CONVERGENCE OF ABERRANT ELECTROPHYSIOLOGICAL CORRELATES OF SALIENCE, AFFECTIVE PROCESSING AND STRESS REACTIVITY IN PATIENTS WITH SCHIZOPHRENIA

Elizabeth H. Andersen

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Approved by:

Aysenil Belger

Kelly Giovanello

Diana Perkins

Donita Robinson

Karen Grewen

Gabriel Dichter

Rebecca Santelli

ABSTRACT

Elizabeth H. Andersen: Convergence of Aberrant Electrophysiological Correlates of Salience, Affective Processing and Stress Reactivity in Patients with Schizophrenia.
(Under the direction of Aysenil Belger)

Patients with schizophrenia exhibit debilitating deficits in attention and affective processing, which are often resistant to treatment and associated with poor functional outcomes. Attentional and affective processing relies on a distributed neural network of fronto-limbic circuits, which enable cognitive control and affective processing, and assist in their interaction to regulate emotional responses. Despite evidence of intact affective valence processing, schizophrenia patients are often unable to employ cognitive change strategies to reduce attentional capture by emotionally salient stimuli, or modulate neurophysiological responses to aversive stimuli. Aberrant neurophysiological correlates of orienting to task-relevant emotional stimuli are also present in unaffected first-degree relatives of schizophrenia patients, suggesting they may represent vulnerability markers. However, less is known about the attentional processing of emotionally salient, task-irrelevant information in these groups, which is examined in Experiment 1 (Chapter 2). Results suggest that despite intact novelty detection, schizophrenia patients and relatives shared deficiencies in attentional processing of emotionally salient information. First-degree relatives exhibited a unique enhancement of the electrophysiological correlate underlying salience evaluation, possibly indicating a compensatory engagement of neural circuitry.

While fronto-limbic circuits are fundamental for affective processing and its modulation by higher order cognitive control, this network also plays a critical role in stress regulation, and is disproportionally affected by the deleterious effects of stress. To understand the efficiency and resilience of fronto-limbic circuitry in adapting and recovering from stress exposure in schizophrenia, Experiment 2 (Chapter 3) investigated the effect of an acute experimental psychosocial stressor on neurophysiological indices of fronto-limbic-mediated emotional regulation processes. Results suggest that stress exposure modified electrophysiological correlates of affective processing in patients and controls. Furthermore, patients

demonstrated aberrant fronto-limbic oscillatory indices of affective processing, as indicated by exaggerated neural excitability and inefficient frontal cognitive control, and maladaptive stress function. This imbalance between heightened neural responsivity and inefficient frontal regulation may reflect an atypical arousal state that may in turn interfere with fronto-limbic processing and promote symptomatology. Elucidating the neurophysiological correlates underlying salience detection, affective processing, and their modification by stress, will be crucial for identifying vulnerability markers, and for developing innovative treatment strategies targeting the fronto-limbic circuitry to relieve psychopathology.

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PREFACE

Chapter 1

Chapter 1 is an introduction to the topics of cognitive and affective salience processing, fronto-limbic-mediated stress and emotion regulation, the interaction between stress and neurophysiological correlates of affective processing, and how these processes are disrupted in schizophrenia. It provides the background and justification for the two projects presented in Chapters 2 and 3.

Chapter 2

Chapter 2.2 was published in the *Clinical EEG and Neuroscience* journal (Andersen et al., 2016), and formatted to meet the editing standards while keeping the integrity of the manuscript intact, per the request of Sage Publishing. In addition to performing the analyses and interpreting the results, I drafted the manuscript and critically revised the manuscript with help from the other authors.

Chapter 3

Chapter 3 is a manuscript in preparation. I administered the clinical and neurocognitive interviews and assessments, collected the EEG and ECG data, and performed the analyses.

Chapter 4

Chapter 4 is the Conclusions chapter, where I summarize important findings, discuss implications and significance, and propose future directions.

To prevent redundancy, all references are compiled at the end.

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LIST OF ABBREVIATIONS

5HT2A	5-hydroxytryptamine 2A serotonin receptor
ACTH	adrenocorticotropic hormone
AIC	anterior insular cortex
ANOVA	analysis of variance
ANS	autonomic nervous system
AVLT	Auditory Verbal Learning Test
BCAET	Baron-Cohen “Reading the Mind in the Eyes” Test–Revised
BNM	brain network modulation
BNST	bed nucleus of the stria terminalis
BPM	beats per minute
CAINS	Clinical Assessment Interview for Negative Symptoms
CAN	central autonomic network
CBT	cognitive behavioral therapy
CEN	central executive network
CPT-IP	Continuous Performance Test-Identical Pairs
CRH	corticotropin-releasing hormone
CSF	cerebral spinal fluid
CT	computed tomography
D2	D2 subtype of dopamine receptor
dACC	dorsal anterior cingulate cortex
DKEFS-CWIT	Delis-Kaplan Executive Function System–Color-Word Interference Test
DLPFC	dorsal lateral prefrontal cortex
DMN	default mode network
DSI	Daily Stress Inventory
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DTI	diffusion tensor imaging

ECG	electrocardiogram
EEG	electroencephalography
EP	evoked power
ER	emotion regulation
ERD	event-related desynchronization
ERP	event-related potential
ERQ	emotion regulation questionnaire
ERSP	event-related spectral perturbation
FA	fractional anisotrophy
FDR	first-degree relative
FEIT	Facial Emotion Identification Test
FRN	feedback-related negativity ERP component
GABA	gamma-Aminobutyric acid
GR	glucocorticoid receptors
GWAS	genome-wide association study
H-MRS	proton magnetic resonance imaging
HP	heart period
HPA	hypothalamic-pituitary-adrenocortical axis
HR	heart rate
HRV	heart rate variability
IAPS	International Affective Picture System
ITC	inter-trial phase coherence
LPP	late positive potential
LTP	long-term potentiation
MEG	magnetoencephalography
mGluRs	metabotropic glutamate receptors
MIST	Montreal Imaging Stress Test
MR	mineralocorticoid receptors

