Participants were proficient in English, had no medical or neurological condition that could affect brain function, no history of substance abuse in the past month or substance dependence in the past 6 months, no clinically significant head trauma or full scale IQ < 70 [estimated by The Wide Range Achievement Test (WRAT-4) Reading subscale (Wilkinson and Robertson, 2006)]. Participants (age 10–30) were classified into three groups based on clinical diagnosis of psychosis spectrum features: clinical risk for psychosis (CR, n = 32; mean age [SD] = 20.2 [3.7]), schizophrenia spectrum disorders (PS, n = 26; mean age [SD] = 21.2 [3.6]), and healthy control (HC, n = 33; mean age [SD] = 19.0 [3.9]). HC were further excluded for family history of psychosis in a first-degree relative. There were no significant differences across groups in age, years of education, sex, racial composition or handedness (Table 1) (see Fig. S1, Supplementary materials for a histogram of age in the sample).

2.2. Clinical assessment

Psychopathology was assessed in all participants using a comprehensive interview (Calkins et al., 2017) consisting of modules of the K-SADS, the Structured Interview for Prodromal Syndromes [SIPS, version 4.034 (Miller et al., 2003)], and the psychotic and mood differential diagnosis modules (C/D) of the Structured Clinical Interview for DSM-IV (First et al., 1995). All participants were assessed for lifetime DSM Axis I disorders, including psychotic, mood, and substance related disorders.

Table 1
Demographics, symptoms and behavioral performance measures of healthy controls, clinical high risk and psychosis patients.

		Healthy controls (32)		Clinical risk (32)		Psychosis (26)		Significance
		Mean	SD	Mean	SD	Mean	SD	p
Age		19.0	3.9	20.2	3.7	21.2	3.6	.093
Education		12.1	3.6	12.1	2.8	12.4	2.1	.906
Sex (% male)[a]		39		59		58		.213
Handedness (% right)[a]		97		75		81		.124
Race	% Caucasian	58		22		54		.133
	% other	42		78		56		
CAINS	Map	6.0	4.0	9.8	5.8	13.7	9.5	<.001
	Express	1.4	2.1	2.2	3.1	4.5	5.0	.003
	Total	7.4	5.6	11.7	8.1	18.2	13.2	<.001
SIPS	Positive	1.2	1.6	7.9	4.7	18.3	4.7	<.001
	Negative	1.7	2.4	7.0	4.4	15.3	7.3	<.001
	Disorganized	0.5	0.9	3.7	2.7	9.0	3.4	<.001
	General	0.3	0.7	3.9	3.6	7.7	4.7	<.001
Accuracy (%)		84.6	22.9	75.0	24.4	82.3	23.3	.227
Bias (%)		68.0	17.8	64.8	23.6	63.0	26.8	.345
Response time (ms)		1191	327	1397	679	1427	473	.076

Note: CAINS (Clinical Assessment Interview for Negative Symptoms); maps (motivation-pleasure); express (emotional expression); SIPS (Structured Interview for Prodromal Symptoms).
[a] Non-parametric test confirming the distribution of sex, race, handedness and EEG order is the same across the three groups (Kruskal-Wallis test).

CR criteria required a rating between 3 and 5 (sub-psychotic) on at least one positive subscale item or a rating between 3 and 6 on at least two negative and/or disorganized items from the Scale of Prodromal Symptoms [SOPS (Miller et al., 2003), rated from the SIPS interview] within the past 6 months (for details, see Calkins et al., 2017).

Negative symptoms of psychosis were assessed using the Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring et al., 2013); a semi-structured interview with 13 items representing two factors: motivation-pleasure and emotional expression. We have previously adapted the CAINS to activities and lifestyles of young people (Gur et al., 2015).

Clinical interviews were administered by bachelor's or master's level assessors who underwent formal training and participated in ongoing consensus conference meetings (Calkins et al., 2017). Information obtained was reviewed by a panel comprising at least two doctoral level clinicians to achieve consensus symptom ratings and clinical diagnoses.

2.3. Delayed aversive conditioning task

The conditioned stimuli (CS) were color photographs of three male faces, selected from a database based on reliable ratings of neutral emotional valance and low arousal (Cao et al., 2014; Keutmann et al., 2015). One face was presented per trial for 5500 ms and participants were asked to indicate, by a button press, whether or not they anticipated that it would be followed by a sound. The unconditioned stimulus (US) was an aversive 500 ms 110 dB white noise burst, which co-terminated with the faces on 100% (aversive condition), 50% (unpredictable condition), or 0% (non-aversive condition) of trials, respectively. A crosshair was displayed for 1500 ms between trials. Each face was presented 30 times, in a randomized order, for a total of 90 trials. The allocation of face identities to each condition was randomized across participants.

