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Acute stress modifies oscillatory indices of affective processing: Insight on the pathophysiology of schizophrenia spectrum disorders

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HIGHLIGHTS

- Frontal-theta mediated affective processing is preferentially impacted by acute psychosocial stress.
- Stress-induced oscillatory changes observed in controls were persistently present in SCZ patients.
- Emotional framing uniquely modifies oscillatory activity in controls, but not in SCZ patients.

ABSTRACT

Objective: The current study evaluated the differential impact of acute psychosocial stress exposure on oscillatory correlates of affective processing in control participants and patients with schizophrenia spectrum disorders (SCZ) to elucidate the stress-mediated pathway to psychopathology.
Methods: EEG was recorded while 21 control participants and 21 patients with SCZ performed emotional framing tasks (assessing a key aspect of emotion regulation (ER)) before and after a laboratory stress challenge (Trier Social Stress Test). EEG spectral perturbations evoked in response to neutral and aversive stimuli (presented with positive or negative contextual cues) were extracted in theta (4–8 Hz) and beta (12–30 Hz) frequencies.
Results: Patients demonstrated aberrant theta and beta oscillatory activity, with impaired frontal theta-mediated framing and beta-derived motivated attention processes relative to controls. Following stress exposure, controls exhibited impaired frontal theta-mediated emotional framing, similar to the oscillatory profile observed in patients before stress.
Conclusions: The acute stress-induced oscillatory changes observed in controls were persistently present in patients, indicating an inefficiency of fronto-limbic adaptation to stress exposure.
Significance: Results provide novel insight on the electrophysiological correlates of arousal and affect regulation, which are core homogeneous symptom dimensions shared across neuropsychiatric disorders, and shed light on putative mechanisms in the translation of stress into psychopathology.

1. Introduction

Stress is considered a key precipitating factor in the development and maintenance of psychopathology, including schizophrenia spectrum disorders (SCZ) (Corcoran et al., 2003; Venkatasubramanian et al., 2010; Garner et al., 2011), in part through modification of affective frontal and limbic networks (Arnsten, 2011). SCZ disorders are considered some of the most disabling psychopathologies (Chaudhury et al., 2006), resulting from a combination of genetic and environmental insults (Ross et al., 2006). SCZ is characterized by profound deficits in cognitive and affective processing and underlying frontal executive and limbic affective brain dynamics (Friston, 1999; Moran and Hong, 2011; Uhlhaas et al., 2008; Uhlhaas and Singer, 2014), which are resistant to pharmacotherapy, are associated with poor functional outcome, are exacerbated by stress, and are transdiagnostic features of neuropsychiatric disorders (Horan et al., 2013; Strauss et al., 2013). While acute stress has been shown to selectively

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impair frontal function, the neurophysiological mechanisms underlying the effect of stress on affective processing and adaptation of affective circuitry to stress exposure are unclear and represent a gap in the existing literature. This is the first study to characterize the impact of acute psychosocial stress exposure on neurophysiological correlates of affective processing in control individuals and in patients with SCZ. Understanding the effect of stress on affective neural networks in those with-versus-without psychopathology may provide insight into the early causes of affective circuitry disruption and emotion regulation (ER) impairment.

A dynamic balance of frontal executive and affective limbic networks are engaged both in response to stress exposure (Dedovic et al., 2009; Ulrich-Lai and Herman, 2009) and in the alteration of emotional responses, or emotion regulation (Ochsner et al., 2002, 2004; Phan et al., 2005; Phillips et al., 2008). Acute stress disproportionately impacts frontal-mediated processes, including working memory (Schoofs et al., 2008; Qin et al., 2009; Gärtner et al., 2014), attention (Liston et al., 2009), and cognitive control (Raio et al., 2013), and exaggerates limbic engagement (van Marle et al., 2010) to heighten emotional salience and arousal for aversive stimuli (Oei et al., 2012; Kinner et al., 2014). Frontal networks are required to suppress limbic activity to modify emotional responses and respond appropriately to environmental challenges (Ochsner et al., 2002; Phan et al., 2005; Kompus et al., 2009). Thus, ER strategies relying on frontal control are more challenging to implement in stressful contexts (Raio et al., 2013) and in chronic stress conditions like schizophrenia spectrum disorders (Walker et al., 2008; Horan et al., 2013), which are characterized by heightened sensitivity to psychosocial stress, elevated baseline hypothalamic pituitary adrenal (HPA) axis activity (Pruessner et al., 2017), and an imbalance of frontal and limbic recruitment (Dichter et al., 2010; Aupperle et al., 2012).

The physiological and emotional response to aversive events is malleable and changes with cognitive context to appropriately adapt to environmental challenges (Goldin et al., 2008). Framing, or the presentation of stimuli according to a contextual cue (e.g., positive or negative), requires minimal effort (i.e., is relatively automatic) to alter the emotional response to the stimuli (Gross and D'Ambrosio, 2004), and predominately relies on medial prefrontal cortex involvement (Phillips et al., 2008). While emotional framing is a rudimentary process, it represents a fundamental construct of affective processing, as it manipulates stimulus salience and directs attention to influence behavior, emotional responsivity and the successful reappraisal of emotional events (Nabi, 2003).

The successful execution of ER strategies has been shown to modify electrophysiological correlates of affective processing, including oscillations in theta frequency range (4–8 Hz) (Ertl et al., 2013). Increases in theta oscillatory activity, localized to frontal scalp locations, have been reported to accompany successful reappraisal of emotional events, representing enhanced frontal network recruitment (Ertl et al., 2013; Cavanagh and Frank, 2014). Previous research has implicated theta oscillations in the dynamic integration and coordination of fronto-limbic interactions (Javitt et al., 2008; Uhlhaas et al., 2008; Lesting et al., 2011; Narayanan et al., 2011), as increased theta oscillations in frontal and limbic regions and enhanced theta coherence between the prefrontal cortex and limbic regions are found during fear conditioning and extinction behaviors in animals (Lesting et al., 2011; Narayanan et al., 2011), as well as memory processing in humans (Anderson et al., 2010). Accordingly, disruptions in theta oscillatory activity may produce impairments in functional connectivity between frontal and limbic brain regions critical for affective processing (Lesting et al., 2011), and may subserve affective processing abnormalities in SCZ.