MRI	functional magnetic resonance imaging
NAART	North American Adult Reading Test
NMDA	N-methyl-D-aspartate
PANAS	Positive and Negative Affect Schedule
PANSS	Positive and Negative Syndrome Scale
PCP	phencyclidine
PET	positron emission tomography
PFC	prefrontal cortex
PSS	Perceived Stress Scale
PTSD	post-traumatic stress disorder
PVN	paraventricular nucleus of the hypothalamus
RDoC	Research Domain Criteria Initiative
RSA	respiratory sinus arrhythmia
RT	reaction time
sAA	salivary alpha amylase
SAM	self-assessment manikin
SCID	structured clinical interview for DSM
SCI-PANSS	Structured Interview for Positive and Negative Syndrome Scale
sCORT	salivary cortisol
SCZ	schizophrenia
SES	socioeconomic status
SNPs	single nucleotide polymorphisms
SOPS	Scale of Prodromal Symptoms
SSR	subjective stress and affect rating
TSST	Trier Social Stress Test
VST	Visuospatial Sequencing Test

CHAPTER 1: INTRODUCTION

1.1 Clinical Overview of Schizophrenia

Introduction

Schizophrenia is a complex heterogeneous disorder with dynamic symptom manifestations spanning cognitive, psychological and behavioral processing domains. As the most common type of psychosis, schizophrenia affects twenty-one million people worldwide (World Health Organization [WHO]) and represents an overwhelming economic burden on society (Chaiyakunapruk et al., 2016). It is recognized as a chronic and severe mental illness, characterized by debilitating disruptions in disorganized thinking and behavior, distortions of reality, and profound deviations in cognitive and affective function (American Psychiatric Association, 2013). Patients experience periods of remission and relapse throughout their lifetime, with some individuals experiencing intermittent symptoms and some following a course of progressive deterioration. The *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-V) criteria for a schizophrenia diagnosis involves persistent symptoms in two of five symptom domains, including delusions, hallucinations, disorganized speech, disorganized behavior and negative symptoms. Patients diagnosed with schizoaffective disorder experience depression or bipolar symptoms in parallel with schizophrenia symptoms, while a schizophreniform diagnosis is dependent on symptoms lasting less than six months. Symptoms of schizophrenia typically emerge during young adulthood (18-35), with approximately 1.4:1 incidence ratio for males and females and a female dominated older onset (Abel et al., 2010). While female schizophrenia patients express greater depression symptoms, males typically experience heightened negative symptoms contributing to a more severe course of illness.

Neurobiology of Schizophrenia and Potential Risk Factors

Schizophrenia results from a combination of genetic and environmental insults, which through altered signaling pathways, are thought to cause reductions in dendritic spine density (Glantz and Lewis, 2000), deficiencies in synaptic transmission (Yin et al., 2012) and ultimately, compromise the construction

of neural circuitry (Garey, 2010; Penzes et al., 2011). The cortical deterioration observed in schizophrenia is accompanied by a collection of symptoms encompassing an extensive range of behavioral and cognitive abnormalities. Nevertheless, schizophrenia is first and foremost an information processing disorder in which patients experience a notable decline in numerous domains of cognition (Aas et al., 2014), including attention (Cornblatt and Erlenmeyer-Kimling, 1985), working memory (Manoach, 2003), response selection and inhibition (Kiehl et al., 2000), and attribution of salience (Kapur, 2003). Schizophrenia patients typically experience their first psychotic episode during late adolescence or early adulthood, consistent with the significant neural network refinement that occurs during this period (Penzes et al., 2011). As a neurodevelopmental disorder, environmental factors during fetal life are proposed to modify neurodevelopmental trajectories and promote the manifestation of symptoms during adolescence and adulthood (Wójciak et al., 2016). The following sections summarize the pertinent neural mechanisms promoting the pathophysiology of schizophrenia, including genetic and environmental interactions, disruptions in neurotransmitter transmission, and structural and functional brain abnormalities.

Environment

A convergence of environment and genetic influences is thought to promote vulnerability for psychosis (Caspi and Moffitt, 2006). Early developmental insults, including infections in utero (i.e., rubella, influenza, and poliovirus) (Brown and Susser, 2002) and increased prenatal stress, may disrupt the maternal cytokine response leading to obstetric complications in the mother (Patterson, 2002), which are thought to predispose vulnerability for schizophrenia (Ross et al., 2006). These early neurodevelopmental lesions may establish vulnerability to atypical late neurodevelopmental processes which interact with environmental factors, including social adversity accompanying immigration (Weiser et al., 2008), urbanicity (Krabbendam, 2005), season of birth (Mortensen et al., 1999), and exposure to psychoactive substances such as cannabis (Arseneault et al., 2002), to promote the emergence of psychosis (Pantelis, 2005). While numerous environmental influences have been proposed to contribute to the manifestation of schizophrenia, the validity of the claims remains inconclusive. Nevertheless, genetic and environmental influences likely play a synergistic role in promoting disease onset through the genetic control of sensitivity to the environment.