2.4. ERP data acquisition and processing

EEG recording took place in a sound-attenuated room. Participants were monitored via closed circuit TV. To minimize movement artifact, participants were familiarized with the testing environment and procedures, and were given instructions to minimize movement.

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EEG data were recorded from 65 electrodes according to the International 10/20 system. Eye movements and blinks were recorded from bipolar EOG electrodes positioned at left outer canthus and supraorbital locations. A BioSemi Active2 amplifier system with 24-bit A/D conversion, ADC "amplifier zero" reference, and customized electrodes with integrated first stage amplifier was used. Data were digitally sampled at a rate of 512 Hz and low-pass filtered at 100 Hz (−3 dB).

The digitized EEG recordings were processed off-line using Brain Vision Analyzer 2.0 (Brain Products GmbH). Data were digitally filtered between 0.5 and 70 Hz (24 dB/oct) and eye movement artifact was removed using an automated algorithm (Gratton et al., 1983). Intervals with additional EEG artifact (activity exceeding ±75 μV) were excluded from further analysis. Remaining artifact-free waveforms were segmented into individual 1200 ms epochs, beginning 200 ms before the onset of each face. These were re-referenced to a linked mastoids reference and grouped by condition to form average ERP waveforms. The first five trials of each condition were excluded based on the performance accuracy data, which showed that virtually all participants had by that point learned to predict the presence and absence of aversive feedback for the 100% and 0% trials, respectively. Excluding these early ambiguous trials allowed us to focus on brain responses to differentially learned associations. In addition to the 3 experimental face conditions (aversive, non-aversive, unpredictable), a 'predictable' condition waveform was created by averaging together every second trial from the 0% and 100% feedback conditions. This predictable condition matched the unpredictable condition on both the total number of stimuli and the proportion paired with aversive feedback (50%), but there was no uncertainty regarding the feedback on each individual trial.

Peak amplitudes and latencies were identified using an automated algorithm. Appropriate time window, polarity, and focal electrodes were selected, based on examination of the grand average waveforms, for four components of interest (Bentin et al., 1996; Jaworska et al., 2011; Luo et al., 2010; Sutton et al., 1965; Williams et al., 2006): P120 (80–160 ms peak at O1 and O2), a measure of early perceptual processing; N170 (120–220 ms trough at P7 and P8), reflecting the structural encoding of faces; VPP or Vertex Positive Potential (120–220 ms peak at F3 and F4), representing the integration of face perception with emotional valence; and P300 (400–600 ms peak at POz), reflecting conscious contextual evaluation and directed attention towards a face.

2.5. Statistical analysis

A general linear model (GLM) was applied to each of the peak amplitude and latency measures with group (HC, CR and PS) as a between-subjects factor, and hemisphere and experimental condition as within-subject factors. Two orthogonal experimental dimensions were assessed in separate analyses: aversive vs. non-aversive conditioning and unpredictable vs. predictable conditioning. Age and sex were included as predictors in the model. A detailed examination of age effects is presented in the Supplementary material. We were specifically interested in interactions of group and condition, thresholded at significance $p < .05$. For significant interactions, follow-up 2 × 2 ANOVAs and paired samples *t*-tests were conducted to identify the source of differences.

Behavioral performance was quantified as total percentage accuracy to aversive and non-aversive conditions. Response bias was calculated as the percentage of responses in the unpredictable (50%) condition predicting an aversive outcome, reflecting the extent to which aversive feedback was expected. Mean response latency was also assessed across conditions.

For ERP components exhibiting significant group by condition interactions, Pearson correlations were computed to assess the relationship between the differential ERP response and negative symptomatology. Correlations were run separately within each group, with an exploratory significance threshold of $p < .05$.

3. Results

3.1. Symptoms

Groups differed on levels of negative (CAINS) and prodromal (SOPS) symptoms with CR having higher symptoms than HC and lower symptoms than PS (Table 1).

3.2. ERPs

3.2.1. Aversive versus non-aversive

There was a significant group by condition interaction for the P300 ($F[2,84] = 3.31$; $p = .041$), which reflected an enhanced response to the aversively versus non-aversively conditioned stimuli in HC ($F[1,30] = 5.06$; $p = .032$) that was absent in both PS and CR (see Fig. 1). Groups differed, overall, in P300 amplitude, with HC showing the largest and CR having the smallest response across both conditions ($F[2,84] = 6.19$; $p = .003$). There were no significant group by condition effects for P300 latency.