While beta oscillatory activity (12–30 Hz, especially low beta [12–16 Hz]) has not been explicitly studied in ER paradigms, beta oscillations have been implicated broadly in affective processing, including valence discrimination (Csukly et al., 2016), differentiating evocative images with high arousal (Güntekin and Başar, 2010), angry faces (Güntekin and Basar, 2007), and target detection (Güntekin et al., 2013). Furthermore, beta activity is associated with stimulus-driven salience (Kisley and Cornwell, 2006) and arousal (Hong et al., 2008; Kisley and Cornwell, 2006), and is prominent in the insula (Shepherd et al., 2012; Liddle et al., 2016), a central network region consistently implicated in psychopathology (Fornito et al., 2009; Glahn et al., 2008; Kasai et al., 2003; Shepherd et al., 2012; Li et al., 2010; van der Meer et al., 2014).

Consistent with neuroimaging research, acute stress exposure has been found to weaken frontal-related processes, including theta-mediated working memory (Gärtner et al., 2014) and mental arithmetic (Gärtner et al., 2015) tasks. Theta oscillatory activity has been shown to increase during feedback-based category learning in individuals exposed to acute stress (Paul et al., 2018). Stress is further reported to disrupt resting alpha asymmetry (Lewis et al., 2007) and increase beta activity during a challenging Stroop task (Alonso et al., 2015). Additionally, disruptions in theta and beta oscillatory activity are consistently found in psychopathology impacted by stress exposure, including SCZ. Patients with SCZ exhibit aberrant theta and beta oscillatory activity, including deficits in theta-derived mismatch negativity (MMN) (Lee et al., 2017) and executive control (Berger et al., 2016), weakened beta desynchronization for negative stimuli (Csukly et al., 2016), and atypical beta activity in the insula (Liddle et al., 2016). Previous studies on the impact of stress on brain dynamics associated with affective processing are limited, and thus warrants additional research.

Disruptions in affective circuitry may mediate the stress-related pathway to psychopathology. The rigidity of fronto-limbic affective circuitry, or its inability to appropriately respond to emotion and adapt to psychosocial stress exposure, is associated with the development and exacerbation of symptoms in vulnerable individuals (Jones and Fernyhough, 2007; Walker et al., 2008). Psychosocial stress and disruption in ER often precede the onset of psychiatric illness (Myin-Germeys and van Os, 2007; Myin-Germeys et al., 2008; Lataster et al., 2010; Walker et al., 2013), and critically impact social, cognitive, and interpersonal functioning (Porges, 2007; Phillips et al., 2008; Livingstone et al., 2009). Converging evidence from animal (Desbonnet et al., 2012; Cohen et al., 2013) and human research (Jones and Fernyhough, 2007) emphasizes the role of psychosocial stress in particular (e.g., life events, childhood adversity) in the etiology of neuropsychiatric disorders, including SCZ. The integrity of fronto-limbic circuitry in vulnerable individuals exposed to early life stress is found to protect against the precipitation of disease (Cisler et al., 2013), suggesting that differential engagement of frontal and limbic networks following stress exposure may modify the relationship between stress and psychopathology. It is unclear whether stress-induced alterations in neural oscillations play a role in the link between stress exposure and impairment in ER. The evidence that stress and ER compete for frontal neural networks and associated oscillatory activity (Gärtner et al., 2014), which are disproportionately impacted by acute stress exposure (Arnsten, 2009), would support this supposition.

The primary objective of the current study was to examine whether acute psychosocial stress exposure modified the changes in theta and beta oscillatory activity that subserve effortless ER. As frontal and limbic networks involved in ER, and their underlying neural oscillatory activity, are particularly vulnerable to the deleterious effects of stress (Arnsten, 2009, 2011; Gärtner et al., 2014), we hypothesized that in response to a controlled, experimental

stressor, control individuals would demonstrate disturbed frontal theta-mediated affective framing and parietal beta-derived valence discrimination. To understand the relevance of any stress-related effects on fronto-limbic oscillations for the potential development of psychopathology, we compared control participants to patients with schizophrenia spectrum disorders, as they are some of the most disabling psychopathologies potentially triggered or exacerbated by stress and have core deficits in cognitive and affective processing. Consistent with an allostatic load model of psychopathology (McEwen, 2000), we reasoned that exposure to repeated stress or stress during critical developmental periods would lead to an inability to exhibit fronto-limbic adaptation to acute stress in vulnerable individuals (e.g., those who develop SCZ). Consequently, we hypothesized that the negative acute oscillatory changes and ER disruptions observed in control participants in response to acute psychosocial stress would be persistently present in patients with SCZ.

2. Methods

2.1. Participants and clinical measures

Male participants between the ages of 18 and 35 were enrolled in the current study. Participants included 21 patients (SCZ) (mean age (SD) = 25.81(4.25)) meeting criteria for schizophrenia (n = 14), schizoaffective (n = 4) or schizophreniform (n = 3) disorder, and 21 control (CON) participants (mean age (SD) = 23.81(4.61)). Patients were referred to the study by their treating psychiatrist, who deemed them clinically stable and well-suited for the study, and control participants, who were not taking antipsychotic medications and did not have first-degree relatives with schizophrenia, were recruited from the surrounding community using flyers. Diagnostic status was determined using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), and subsequently confirmed with DSM-V criteria. Control participants had a higher self-reported education ($p < 0.001$), yet there were no group differences in age or average parental education. All patients were medicated with first-generation (n = 2) or second-generation (n = 19) antipsychotics, and four patients reported using antidepressant medications, including Bupropion, Cymbalta, and Trazodone (n = 2). Two patients additionally reported using beta-blockers (Metoprolol, Atenolol), and one patient reported using a calcium channel blocker (Amlodipine Besylate). Participants were all English speaking, with normal or corrected to normal vision, and did not have a history of neurological disorders.