Stress aggravates synaptic pathologies observed in schizophrenia and is considered a significant environmental trigger in the etiology of schizophrenia (Corcoran et al., 2003). A more in depth description of the stress system and implications of stress in psychosis can be found in section 1.3. Briefly, the cascade of events following stress exposure stimulates structural changes in the brain, including reduced dendritic arborization and spine density (Radley, 2005), and exposure to repeated, chronic stress associated with extreme life events, such as childhood trauma, may provoke the development of psychotic symptoms (Liston et al., 2009). Stress interferes with already vulnerable circuitry in schizophrenia patients to intensify cortical atrophy and threaten neural network integrity (Arnsten, 2011). Because prefrontal cortical circuits are disproportionately affected by the stress-induced cortical disturbances, processes governed by the prefrontal cortex, including working memory, attentional control, and behavioral flexibility are particularly susceptible to disruption in patients (Arnsten, 2009, 2011). Given the substantial neural modifications and disruptions in cognitive processes inflicted by stress exposure, it is not surprising that stress is considered a precipitating factor for psychosis in vulnerable individuals.

Disruptions in Neurotransmitter Transmission

Hyperdopaminergic transmission is thought to play a pivotal role in the etiology of schizophrenia and is considered one of the most prevailing theories in psychiatry (Howes and Kapur, 2009). The dopamine hypothesis of schizophrenia emerged concurrently with the introduction of the conventional antipsychotic drugs which target the D2 dopamine receptor subtype and were found to alleviate positive symptoms. Moreover, psychostimulants that trigger dopamine release cause psychosis symptoms or exacerbate symptoms in patients (Ross et al., 2006). Studies implementing positron emission tomography (PET) report that patients exhibit presynaptic dysregulation of dopamine, with increased dopamine release in response to impulse and elevated dopamine synthesis, and confirm that the hyperdopaminergic state is associated with psychotic symptoms in patients (Kapur, 2003; Soares and Innis, 1999). Furthermore, genome-wide association studies (GWAS) have identified the D2 receptor gene (DRD2) as a potential candidate gene of interest in schizophrenia, further signifying a fundamental role of dopamine in the pathophysiology of schizophrenia.

However, antipsychotic drugs targeting the dopamine D2 receptor are only minimally effective in relieving symptomatology in the majority of schizophrenia patients, suggesting that dopamine is only a

small piece of the puzzle. In addition to atypical dopamine activity, disruptions in glutamatergic transmission may underlie prominent symptoms of schizophrenia. Proton magnetic resonance imaging (H-MRS) has permitted the study of glutamate function in vivo in schizophrenia patients by measuring glutamate and its metabolites (Poels et al., 2014). Aberrant glutamate activity and hypofunction at N-methyl-D-aspartate (NMDA) and metabotropic glutamate receptors (mGluRs) resulting in elevated glutamate may also contribute to the pathophysiology of schizophrenia, as phencyclidine (PCP) and ketamine block NMDA receptors and produce schizophrenia-like psychotic symptoms (Coyle, 2006).

Furthermore, while deficiencies in inhibitory gamma-Aminobutyric acid (GABA) neurotransmission have been associated with cognitive dysfunction and have a proposed role in dopamine regulation, the influence of GABA in the neuropathology of schizophrenia remains controversial (Chiapponi et al., 2016). The integration and synergistic interaction of neurotransmitter systems underlies the neurophysiology of schizophrenia and motivates a circuit based framework, systems-level approach to understanding schizophrenia (Lisman et al., 2008).

Structural Brain Abnormalities in Schizophrenia

Global deficits in structural brain morphology have been reported in schizophrenia. Early structural MRI and computed tomography (CT) studies of schizophrenia confirmed post-mortem findings of a widening of lateral and third ventricles in patients, though these findings are not specific to schizophrenia (Ross et al., 2006). Cortical atrophy is consistently observed in schizophrenia patients, with dramatic reductions in frontal lobe, amygdala, insula, thalamus and hippocampal gray matter volume (Wójciak et al., 2016), and gray matter may decline with illness progression (Haijma et al., 2013). Furthermore, a disproportionate deterioration of frontal neural integrity, particularly the dorsal lateral prefrontal cortex (DLPFC), and frontal network architecture is thought to underlie devastating psychological, cognitive and behavioral symptom pathology in schizophrenia patients (Arnsten, 2011; Weinberger, 1987).

Schizophrenia as a Disconnection Syndrome

Schizophrenia can be appreciated as a disconnection syndrome, with vast disruptions in efficient coordination and integration of neural networks (Friston, 1999, 2011). With recent advances in imaging technology, researchers can expand beyond the concentration on distributed anatomical abnormalities, to

elucidating the compromised structural and functional integrity of neural network construction subserving schizophrenia. Anatomical connectivity can be assessed using diffusion tensor imaging (DTI), which concentrates on the fractional anisotrophy (FA) metric to evaluate microstructural properties of white matter tracts. DTI studies have revealed that patients with schizophrenia demonstrate reduced FA in frontal and temporal lobes, along with aberrations within the fiber bundles connecting these regions (Wheeler and Voineskos, 2014), suggesting alterations in structural connectivity in schizophrenia.

In addition to structural connectivity assessments using DTI, functional MRI studies are useful for investigating functional connectivity among brain regions by assessing synchronized blood oxygenation levels, an indirect measure of functional integration. The inefficiency of network connectivity and functional integration, especially between frontotemporal brain regions, is a fundamental feature of schizophrenia, with hypo and hyper task-related connectivity reported (Friston, 2011; Lynall et al., 2010). Aberrant activity in the default mode network (DMN), which is active during rest and suppressed during attention-demanding tasks, is one of the most robust findings of network disruptions in schizophrenia, and impaired DMN suppression is related to abnormalities in neural networks associated with language, attention, and working memory (Fitzsimmons et al., 2013; Garrity et al., 2007).

Along with neuroimaging studies, EEG measures of oscillatory activity offer valuable insight into the integrity of functional networks, as the integration of information among distributed brain regions and efficiency of connections relies on oscillations and their synchronization. Oscillatory indices of cognitive and affective processing are disrupted in patients with schizophrenia, and provide additional evidence of deficient network activity and dysconnectivity. Measurement and interpretation of neural oscillatory activity is described in more detail in section 1.2.