There were no group or group by condition effects for P120, N170 or VPP components in the aversive contrast. However, there was a condition effect for the VPP, involving greater amplitude, across all participants, in response to aversively conditioned faces in the left hemisphere ($F[2,84] = 14.41$; $p < .001$). This observation is consistent with the VPP being sensitive to emotional significance.

3.2.2. Unpredictable versus predictable

A significant group by condition interaction was observed for the VPP ($F[2,84] = 3.81$; $p = .026$). As illustrated in Fig. 1, CR ($t[31] = 2.52$; $p = .017$), but not HC or PS, had increased amplitude for the unpredictable stimulus. This differential response, in CR, was unrelated to the P300 response to aversive versus non-aversive cues ($r = -0.02$, $p = .91$).

Overall group effects were observed for N170 ($F[2,84] = 4.93$; $p = .009$) and P300 ($F[2,84] = 4.93$; $p = .043$) amplitude; CR had reduced amplitudes compared to HC (N170: $F[1,60] = 7.62$; $p = .008$; P300: $F[1,60] = 5.90$; $p = .018$), while PS versus HC differences were non-significant. There were no group by condition interactions for either of these components.

3.3. Behavioral performance

Behavioral data from 87 participants were available for analysis; one PS participant's behavioral data did not record, and three participants (HC = 1, CR = 2) consistently responded after the tone. Although the clinical groups showed poorer performance according to accuracy and response time on average, these differences were not significant (Table 1) and indicate that all groups learned to perform the task. No group differences were found in bias towards expecting the aversive outcome.

3.4. Exploratory correlation with symptoms

Behaviorally, poorer task accuracy related to more severe positive symptoms in CR ($r = -0.371$, $p = .048$) and negative symptoms in PS (CAINS: $r = -0.420$, $p = .041$; SIPS: $r = -0.485$, $p = .041$) and across the sample (CAINS: $r = -0.282$, $p = .009$). CR who showed a reduced differential P300 response to aversive stimuli (i.e., were more abnormal compared to HC) had less severe negative symptoms (CAINS) ($r = 0.352$, $p = .048$). In contrast, CR with increased VPP response to stimuli with unpredictable outcome (i.e., were more abnormal) had less severe positive symptoms ($r = -0.556$, $p = .001$). In PS, reduced N170 amplitude across conditions was associated with more severe negative symptoms (CAINS) ($r = 0.478$, $p = .014$). Across groups, reduced N170 amplitude i.e. more positive (averaged across unpredictable and predictable conditions) related to higher SIPS positive ($r = 0.221$, $p = .042$) and

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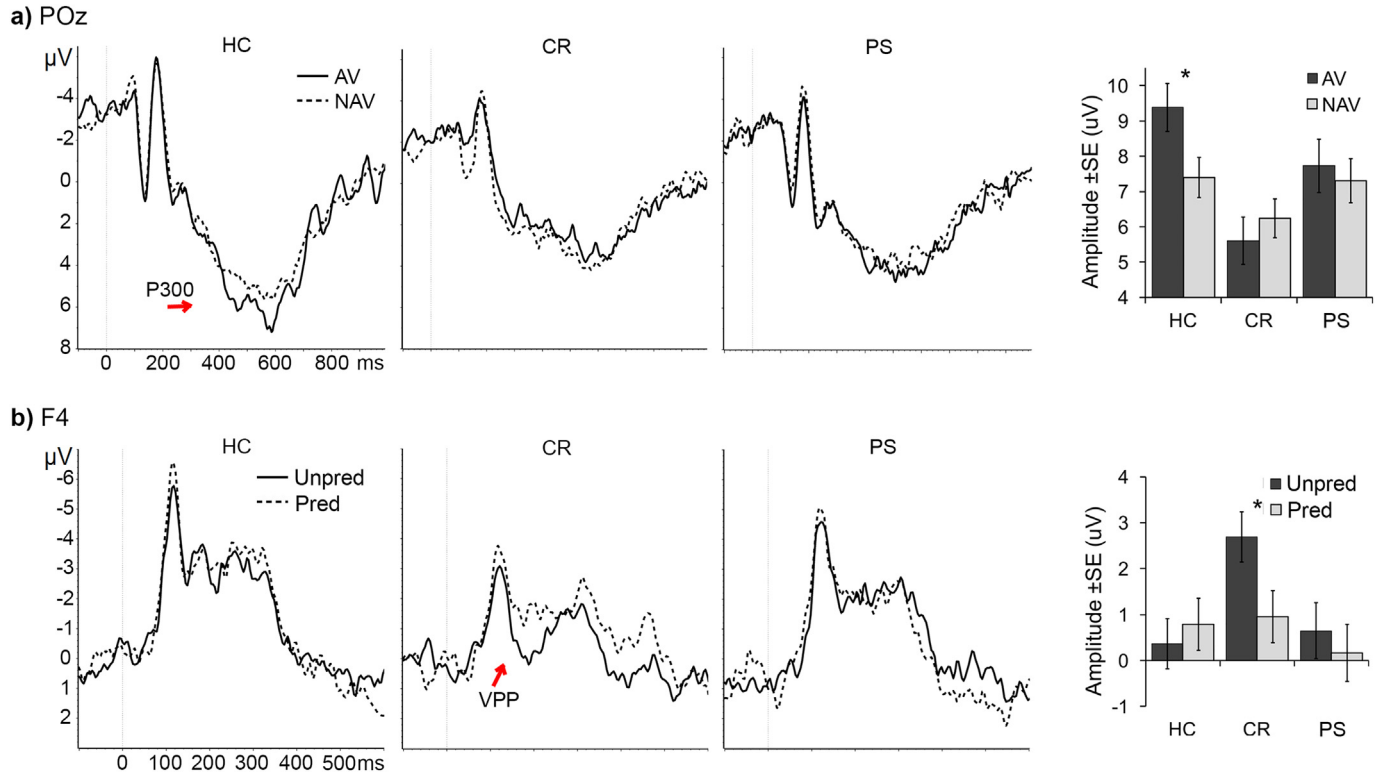