The Structured Interview for Positive and Negative Syndrome Scale (SCI-PANSS; Opler et al., 1992) was administered to patients to evaluate positive, negative, and general symptom subscales, and the Clinical Assessment Interview for Negative Symptoms (CAINS; Kring et al., 2013) was administered to all participants to assess negative symptoms (e.g., motivation, pleasure, and emotional expression). Drug and alcohol behaviors were evaluated using the self-report Alcohol Use Scale/ Drug Use Scale (AUS/DUS; Drake et al., 1989). Patients with SCZ demonstrated significantly higher CAINS symptoms relative to controls, however, there were no group differences in self-reported drug and alcohol use ($p > 0.05$) (see Table 1 in Andersen et al., 2018).

2.1.1. Subjective stress and affect questionnaires

The Emotion Regulation Questionnaire (ERQ; Gross and John, 2003) was administered to assess cognitive reappraisal and expressive suppression abilities, and the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) evaluated subjective levels of affect before and after stress exposure. Groups did not differ on subjective measures of affect (PANAS, ERQ) ($ps > 0.05$).

2.2. Tasks and procedures

2.2.1. General procedure

Participants provided informed consent approved by the University of North Carolina at Chapel Hill Institutional Review Board, which was followed by interview and psychophysiological recording sessions on separate days. The psychophysiological recording session was performed at 1:00 PM for all participants to obtain stable endogenous cortisol levels and capture the most accurate endocrine response to the stress manipulation (Allen et al., 2014). Participants were instructed to refrain from smoking and caffeine consumption two hours prior to the study session, and received $20.00 per hour for their participation. A schematic of the experimental design is presented in Fig. 1.

2.2.2. Stress protocol

The Trier Social Stress Test (TSST) is an acute psychosocial experimental stressor which reliably induces a well-characterized hypothalamic pituitary adrenal (HPA) axis cortisol response in diverse populations (Kirschbaum et al., 1993; Allen et al., 2014). Briefly, the TSST combines the preparation (3-minutes) and delivery (5-minutes) of a mock job interview with challenging mental arithmetic (i.e., subtract 7 from 2000) (5-min) in front of a committee of "academic experts" (Kirschbaum et al., 1993). Salivary cortisol (sCORT) was collected at 6 time-points during the psychophysiological session: during capping and set up (C1), following instructions for the TSST stressor (C2), immediately after the TSST math test (C3), and 25 minutes (C4), 45 (C5) and 80 (C6) minutes following stress onset (C2) to capture the characteristic HPA-mediated sCORT response, and confirm validity of the stress manipulation. Psychophysiologic data and subjective stress

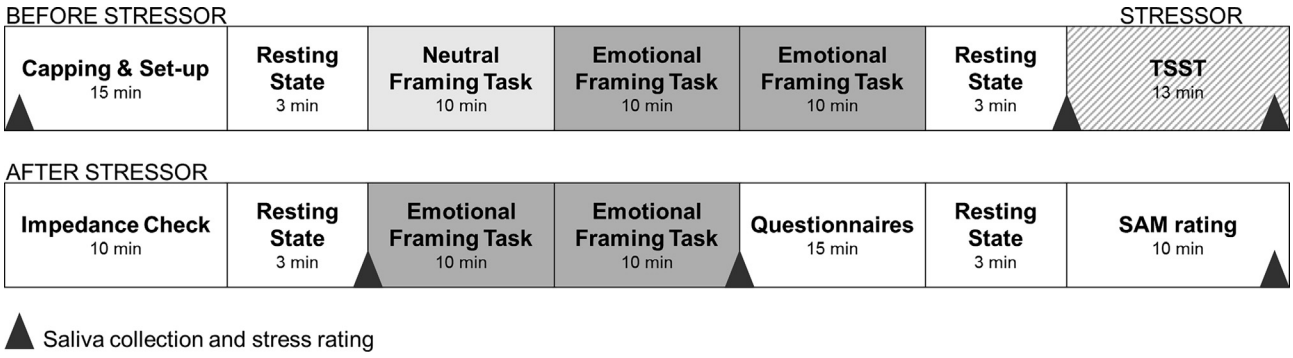

Fig. 1. Diagram of study design. Timeline of the neurophysiology recording session. Session started at 1:00 PM for all participants. Order of emotional framing tasks was counterbalanced between participants. TSST: Trier Social Stress Test; SAM: Self-assessment manikin.

and affect measurements are reported previously (Andersen et al., 2018).