Disparities in Treatment Efficacy and Symptom Management

The combination of pharmacotherapy, along with psychosocial and psychotherapeutic interventions, is often the most effective method to ameliorate symptoms of schizophrenia. However, pharmacological agents have only progressed modestly since the first antipsychotic medication was introduced 60 years ago, and offer minimal symptom relief with considerable adverse side-effects (Bruijnzeel et al., 2014; Ross et al., 2006). Consequently, advancing the understanding of the neurobiological correlates underlying schizophrenia is critical for improving illness prognosis. While anti-

psychotic medications targeting D2 dopamine receptors are typically effective at dampening positive and disorganization symptoms, the side-effects are sometimes intolerable and lead to reduced medication compliance. Furthermore, these first-generation drugs, including chlorpromazine and haloperidol, introduce devastating neurological side effects such as tremor, rigidity, dystonia and dyskinesia, along with metabolic and gastrointestinal adverse effects. In addition to targeting the D2 dopamine receptors, second generation antipsychotics (atypical), including clozapine and olanzapine, block serotonin 5-hydroxytryptamine 2A (5HT2A) receptors and have demonstrated efficacy at minimizing the neurologic side effects; however, they are not free of adverse side-effects and are associated with substantial weight gain and risk for type-II diabetes (Bruijnzeel et al., 2014). With the exception of clozapine, which has been shown to be more effective in reducing negative symptoms, there are no major differences in efficacy between first and second generation antipsychotics.

Negative Symptoms and Treatment Considerations

In addition to the more recognized positive symptoms such as hallucinations and delusions, schizophrenia patients experience a debilitating collection of negative symptoms, including blunted expression of emotion, diminished participation in interpersonal relationships, apathy, avolition and anhedonia which are less responsive to current psychopharmacological methods and are associated with a poor functional outcome (Erhart et al., 2006; Green et al., 2004; Williams et al., 2008). Psychosocial therapies, including cognitive behavioral therapy (CBT), social skills training, family psychoeducation, assertive community treatment and supported employment are valuable treatment options for targeting the persistent negative symptoms to improve illness prognosis and quality of life (Kreyenbuhl et al., 2010). More recently, repetitive transcranial magnetic stimulation to the DLPFC has demonstrated some efficacy in improving cognitive function in patients with schizophrenia (Barr et al., 2013). As antipsychotic drugs blocking dopaminergic activity are disproportionately effective at ameliorating positive symptoms rather than negative symptoms, a network pharmacological approach, or devising drugs that act on multiple targets simultaneously rather than single-target agents, is proposed to more adequately address the large-scale brain network dysfunction observed in schizophrenia (Hopkins, 2007; Kapur, 2003). Advancing treatment approaches for cognitive and emotional symptoms of schizophrenia relies on elucidating the molecular, cellular and systems-level pathogenesis of schizophrenia. With stagnant

pharmacological treatment progression and only partially effective and intolerable medications available, identifying novel endophenotypes and treatment targets is critical.

Prognosis and Quality of Life

Schizophrenia is a chronic debilitating disorder that has profound psychological, behavioral, emotional and financial impact on the individual and family. Cognitive and negative symptoms, along with poor hygiene and low education levels, interfere with patients' ability to live productive and meaningful lives and often promote occupational and social dysfunction (Bobes et al., 2007). Patients tend to self-medicate with drugs and alcohol, which along with comorbid medical conditions including obesity, diabetes, hypertension and coronary heart disease, contribute to an abbreviated life span. Extensive support and supervised housing is required, adding to the financial burden on the patients and their families (Kitchen et al., 2012). With this dismal prognosis, advancing the understanding of the pathophysiological mechanisms promoting vulnerability and neurobiological correlates underlying schizophrenia is crucial for devising more effective treatment approaches and improving the quality of life for patients with schizophrenia.

1.2 Schizophrenia as a Dysregulated Salience Syndrome

Introduction

Salience processing involves the reactive cognitive elaboration of unique stimuli or stimulus features which facilitates directed attention and goal-oriented motivational behaviors (Kapur, 2003). The convergence of psychological state, previous experiences, goals, and autonomic and homeostatic functions of the brain influence the perception of a stimulus as "salient". The emotional response to novel salient stimuli is context dependent and malleable in order to adapt to situational demands. Inappropriate attribution of salience and aberrant perceptual integration are proposed to subserve clinically relevant domains of cognitive and affective processing.

While schizophrenia patients typically exhibit clinical symptoms of attenuated outward expression of emotions, or blunted affect, experience a diminished capacity for pleasurable or hedonic experiences, anhedonia, and report an enhanced experience of aversive emotion, patients generally present preserved "in-the-moment" responses to emotional stimuli, with relatively appropriate subjective ratings of hedonic

reactions to evocative stimuli in laboratory settings (Cohen and Minor, 2008; Horan et al., 2010; Kring and Moran, 2008; Strauss and Gold, 2012). Nevertheless, patients have difficultly disengaging attention from unpleasant environmental cues, demonstrate exaggerated devotion of attention to negative stimuli, and exhibit both hedonic and aversive emotions when exposed to positive and neutral stimuli (Cohen and Minor, 2008). The inappropriate salience attribution, impaired sensory filtering and elevated reactivity to irrelevant neutral information observed in patients (Anticevic and Corlett, 2012) may promote disruptions in response selection and regulating negative emotional responses, further exasperating negative symptom severity (Strauss et al., 2011).