Fig. 1. Grand average ERP waveforms and peak amplitudes of healthy controls (HC) clinical high risk (CR) and psychosis patients (PS) groups for a) the P300 at POz (central-parietal-occipital) during aversive (AV) and non-aversive (NAV) conditions b) the VPP at F4 (right frontal) during unpredictable (Unpred) and predictable (Pred) conditions.

negative symptoms ($r = 0.240$, $p = .027$) (see Supplementary material Tables S1 and S2 for all correlations).

4. Discussion

To our knowledge, this is the first study to investigate aversive conditioning of socially relevant stimuli using ERPs in high-risk for psychosis. While all groups explicitly learned the association between neutral faces and aversive feedback, the clinical groups lacked the differential P300 response to the aversively conditioned face shown by HC. CR additionally differed from both PS and HC, showing an increased VPP to faces signaling an uncertain outcome. Thus, acquisition of associations between social stimuli and emotionally relevant information is disrupted in clinical risk for psychosis.

The P300 component reflects attention towards motivationally relevant stimuli, and is sensitive to emotional salience in facial expressions (Eimer et al., 2003; Hajcak et al., 2010), particularly threatening emotion (Eimer and Holmes, 2002; Weinberg et al., 2013; Williams et al., 2006). The increased P300 response to aversive faces observed in HC is a replicated finding (for a review see (Miskovic and Keil, 2012)) and is consistent with assignment of greater salience to a stimulus that predicts an aversive outcome. The absence of such an augmented response in our clinical groups indicates a deficit in the salience response to social stimuli at the neuronal level, despite having cognitively learned the appropriate association.

In previous studies where salience has been manipulated in faces through the emotion depicted, PS showed reduced ERP amplitude overall, and reduced differentiation between emotional valences, most commonly in N170 (Bediou et al., 2007; Jetha et al., 2013; Lee et al., 2010; McCleery et al., 2015; Turetsky et al., 2007) and P300 (Caharel et al., 2007; Johnston et al., 2005; Turetsky et al., 2007). In a study of CR, a similar pattern of reduced response in earlier components including the N170 was found (the P300 was not studied) (Wölwer et al., 2012). These findings are consistent with attenuated emotional salience processing. By using an aversive conditioning paradigm, we demonstrate deficits in processing social stimuli with *acquired* emotional value in CR. Notably, we did *not* observe any differences in the N170 response to these neutral faces. It was only in the subsequent salience response that an abnormality emerged.

The lack of P300 differentiation in clinical groups may be partly due to a generalized perception of threat in the face stimuli. The 'aberrant salience hypothesis' in schizophrenia proposes that salience is given inappropriately to irrelevant, or non-salient, stimuli due to dopamine excess in subcortical regions (Kapur, 2003). In support of this, patients show increased P300 (An et al., 2003; Herrmann et al., 2006) and heightened amygdala activity (Anticevic et al., 2012; Potvin et al., 2016) to neutral relative to aversive stimuli. While in other studies, patients (Tremeau et al., 2015) and familial high-risk individuals (Eack et al., 2010) make more negative evaluations about neutral faces.