2.2.3. Emotional oddball framing paradigm

Participants performed emotional oddball framing tasks (modeled after Kisley et al., 2011) while EEG was recorded before and after a psychosocial stressor to determine the influence of stress exposure on modifying affective electrophysiology. Images selected from the International Affective Picture System (IAPS; Lang et al., 2008) were organized into blocks consisting of a "target" stimulus, which depicted aversive (e.g., images of mutilation, disease, and human violence; valence mean = 2.2 ± 1.5 (7-point scale); arousal mean = 5.8 ± 2.3 (7-point scale)) or neutral (e.g., images of household items and neutral human faces; valence mean = 4.7 ± 1.4; arousal mean = 3.6 ± 2.0) emotional content, embedded among four neutral, non-arousing "filler" stimuli. Target stimuli were located in the third, fourth or fifth image position (i.e., followed by at least two neutral "fillers"). Neutral and aversive blocks were matched for human content. A neutral framing condition was performed first, requiring participants to determine whether there was an animal (in both neutral and emotional contexts) in the image presented previously. Four 10-minute emotional framing conditions (positive and negative before and after stressor) containing a random selection of 30 neutral and 30 aversive blocks were counterbalanced between participants, and prompted participants to categorize the image shown previously as "positive" or "negative" according to the condition. Images were presented for 1000-ms, followed by a framing cue terminated by response (up to 5000-ms), and variable interstimulus intervals between 400–600-ms. Participants used self-assessment manikins (SAMs) to provide valence and arousal ratings for 20 representative images (15 aversive, 5 neutral) at the conclusion of the session (Bradley and Lang, 1994).

2.3. EEG recording and processing

EEG was acquired using a 128-channel Hydrocel Geodesic Sensor Net (Electrical Geodesics Inc., Eugene, OR) placed according to the international 10–20 System (Klem et al., 1999) with Net Amps 300 (1.0.1) amplifier and Net Station 4.5.1 software on an iMac computer. Data were filtered online at 0.05 Hz with a sampling rate of 1000 Hz (except for 5 participants, which were digitized at 250 Hz), and were referenced online to central Cz electrode. Impedances were maintained below 50 kΩ for the duration of the session, which is acceptable with the use of a high input-impedance amplifier (Ferree et al., 2001). Tasks were programmed in E-Prime 2.0 with E-Studio 2.0.8.74 and synchronized with EEG recording using E-Prime extension for Net Station. Data were exported from Net Station in simple binary format and uploaded in EEGLAB version 13.4.4b, a Matlab open source toolbox for processing and analysis (Delorme and Makeig, 2004).

EEG datasets were down-sampled to 250 Hz, high pass filtered at 1.0 Hz, and low pass filtered at 55 Hz using a Hann filter (78 filter order with transition bandwidth of 10) with −6 dB cutoff to remove 60 Hz line noise. Raw data were cleaned and bad channels were removed using an EEGLAB extension, *clean_rawdata* with a standard deviation of 20 (Miyakoshi and Kothe, 2013). Data were further subjected to manual inspection and rejection of major artifacts before re-referencing the data to average channel values and interpolating bad channels. Three second epochs (-1s-2 s) were generated for each stimulus type and epochs containing abnormally distributed data were rejected. After artifact rejection, approximately 84.51% of trials during the neutral (animal) framing condition (CON: 25.29(2.44); SCZ: 25.43(2.80)), 81.85% of trials before stress (CON: 24.13(2.97); SCZ: 24.98(1.98)) and 82.80% of trials after stress (CON: 24.61(2.60); SCZ: 25.01(3.48)) were maintained. All cleaned, epoched data were loaded into an EEGLAB STUDY to compute the time-frequency transform using the 'newtimef' function, and extract non-phase locked event-related spectral perturbations (ERSP). Increased ERSP relative to baseline reflects event-related synchronization (ERS), whereas deflections in ERSP power are referred to as event-related desynchronization (ERD) (Pfurtscheller, 2001). The decomposition was performed using a wavelet transform with a 3-cycle wavelet to yield Time X Frequency spectrograms with frequencies from 3 to 50 Hz from selected frontal, central, and parietal electrodes.

Previously defined theta (theta-1: 3.5–6 Hz, theta-2: 6–8.5 Hz; Ertl et al., 2013) and beta (beta-1: 12–16 Hz, beta-2: 17–20 Hz, beta-3: 21–28 Hz; Csukly et al., 2016; Del Zotto et al., 2013) frequency ranges were extracted from the pre-computed matrices between 100–500-ms (early window) and 600–1000-ms (late window) post-stimulus to temporally isolate early sensory and late cognitive stages of neural processing. Beta was analyzed from the midline parietal electrode (Pz), consistent with the parietal-dominated affective processing found in Csukly et al. (2016), and frontal theta was analyzed from an average frontal montage (F3, Fz, F4) (Missonnier et al., 2006) to probe oscillatory correlates of cognitive control.

2.4. Saliva sampling and analysis

Participants inserted a cotton swab (Salivette-Sarstedt, Germany) under their tongue for two minutes at each saliva collection. sCORT was measured using an enzyme immunoassay kit (Salimetrics, PA), with a 0.003 μg/dl lower limit of sensitivity and a standard range of 0.012 to 3.0 μg/dl. The average intra-and inter-assay coefficients of variance were 3.5% and 5.1%, respectively. sCORT is expected to peak approximately 25 minutes post-stress at C4, reflecting relatively slow HPA reactivity (Foley and Kirschbaum, 2010). The trapezoid-derived area under the curve measurement with respect to increase was calculated for sCORT (AUC_{i_CORT}) (Pruessner et al., 2003). Peak measurements were computed by subtracting baseline (C2) from Cort4_peak (C4), and from each individual's own post-stress peak value ($Cort_i$_peak). The volume of saliva collected did not differ by group ($p > 0.05$). Subjective ratings of stress and affect composites were collected using a 10-point Likert scale along with the saliva samples to validate the stress procedure (Andersen et al., 2018).

2.5. Statistical analysis

Statistical analyses were performed using IBM SPSS, version 24.0. Analyses and results for subjective stress and affect, and image ratings are presented in Supplementary Material. A preliminary analysis confirmed the reliability of the emotional oddball framing tasks in detecting valence discrimination (greater beta ERD for aversive compared with neutral stimuli) in the neutral (animal) condition, without emotional framing contamination (Supplementary Material). The neutral condition additionally permitted the refinement of frequency parameters for subsequent analyses. Following confirmation of task reliability, data analyses for affective ERSP were performed to test the following: (1) group differences in the effect of stress on beta-ERD-mediated valence discrimination, and (2) whether stress influences the frontal theta-derived positive framing of aversive stimuli differently between groups.