Aberrant salience impacts the development and maintenance of psychotic symptoms through insula dysfunction and atypical dopaminergic transmission. Appropriate salience attribution is critical for the selection of task-relevant information, and involuntary orientation to salient, motivationally-relevant and potentially significant stimuli in the sensory environment. Disruptions in salience attribution interfere with attentional and cognitive processing of emotional information, suggesting that abnormalities in affective processing and regulation may revolve around a central deficit in salience processing. The following sections describe the neurobiological correlates of salience processing, including a discussion of the insula-centered salience network, dopamine transmission, and how these systems are disrupted in psychosis. In addition, the utility of electroencephalography (EEG) in elucidating salience and affective processing disparities in patients with schizophrenia is discussed.

Neural Indices of Salience and Affective Processing

Efficient attention and response selection, reliant on appropriate salience attribution, is critical for adapting to environmental demands and optimizing behavior and response selection. A negativity bias has been proposed to explain the exaggerated attention and affective response to emotionally salient, aversive stimuli. This emotional processing disparity is thought to serve an evolutionary role to allow individuals to exert more energy in dangerous circumstances and prioritize their attention to best adapt and survive their environment (Ito and Larsen, 1998). However, sometimes it is necessary to prioritize alternative cognitive resources without affective interference. Consequently, the disproportionate emotional response for aversive stimuli can be downregulated using emotion regulation strategies to

optimize behavior. The down-regulation of the emotional response can be achieved by implementing antecedent-focused strategies, such as cognitive reappraisal, or response-focused strategies, including expressive suppression (Goldin et al., 2008). Antecedent-focused strategies involve modifying internal (e.g., increasing or decreasing certain thoughts) or external (e.g., physical environment where emotions are more likely to occur) emotion eliciting factors prior to the emotion being experienced, and by changing the way evocative stimuli are appraised (i.e., directing attention to certain features of the environment, or framing the environment in a positive or negative emotional context) (Gross and Muñoz, 1995). While antecedent-focused strategies can manipulate both the experience and expression of emotion, response-focused strategies, such as masking sadness with a smile, only impact the emotional expression, and are therefore less effective in generating ideal emotional outcomes (Livingstone et al., 2009).

The successful implementation of emotion regulation strategies requires the enhanced engagement of frontal executive control regions, including prefrontal cortex (PFC) and anterior cingulate cortex (ACC), and the simultaneous suppression of ventral affective limbic regions, including amygdala and insula, to manipulate an emotional response (Goldin et al., 2008; Ochsner et al., 2002, 2004; Phan et al., 2005). In response to non-emotional task relevant stimuli, top-down frontoparietal neural networks are recruited, while ventral limbic regions are simultaneously suppressed to optimize task-related cognitive resources and prevent affective interference. Patients, however, are unable to maintain an appropriate balance between the recruitment of frontal attentional networks and engagement of affective limbic networks, resulting in compromised attentional processing and exaggerated affective interference (Dichter et al., 2010). A disruption in the dynamic reciprocal interaction between frontal executive attention networks and limbic affective regulation may promote dysregulation of emotion and attentional processing, and interfere with appropriate evaluation of affective stimuli during attention-demanding tasks (Dichter et al., 2010). The disproportionate limbic recruitment and failure to shift between attentional and affective domains to prioritize attentional resources promote aberrant salience attribution and response selection.

Salience Network

The neural processing of salient information synthesizes external sensory and internal emotional and visceral state information to motivate attention and behavioral outcomes, and relies on the integration of information among distributed regions, comprising a salience network. This salience neural network revolves around the insular cortex, along with involvement of the dorsal anterior cingulate cortex (dACC), subcortical, and limbic brain regions (Uddin, 2015). The insular cortex is the first cortical target of interoceptive and visceromotor inputs, with multiple functionally distinct regions, and plays an integral role in integrating information as a hub of the salience network. Additionally, the anterior insular cortex (AIC) serves diverse roles in visceral and somatic sensory processing, autonomic regulation of the heart, has structural connections with the amygdala, orbitofrontal cortex and ACC, and exerts influence over the DMN and central executive network (CEN) (Palaniyappan et al., 2012b; Uddin, 2015).

Insula and Salience Dysfunction in Schizophrenia

Atypical insular connectivity and activation patterns accompany the aberrant salience processing observed in schizophrenia. Schizophrenia patients exhibit reduced gray matter volume in bilateral insular cortex (Fornito et al., 2009; Glahn et al., 2008; Kasai et al., 2003; Shepherd et al., 2012), and deficient activation in response to subjectively salient stimuli and emotion regulation tasks (Li et al., 2010; van der Meer et al., 2014). Because of AIC's crucial role in influencing CEN and DMN network engagement, it is proposed that impaired insular connectivity could contribute to the alternative reality experienced by patients with the difficulty discriminating between self-generated internal salience and external information (Manoliu et al., 2014; Palaniyappan et al., 2012b; Wang et al., 2014; Wylie and Tregellas, 2010). Given these essential functions in physiological arousal and stimulus appraisal, deviations in insular connectivity and activation may subserve the disruption of salience in neuropsychiatric disorders.

Role of Dopamine in Aberrant Salience

Attribution of motivational salience is a critical component of appetitive behavior, reward prediction, learning and motivational behaviors (Berridge and Robinson, 1998), and is mediated by the dopamine system, which is dysregulated in patients with schizophrenia. The mesolimbic dopaminergic

system subserves motivational salience attribution by signifying a neural representation of external stimuli as attractive or aversive to promote appropriate cognitive and behavioral actions (Kapur, 2003). Consequently, abnormal dopamine transmission, particularly the hyperdopaminergic state observed in psychosis, may promote aberrant salience by generating stimulus-independent attribution of motivational salience (Kapur, 2003). The inappropriate assignment of valence to external objects and internal representations amplifies the significance of unimportant, irrelevant perceptions and ideas which are experienced as hallucinations and ultimately result in delusions following cognitive conceptualization of the aberrant salience representations (Kapur, 2003; Uddin, 2015). Accordingly, improved salience processing accompanies the administration of antipsychotic medications targeting dopaminergic D2 receptors.