Although the VPP is modulated by emotional valence (Johnston et al., 2005), the lack of VPP enhancement in HC indicates that the enhanced VPP response observed here in CR reflects a processing abnormality. The VPP reflects integration of facial perception with emotional valence (Adolphs, 2002) and is more sensitive to emotion than the concomitant face-specific N170 (Weinberg et al., 2013), perhaps reflecting larger contributions from frontal sources (Hajcak et al., 2010; Williams et al., 2006). The abnormal emotive response in CR occurred for the unpredictable but not aversive dimension, indicating that CR was specifically reacting to the uncertainty of a forthcoming aversive experience rather than the expectation of it. Unpredictability or uncontrollability of an aversive outcome can be stressful in itself and lead to significant suffering as demonstrated in many animal and human studies (Mineka and Kihlstrom, 1978). Individual variation in intolerance for uncertainty is related to increased startle to unpredictability (50%) of a CS (Chin et al., 2016). We surmise that CR exhibit a compensatory response involving frontal regulation, for increased sensitivity to social cues of unpredictable significance. The VPP enhancement did not continue in PS and, within CR, was greatest in those with less severe positive symptoms. It may be that this is specific to risk

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and is lost with conversion to psychosis, consistent with the idea that neurobiology evolves over the course of the illness and early compensatory mechanisms eventually fail (Krystal and Anticevic, 2015).

A fair amount is known concerning the underlying brain circuitry of aversive conditioning with use as a translational research paradigm. The basolateral nucleus (BLA) of the amygdala exhibits plasticity as it encodes cues that predict aversive or non-aversive outcomes (Rogan et al., 1997). Cue-induced responses are regulated by reciprocal connections between BLA and medial prefrontal cortex (mPFC) (Laviolette et al., 2005). While activation of these circuits has been shown to produce cue-induced fear responses, inhibition of this directional output inhibits fear-related responses (Burgos-Robles et al., 2017). The P300 response reflects activation of a diffuse cortical network that is sensitive to prefrontal modulation (Soltani and Knight, 2000). An aberrant P300 salience response might be initiated by BLA-mPFC circuits activated in response to non-threatening cues, and this is consistent with the limited fMRI literature that suggests abnormally elevated rather than reduced reactivity (Jensen et al., 2008; Satterthwaite et al., 2010).

Much less is known regarding the neural circuitry underlying the response to uncertainty. However, relevant information can be gleaned from the "rat betting task," a model task that requires the animal to choose between predictable versus unpredictable rewards of equal expected value (i.e., a guaranteed reward on every trial vs. 50% probability of a double reward). Intriguingly, findings from this task indicate that sensitivity to unpredictability is not affected by BLA activity, but instead on increased activity in the lateral orbital frontal cortex (OFC). Inactivation of the OFC eliminates any differential responses across these two conditions (Winstanley and Floresco, 2016). This suggests that our CR VPP finding, as it relates to unpredictability, reflects abnormally elevated lateral OFC activity, which may be entirely independent from the BLA-mPFC response to aversive cues. The observation that only the latter is present in PS supports this idea of two independent anomalies.

Without longitudinal data, we cannot distinguish between the possibility that the CR anomaly is a compensatory strategy, which is lost following the onset of psychosis, versus the possibility that it is a marker that distinguishes those CR who will or will not ultimately transition to psychosis. However, if the VPP response was a risk marker, we might expect to see it correlated with the abnormal P300 response that characterized both the CR and PS, and this was not observed. Finally, this analysis focused on the evoked potential response elicited by the facial cue. However, future analysis of conditional changes in the frequency spectra across the subsequent evaluative and anticipatory period prior to the aversive US may also be informative.

In conclusion, these findings contribute to our understanding of the neurophysiology of socio-emotional processing deficits in psychosis. Abnormalities in forming associations between social and emotionally salient information are present in individuals at clinical risk for psychosis at the neural level. Our findings are congruent with a failure to appropriately allocate negative salience to social cues associated with psychosis and a psychosis risk state, and a compensatory emotional reactivity to social cues of uncertain outcome unique to the putative prodromal stage.

Conflict of interest

Dr. R.C. Gur reported receiving royalties from the Brain Resource Centre and consulted to the MindPrint Learning. The remaining authors reported no biomedical financial interests or potential conflicts of interest.

Contributors

AJW conducted the analyses and wrote the initial draft of the manuscript. BT oversaw the design of the study to which DHW, RCG, REG and MEC contributed to, and the analyses and interpretation of the data. PER carried out data collection and management. All authors contributed to the final manuscript. MEC oversaw the clinical assessment of participants with REG.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.06.027.

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