2.5.1. Affective oscillatory activity

Preliminary analyses established that Beta-1 ERD was strongest during the late window, and differentiated stimulus type at electrode Pz; therefore, these parameters were used in subsequent beta analyses (Supplementary Material). A Group X Framing

Condition (positive, negative) X Stimulus (aversive, neutral) X Session (before and after stress) repeated measures (rm)-ANOVA was used to assess the effect of stress on Beta-ERD. Low and high average frontal theta during early and late windows were included in a Group X Condition X Stimulus X Session X Frequency (theta 1, theta 2) X Window (early, late) rm-ANOVA to determine group differences and the effect of stress on theta-mediated early sensory orienting and later cognitive regulation processes. Interactions were further investigated using planned post-hoc pairwise contrasts, Bonferroni-corrected for multiple comparisons, and sphericity violations were corrected using the Greenhouse-Geisser epsilon procedure for all rm-ANOVA analyses.

2.5.2. Psychoendocrinology

A Time (5-timepoints) X Group rm-ANOVA was performed to assess stress-induced changes in sCORT during the TSST manipulation. C1 was removed from the analysis because it was not an accurate baseline measurement. An ANOVA was performed to assess group differences in AUC_i and peak values.

3. Results

3.1. Psychoendocrinology measurements

A main effect of Time for sCORT ($F(1.44,49.04) = 22.13$, $p < 0.001$, $\eta_p^2 = 0.39$) indicated that sCORT increased significantly during stress exposure according to a quadratic trend ($F(1,34) = 25.04$, $p < 0.001$, $\eta_p^2 = 0.42$), thus validating the stress manipulation. There were no significant group differences found for AUC_i and peak values (Fig. 2).

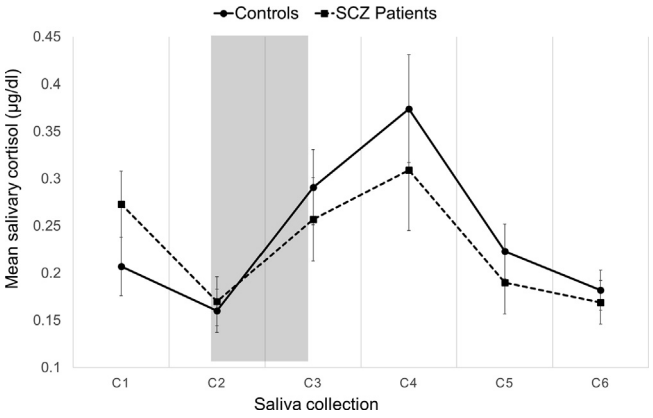

Fig. 2. Cortisol response curves for controls and patients with SCZ. Salivary cortisol (µg/dL) response curves for patients with schizophrenia spectrum disorders (SCZ) and controls during the psychophysiological recording session. Means (and standard errors) presented. Shaded box represents stress exposure (Trier Social Stress Test).

3.2. Oscillatory indices of affective processing

3.2.1. Stress effects on theta oscillatory correlates of emotional framing

An increase in theta ERSP (i.e., theta synchronization (ERS)) was found in the early window across stimulus types, whereas a decrease in ERSP (i.e., theta desynchronization (ERD)) was observed in the late window by a main effect of Window ($F(1,37) = 74.84$, $p < 0.001$, $\eta_p^2 = 0.67$) on theta ERSP. Theta-2 ERD was stronger (Frequency X Window; $F(1,37) = 4.09$, $p = 0.05$, $\eta_p^2 = 0.10$) and differentiated stimulus type (Frequency X Window X Stimulus; $F(1,37) = 7.98$, $p < 0.01$, $\eta_p^2 = 0.18$) during the late window (Stimulus X Window; $F(1,37) = 8.94$, $p < 0.01$, $\eta_p^2 = 0.20$). Furthermore, late theta-2 ERD was particularly impacted by stress (Stress X Frequency X Window; $F(1,37) = 4.33$, $p < 0.05$, $\eta_p^2 = 0.11$), especially for aversive stimuli (Stress X Stimulus; ($F(1,37) = 7.28$, $p = 0.01$, $\eta_p^2 = 0.16$).

Controls demonstrated successful affective framing before stress, with greater theta-2 (reduced ERD) during the positive condition for aversive stimuli in the late window (Condition X Frequency X Window X Group; $F(1,37) = 4.32$, $p < 0.05$; $\eta_p^2 = 0.10$), which was not maintained after stress. Unlike controls, patients did not show theta ERSP-mediated framing effects before or after stress, as indicated by planned post-hoc comparisons ($ps > 0.05$). While the main effect of Group was not significant ($p = 0.09$), controls exhibited stronger theta ERS during the early window compared with patients (Window X Group; $F(1,37) = 7.31$, $p = 0.01$, $\eta_p^2 = 0.17$), particularly for aversive stimuli during the positive condition ($F(1,37) = 4.61$, $p < 0.05$) (Fig. 3).