Electrophysiological Studies of Salience and Affective Processing

Electroencephalography (EEG) has been extensively used in order to investigate the neural correlates of aberrant affective processing and salience in schizophrenia patients because of its superior temporal resolution and capacity to differentiate between distinct cognitive and perceptual processing dimensions (Hajcak et al., 2010; Luck, 2005; van der Stelt and Belger, 2007). The EEG signal is thought to arise from temporally and spatially aligned dipoles of cortical pyramidal neurons which summate, and the resulting rhythmic field potentials are recorded from the scalp. From the raw EEG signal, researchers can evaluate event-related potentials (ERPs) which are voltage deflections that are time-locked to the onset of a stimulus, or further decompose the signal into magnitude and phase information for different frequencies to examine multiple layers of parallel processing and characterize changes over time with respect to task events. Time-frequency analyses permit the examination of event-related changes in EEG power that are time-locked (event-related spectral perturbation (ERSP)) or phase-locked (evoked power (EP)) with respect to the event, and intertrial phase coherence (ITC), which assesses event-related phase consistency across trials as an index of neural synchrony (Roach and Mathalon, 2008; Uhlhaas and Singer, 2006). Examination of oscillations and their synchrony is a valuable tool for probing circuit level activity, as synchronized neuronal activity allows for coordinated neural activity and interneuronal communication across distributed brain regions. Slow wave frequencies, such as theta, support long distance communication between remote brain regions, while fast wave oscillations, including gamma,

are more restricted to localized circuits due to conduction properties of the brain (Moran and Hong, 2011). The P3 and late positive potential (LPP) ERP components and theta and beta oscillations are particularly relevant for studying salience and affective processing and are discussed in the following sections.

ERP Correlates of Salience and Affective Processing

The P3 ERP component is thought to reflect the automatic orienting to salient environmental information and allocation of attention to task demands (Polich, 2007). Accordingly, deviations in the P3 amplitude may underlie abnormalities in numerous domains of cognition, including attention, working memory, response selection and inhibition, and attribution of salience to task-relevant stimuli exhibited by schizophrenia patients. In fact, a diminished P3 ERP amplitude response during auditory and visual modalities in schizophrenia patients is one of the most robust, replicated findings in schizophrenia research (Kidogami et al., 1991; Mathalon, 2000; Pritchard, 1986; Roth and Cannon, 1972; van der Stelt et al., 2004), and has proposed utility in elucidating intermediate neurobiological processes influenced by genetic variation (Meyer-Lindenberg and Weinberger, 2006). Emotional, motivationally relevant stimuli should automatically capture attention and generate a midline P3a response approximately 300 ms following stimulus onset reflecting the attribution of stimulus significance or salience (Johnson, 1984). The P3b, on the other hand, is elicited between 300 and 500 ms over medial central and parietal scalp locations following target stimulus presentation and can serve as an index for the amount of attention devoted to the stimulus event (Falkenstein et al., 1999; Johnson, 1984; Katayama and Polich, 1998; Polich, 2007).

Additionally, the LPP ERP component is elicited between 400 and 1000 ms at midline parietal electrode sites following novel, emotionally salient stimuli, and serves as an index for the cognitive elaboration of motivationally relevant stimuli, as the LPP amplitude is greater for unpleasant stimuli relative to pleasant or neutral stimuli, regardless if the stimuli are relevant to the primary task (Ito et al., 1998; Hajcak et al., 2010). Successful execution of emotion regulation strategies have been found to alter electrophysiological correlates of affective processing, including LPP amplitude and associated neural oscillatory activity, to support a more adaptive behavioral response (Ertl et al., 2013; Goldin et al., 2008; Hajcak et al., 2010; Kisley et al., 2011; Ochsner et al., 2002, 2004; Phillips et al., 2008; von Scheve,

2012). Specifically, it is possible to relieve the heightened LPP response to aversive stimuli by simply introducing cognitive framing strategies (i.e., positive or negative contextual cues), thereby assessing a key aspect of emotion regulation (Kisley et al., 2011). Furthermore, schizophrenia patients have reported using cognitive reappraisal strategies less often (O'Driscoll et al., 2014) and demonstrate neural deficiencies in emotion regulation, with diminished PFC activation (Morris et al., 2012) and inability to down-regulate the emotional response (LPP amplitude) to unpleasant images using cognitive change strategies (Strauss et al., 2013).

Oscillations and Their Synchronization Underlying Salience and Affective Processing

Schizophrenia is recognized as having profound disruptions in neural connectivity and can be conceptualized as a disconnection syndrome, suggesting that investigating EEG oscillatory activity can provide critical information for understanding the neurobiological correlates of symptom pathology. Deviations in working memory, attention and affective processing expressed in schizophrenia have been connected to widespread deficiencies in oscillatory activity, including activity in theta and beta frequency bands (Basar and Guntekin, 2013; Uhlhaas et al., 2008; Uhlhaas and Singer, 2014). A discussion of theta and beta oscillations and how they are disrupted in schizophrenia is presented in the following sections.

Probing Fronto-Limbic Circuitry Using EEG

Theta oscillatory activity occurs in the frequency range of approximately 4 to 8 Hz, is primarily generated by glutamatergic and GABAergic neurons, and is prominent in the hippocampus where it plays a pivotal role in locomotion, spatial navigation, and memory. The efficient interaction and integration of information between frontal and limbic brain regions can be represented by the synchronization of neural oscillations in low frequencies, including theta (Javitt et al., 2008). Therefore, disruptions in low frequency oscillations may produce impairments in long-distance functional connectivity between frontal and limbic brain regions critical for affective processing (Lesting et al., 2011). Additionally, theta activity supports prefrontal cortex dependent top-down cognitive control and working memory function, with increases in theta oscillatory activity, localized to midline frontal scalp locations, corresponding to greater task demands (Jensen and Tesche, 2002), and the need for cognitive control (Cavanagh and Frank, 2014). An

increase in frontal theta activity has also been reported to accompany successful reappraisal of emotional events, representing enhanced frontal recruitment (Ertl et al., 2013).