3.2.2. Stress effects on beta oscillatory correlates of valence discrimination

A main effect of Stimulus ($F(1,37) = 10.51$, $p < 0.01$, $\eta_p^2 = 0.22$) was found, indicating stronger parietal beta-1 ERD for aversive relative to neutral stimuli during the late window. While beta ERD distinguished stimulus type in control participants during the negative condition before ($F(1,37) = 6.50$, $p < 0.05$) stress and during positive ($F(1,37) = 4.66$, $p < 0.05$) and negative ($F(1,37) = 11.09$, $p < 0.01$) conditions after stress, post-hoc pairwise contrasts revealed that the beta ERD response differed by stimulus valence for patients only during the positive condition after stress ($F(1,37) = 4.26$, $p < 0.05$). A unique framing effect for controls, reflected in reduced beta ERD for aversive stimuli during the positive compared with negative condition, was evident by a significant Condition X Group interaction ($F(1,37) = 13.34$, $p < 0.01$, $\eta_p^2 = 0.27$), which was maintained following stress. A main effect of Stress ($F(1,37) = 8.02$, $p < 0.01$, $\eta_p^2 = 0.18$) on beta ERD was found, indicating that stress exposure weakened beta ERD, particularly for neutral stimuli, revealed in a Stress X Stimulus interaction ($F(1,37) = 4.94$, $p < 0.05$, $\eta_p^2 = 0.12$). Controls additionally demonstrated a significant stress-related decrease in beta ERD for positively framed neutral stimuli ($F(1,37) = 4.26$, $p < 0.05$). A marginal Group effect ($F(1,37) = 3.99$, $p = 0.05$, $\eta_p^2 = 0.10$) was driven by patients' significantly reduced beta ERD for aversive stimuli in the negative condition before ($F(1,37) = 9.61$, $p < 0.01$) and after ($F(1,37) = 7.20$, $p = 0.01$) stress (Fig. 4).

4. Discussion

In this study, fronto-limbic affective circuitry was probed using an emotional framing paradigm and challenged with an acute psychosocial stress manipulation to determine the impact of stress exposure on effortless ER and underlying theta and beta oscillations in control individuals and patients with SCZ. Following psychosocial stress exposure, control participants exhibited acute oscillatory changes associated with ER that were persistently observed in patients with SCZ. Specifically, stress exposure disproportionately impacted later, frontal-mediated framing and motivated attention processes in controls, leaving beta-derived valence discrimination and cognitive appraisal intact. Consistent with a growing body of literature that suggests that stress preferentially modifies frontal-mediated processes, these results indicate that acute stress also interferes with frontal-mediated emotional framing and provides neurophysiological evidence for stress-induced emotional dysregulation. Frontal theta activity may underlie the neural adaption to stress; thus, disruptions in theta oscillatory activity may represent critical neurophysiological mechanisms mediating the stress-related pathway to psychopathology.