Atypical Theta Oscillatory Activity in Schizophrenia Patients

Deficiency in theta activity is proposed to be of particular interest in patients, as theta oscillations are prominent in the hippocampus, a brain region that demonstrates volumetric reductions in SCZ (Mondelli et al., 2010), and because of theta's involvement in affective processing, working memory and cognitive control, which are all impacted in SCZ (Berger et al., 2016; Schmiedt et al., 2005; Uhlhaas et al., 2008). In addition, reduced theta coherence between frontal and temporal regions has been shown to be associated with auditory hallucinations (Ford et al., 2002).

Aberrant Beta Oscillatory Activity in Schizophrenia Patients

Beta oscillations in frequencies between 12 and 30 Hz are generated by glutamate, N-methyl D-aspartate (NMDA) and GABAergic systems and are found in all cortical and some subcortical structures, including the hippocampus and basal ganglia, where they serve to coordinate motor function, and mediate top-down activity in learning, novelty detection, sensory gating and reward evaluation (Uhlhaas et al., 2008). Given the dopaminergic modulation of beta activity in the basal ganglia, it is possible that dysregulated dopaminergic activity may subserve the deficits in beta synchronization observed in SCZ patients.

Salience Disturbance and Cognitive/Behavioral Consequences

Disturbances in the salience network, particularly the insula, may promote prodromal symptoms such as perceptual and cognitive abnormalities, which progressively decline into distortions of reality, aberrant affective processing and disorganization of speech and behavior in established illness (Palaniyappan et al., 2012b). Atypical activity in the salience network is not found in first-degree relatives, suggesting that environmental insults may trigger the deterioration of salience network architecture and function in vulnerable individuals (Palaniyappan et al., 2012a). Consequently, salience network dysfunction is a promising therapeutic target to guide treatment approaches and intervention strategies. Furthermore, brain network modulation (BNM) is an innovative approach combining network

pharmacology to improve plasticity of connections and cognitive training that could enhance salience network activity to provide potential symptom relief for patients with schizophrenia (Palaniyappan et al., 2012b). Mindfulness training (Tang et al., 2012) and neurofeedback (Johnston et al., 2010) strategies have also demonstrated efficacy in improving salience network activity and connectivity. Identifying EEG correlates of salience network efficiency will provide valuable biomarkers that can be used to test the effectiveness of novel treatment strategies and intervention approaches.

1.3 Fronto-Limbic Circuitry Underlying the Relationship Between Stress and Affective Processing in Schizophrenia

Introduction

The regulation of stress and affective systems both rely on fronto-limbic circuitry. Projections from the prefrontal cortex, amygdala, and hippocampus provide feedback for regulating the stress response (Herman et al., 2005). These same regions are integral to appropriately processing emotionally salient stimuli and regulating affective responses. As a result, the disruptions in fronto-limbic circuitry observed in schizophrenia patients may contribute to aberrant stress and affective processing (Dedovic et al., 2009; Zhang et al., 2014). Stress exposure disrupts the dynamic balance between frontal and limbic brain regions, causing reduced frontal engagement and enhanced recruitment of limbic regions, especially the amygdala (van Marle et al., 2010). This in turn heightens the emotional salience and arousal for aversive stimuli, causing greater arousal interference on performance, and makes the implementation of emotion regulation strategies more challenging (Raio et al., 2013). Stress is proposed as an important environmental trigger for psychosis and aberrant stress reactivity may disrupt cognitive treatment efforts reliant on fronto-limbic dependent processes (Corcoran et al., 2003; Garner et al., 2011; Venkatasubramanian et al., 2010). The interaction between fronto-limbic mediated stress and affective processing is described in more detail in the following sections, with particular focus on the hypothalamic-pituitary-adrenocortical (HPA) axis, the autonomic nervous system, and how these systems are dysregulated in patients with schizophrenia. The detrimental effect of stress on the brain and its association with psychosis is also discussed.

Overview of the Stress Response

Hypothalamic-Pituitary-Adrenocortical (HPA) Axis

Exposure to stress, whether it is reactive, anticipatory, physical or psychological, initiates a cascade of events to prepare an organism for the perceived increase in demand of cognitive and physiological resources (Dedovic et al., 2009; Herman et al., 2005). The activation of the HPA axis ultimately releases glucocorticoids to mobilize stored energy, to augment autonomic function, and to provide a negative feedback mechanism to restrict the magnitude and duration of glucocorticoid (cortisol) release (de Kloet et al., 2005; Herman et al., 2005; Ulrich-Lai and Herman, 2009). In response to stress, neurons in the paraventricular nucleus (PVN) of the hypothalamus secrete corticotropin-releasing hormone (CRH), as well as other factors including arginine vasopressin (Ulrich-Lai and Herman, 2009). Together these hormones act on the anterior pituitary to promote adrenocorticotropic hormone (ACTH) secretion, which further stimulates the synthesis and release of glucocorticoids from the adrenal cortex (de Kloet et al., 2005; Dedovic et al., 2009; Herman et al., 2005; Ulrich-Lai and Herman, 2009).