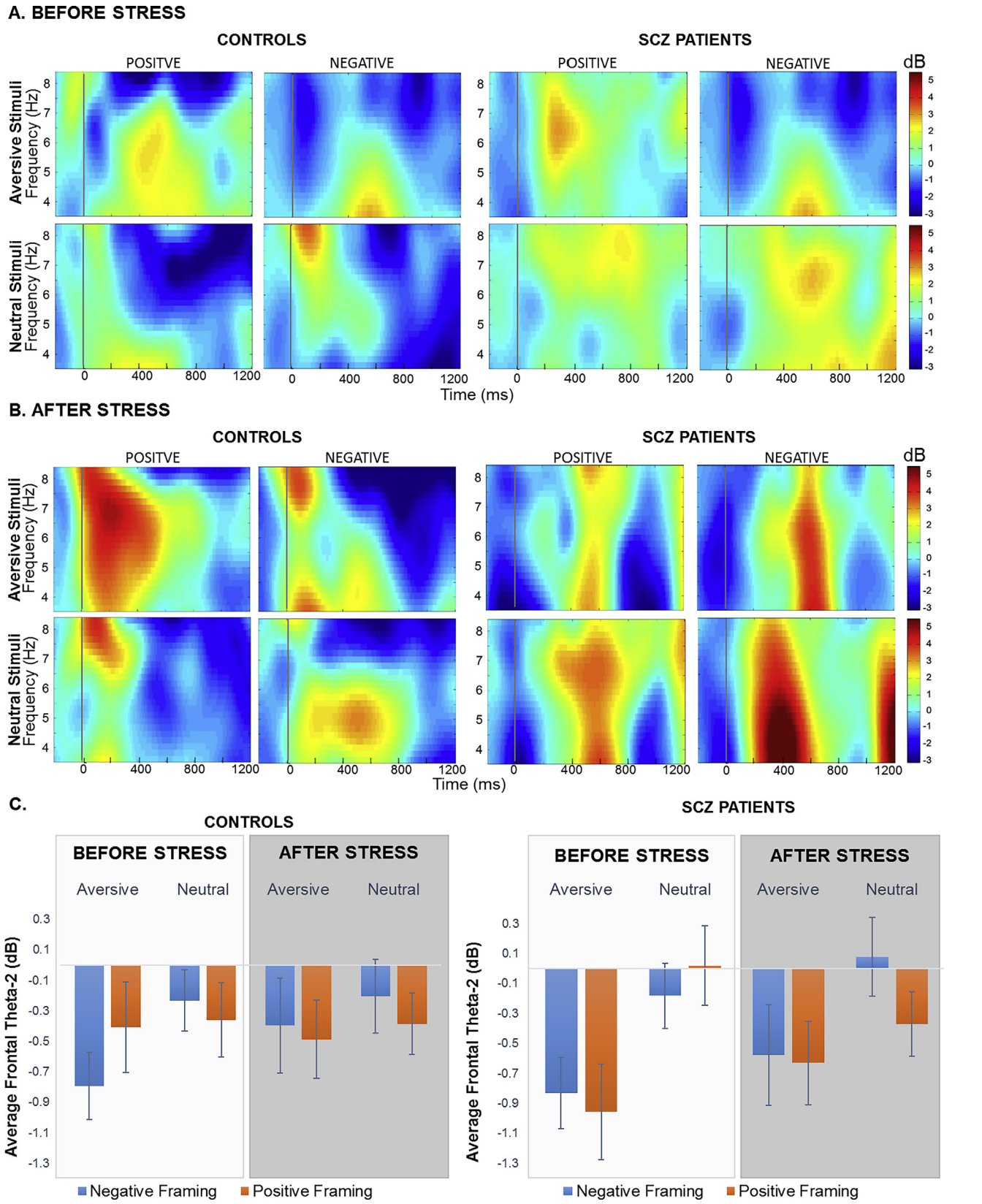

Fig. 3. Stress induced changes in frontal theta ERSP and impacted positive framing. Time-frequency spectrograms depict frontal theta (4–8 Hz) ERSP (event-related spectral perturbation, dB) for emotional and neutral targets during positive and negative framing conditions, before (A) and after (B) stress. Stress exposure increased theta activity, especially for aversive stimuli. (C). Graphical representation of average frontal theta-2 (6–8.5 Hz) during the late window (600–1000 ms) for aversive and neutral stimulus types during negative (blue) and positive (orange) framing conditions. Intact emotional framing was found before stress for controls only. Error bars = standard error.

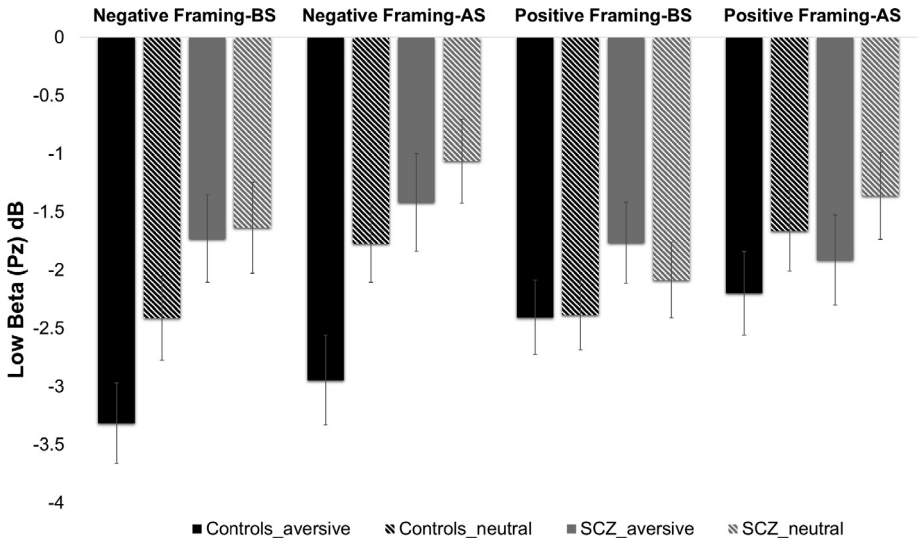

Fig. 4. Valence discrimination reflected in low parietal beta ERD. Graphs illustrate low beta (12–16 Hz) measured from Pz electrode during the late window (600–1000 ms). Beta ERD distinguished stimulus type for Controls (black) during the negative framing conditions before and after stress, but this pattern was not found for SCZ patients (gray).

The acute psychosocial stress manipulation stimulated a predictable neuroendocrine response with increases in sCORT following stress onset, thus validating the stress protocol (Nater et al., 2005; Foley and Kirschbaum, 2010). While not statistically significant from controls, patients exhibited lower sCORT production in response to the TSST task, consistent with previous studies (Jansen et al., 1998, 2000; Brenner et al., 2009). However, an accurate baseline measurement (i.e., allowing time to adjust to the experimental session) would have been necessary to determine whether patients' sCORT response during stress exposure was blunted or normal. We recently reported maladaptive parasympathetic regulation of arousal in this sample of participants, with a decoupling of vagal tone, indexed by respiratory sinus arrhythmia (RSA) and arousal (heart period) during transitional states (Andersen et al., 2018). This indicates that SCZ patients may have a dysregulated stress system that is incapable of adapting appropriately to changes in situational demands.

Psychosocial stress exposure induced a shift to a more arousing, excitable oscillatory profile with aggravated theta activity and weakened beta ERD, and preferentially disrupted frontal theta-mediated affective processing in control participants. The combination of greater theta activity and weakened beta ERD observed after stress is indicative of a divergence in salience attribution and arousal regulation, and is consistent with aberrant frontal and limbic activation following stress in neuroimaging studies (Oei et al., 2012; Shermohammed et al., 2017). Consistent with the current results, Shermohammed et al. (2017) showed that while subjective cognitive reappraisal success remained intact following psychosocial stress exposure, healthy adults exhibited modest stress-induced increases in frontal (prefrontal cortex) and limbic (amygdala) activation during cognitive reappraisal. The increased stress-induced theta activity for aversive stimuli may underlie deficient regulation of brain arousal, in accordance with previous neuroimaging reports (Li et al., 2014), and reflect greater recruitment of attention and cognitive resources necessary for implementing frontal-mediated affective processing under stress. Accordingly, enhanced theta activity was previously found to accompany increasing task demands (Jensen and Tesche, 2002), support cognitive reappraisal in ER paradigms (Ertl et al., 2013), and cognitive control processes (Cavanagh and Frank, 2014). Thus, maladaptive stress regulation in patients and response to acute stress in controls may induce a global brain state of heightened arousal, reflected in disrupted affective oscillatory activity. Along with fostering inappropriate mobilization and defensive behaviors, a maladaptive stress response may contribute to impaired oscillatory activity, thus compromising the integration of neural information and shifting the excitatory-inhibitory balance. Consequently, deficits in arousal regulation may ultimately result in network dysconnectivity, with greater interference on top-down, slow-wave dominated frontal processes (Engel and Fries, 2010), and cognitive and behavioral disturbances. As such, manipulating the synchronization of frontal midline theta oscillations using transcranial direct-current stimulation was reported to significantly improve arousal control in schizophrenia spectrum patients (Reinhart et al., 2015). Therefore, disruptions in arousal regulation, possibly as a result of deficient frontal theta oscillatory activity, may contribute to core affect dimensions of neuropsychiatric disorders.

Control participants revealed expected affective oscillatory patterns in parietal beta-derived cognitive elaboration of aversive stimuli, and differential modulation of frontal-theta by categorical framing cues, whereas patients exhibited deficits in theta and beta-mediated cognitive processes in the absence of stress. The strong early frontal theta activity exhibited by controls may reflect the allocation of attention to signal salience and support later stages of information processing, including the enhanced frontal engagement required by the positive framing condition to successfully dampen the emotional response to aversive stimuli and support PFC-dominated cognitive and attentional processes. Accordingly, frontal theta activity is proposed to underlie PFC and ACC engagement during working memory, cognitive control and performance monitoring (Gevins et al., 1997; Onton et al., 2005; Gärtner et al., 2014), and these regions have reported functional and structural impairments in SCZ (van der Meer et al., 2014). In the current study, patients exhibited an overall deficiency in theta activity, which extended over early synchronized attention allocation (Missonnier et al., 2006) and later desynchronized motivated attention and cognitive regulation processes (Aftanas et al., 2001; Balconi and Lucchiari, 2006). Furthermore, reduced theta activity in patients may reflect a global deficit in cortical communication with deficient neuronal participation and synaptic connectivity (Fitzsimmons et al., 2013; Friston, 1999), as slow-wave oscillations are critical for integrating information processed in remote brain regions (Uhlhaas and Singer, 2014).

Along with intact valence discrimination (i.e., the greater low beta ERD for aversive relative to neutral stimuli), the beta ERD elicited for aversive stimuli also uniquely distinguished framing condition in control participants (i.e., decreased beta ERD for aversive stimuli during the positive relative to negative framing conditions). This beta ERD framing effect mimics the LPP response pattern found in Kisley et al. (2011), thus validating the modified emotional oddball framing paradigm used in the current study. Similar to the LPP, beta oscillations are modified by contextual and regulatory influences and may reflect the convergence of cognitive and affective processes (Hajcak et al., 2009). Patients exhibited weakened beta ERD in response to aversive stimuli during the negative condition relative to controls, as predicted and consistent with Csukly et al. (2016). The atypical parietal beta in patients may reflect aberrant salience attribution, motivated attention and impaired perceptual integration, further representing neurophysiological correlates of insular dysfunction. With a central role in coordinating autonomic, visceral and homeostatic states, and the subjective experience of salience, the insula stands out as a critical node in the psychopathology of SCZ (Wylie and Tregellas, 2010; Sidlauskaite et al., 2014; Uddin, 2015). As such, beta oscillations may underlie insula-mediated state switching, and aberrant beta activity may be an important index of state rigidity in psychopathologies characterized by greater sensitivity to stress exposure and aberrant stress regulation.

The present study has several limitations that should be addressed in future studies. The relatively small sample size of the study, as well as the sample's restriction to males, may limit the power and scope of the inferences. To reduce variability in the sample, and because of the male predominance of SCZ in this age range (Abel et al., 2010), the present study was restricted to males; however, given that men and women differentially respond to ER strategies following stress exposure (Kinner et al., 2014; Kogler et al., 2014), and demonstrate differences in affective processing, such as enhanced negative emotionality in females (Stevens and Hamann, 2012; Gardener et al., 2013), future studies elucidating sex differences on the impact of stress on affective processing and underlying neural oscillations in SCZ will improve generalizability and external validity.

Finally, confounding factors including medication exposure, smoking and caffeine consumption, and body-mass-index (BMI) potentially alter physiological activity. BMI, which is related to cortisol reactivity, was not assessed. All patients were taking antipsychotic agents, however, dosage information and chlorpromazine equivalents were not available for all patients and prevented the assessment of medication effects in the current study. Despite evidence that medication exposure may alter the amplitude of event-related potentials (ERP) (Coburn et al., 1998; Gonul et al., 2003), EEG oscillations do not appear to be influenced by antipsychotics. Previous studies report that oscillatory dysfunction in gamma (Gallinat et al., 2004), theta, delta (Narayanan et al., 2015) and beta (Csukly et al., 2016) frequencies is maintained regardless of medication status, including in un-medicated patients (Boutros et al., 2008). Therefore, it is unlikely that the current neurophysiological results are driven by antipsychotic medication exposure.

5. Conclusion

This is the first study to investigate the neurophysiological mechanisms underlying arousal and affect regulation in response to acute experimental challenge, and may offer novel insight on potential mechanisms supporting the translation of stress into psychopathology. Aberrant arousal regulation and rigidity of fronto-limbic affective circuitry, possibly as a result of impaired frontal theta-mediated processes and beta-derived state switching, may underlie the prominent cognitive and affective symptoms of psychopathology and inform about early stress-induced affective circuitry dysfunction. Results from the current study may motivate future studies to examine therapeutic and intervention approaches targeting fronto-limbic derived stress and emotion regulation to alleviate symptom severity, or prevent the precipitation of symptoms in vulnerable individuals. Stress mediation, for instance, may be an effective supplemental treatment option to complement existing cognitive therapies, including those reliant on ER, to eradicate persistent negative and cognitive symptoms in patients with SCZ. Furthermore, targeting theta and beta activity therapeutically using transcranial magnetic stimulation (TMS; Ferrarelli et al., 2008) or transcranial direct (tDCS; Polanía et al., 2011; Zaehle et al., 2011) and alternating (tACS; Ali et al., 2013; Herrmann et al., 2013) current stimulation may manipulate oscillatory activity to encourage effective neural processing and improve fronto-limbic network efficiency.

Conflicts of interest

The authors do not have any conflicts of interest, financial or otherwise, to disclose.

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Appendix A. Supplementary material

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