Negative Feedback Systems

Converging projections from the medial prefrontal cortex (mPFC), amygdala, and hippocampus integrate at subcortical relay sites, including the bed nucleus of the stria terminalis (BNST), to dynamically coordinate autonomic and neuroendocrine stress responses and accommodate the physical and cognitive demands of the stressor (Herman et al., 2005; Ulrich-Lai and Herman, 2009). While the majority of limbic projections do not directly innervate the PVN, limbic regions express both glucocorticoid (GR) and mineralocorticoid receptors (MR), which permits glucocorticoid-mediated limbic regulation of the HPA response (Herman et al., 2005; Ulrich-Lai and Herman, 2009). Stress-induced glucocorticoid inhibition of HPA activity relies on glutamatergic innervation of GABAergic neurons in subcortical relay regions, such as the BNST, from structures including the hippocampus and prefrontal cortex, to inhibit PVN neurons and promote attenuated cortisol release. Conversely, the amygdala, especially medial and central amygdaloid nuclei, exerts its effects through GABAergic circuits to disinhibit CRH release and potentiate glucocorticoid secretion (Herman et al., 2005). In addition to regulating HPA activity, limbic systems are

heavily implicated in the development of maladaptive stress responses and consequently, the pathophysiology of psychiatric disorders.

Autonomic Stress Response

In addition to the HPA response, the autonomic nervous system (ANS) rapidly responds autonomously to stress by mobilizing energy resources, increasing heart rate, and elevating catecholamine secretion for immediate assessment and reaction to physiological disruptions in homeostasis (Appelhans and Luecken, 2006). The ANS innervates internal organs through the excitatory sympathetic "fight or flight" and the inhibitory parasympathetic "rest and digest" systems, which offer opposing mechanisms to optimize physiological and behavioral responses (Appelhans and Luecken, 2006; Porges, 2007). While the sympathetic division responds to stress exposure by increasing heart rate, dilating airways to facilitate breathing, and releasing stored energy, the parasympathetic system is suppressed to prevent interference of stress-inappropriate processes, such as digestion and urination. The parasympathetic (vagal) and sympathetic branches of the ANS exert competing regulatory influences on the heart rate by influencing the activity of the sinoatrial 'pacemaker' node of the heart. During stressful conditions, vagal tone to the sinoatrial pacemaker node of the heart is suppressed or the "vagal brake" is removed in order to support mobilization, defensive "flight or fight" strategies, while the vagal influence is disinhibited and the vagal brake is maintained or increased to foster calm, engaging social behaviors (Porges, 2007). Deficient neural regulation of the vagal brake promotes maladaptive physiological reactivity and is proposed to account for compromised social engagement and affect expressivity in patients (Porges, 2007). Sympathetic influences, mediated by norepinephrine neurotransmission, offer an excitable effect on the sinoatrial node to slowly increase heart rate; whereas, the parasympathetic system exerts a rapid inhibitory influence on the heart rate through acetylcholine transmission. Consequently, parasympathetic and sympathetic ANS divisions exert antagonistic influences on heart rate, differentially regulating the interval between consecutive heartbeats (heart rate variability (HRV)), and generating heart rate oscillations at distinct frequencies (Porges, 2007). The rapid parasympathetic vagal response is uniquely modified by respiration, with inhalation preventing parasympathetic actions and exhaling reinstating parasympathetic influence to reduce heart rate.

Respiratory sinus arrhythmia (RSA) refers to the parasympathetic mediated heart rate oscillations in synchrony with respiration, reflected in the high-frequency component of HRV, and it is thought to index the efficiency of vagal brake regulation (Lewis et al., 2012; Porges, 2007).

Physiological Arousal and Emotional Response

Emotion regulation and coping strategies rely on the appropriate management of metabolic resources and physiological arousal to initiate situationally-relevant behaviors and emotional responses (Appelhans and Luecken, 2006). The assessment of external stimuli is governed by the central autonomic network (CAN) comprised of brain regions spanning executive and limbic neural networks (including the PFC, ACC, insula, hypothalamus, amygdala, and BNST) along with brainstem regions, which coordinates with visceral afferents conveying information about internal physiological state to adjust arousal and impact emotional expression. The CAN output is transmitted by the ANS to the sinoatrial node to regulate heart rate, reflected in HRV (Appelhans and Luecken, 2006). Furthermore, efficient use of emotion regulation and coping strategies have been reported to be associated with higher levels of parasympathetic mediated HRV, or RSA (Fabes and Eisenberg, 1997; O'Connor et al., 2002), while lower resting RSA levels were related to elevated negative emotional arousal in response to stress (Fabes and Eisenberg, 1997).

Psychophysiological Theories of HRV

Two complementary theories are offered to describe the contributions of ANS and neural regulation systems in modulating emotional expression and physiological arousal. The polyvagal theory, proposed by Porges (2007), is based on an evolutionary framework with three competing stages of ANS. The dorsal vagal complex was proposed to be the first to evolve, comprised of a slow responding, unmyelinated vagus nerve which supports immobilization and passive avoidance, followed by the sympathetic-adrenal system to allow for mobilization and defensive behaviors. Finally, a ventral vagal complex evolved with a fast-acting myelinated vagus nerve to withdraw or extend influence on the sinoatrial node of the heart, and afferent fibers innervating nuclei of facial and trigeminal nerves, to support social communication, and calm, low arousal states. Consistent with the Jacksonian principle of

dissolution and response hierarchy, when the ventral vagal complex is insufficient to manage the metabolic demand, other lower systems dominate to adapt to the situation (Wiest, 2012). Social behavior disturbances, therefore, are proposed to result from a compromised ventral vagal system, resulting in phylogenetically older neural system-dominated mobilization or immobilization behaviors, which are incompatible with appropriate social engagement (Porges, 2007). In contrast, the neurovisceral integration model, introduced by Thayer and colleagues (2000), propose that the CAN is the neurophysiological hub of a dynamical system, through which interactions among lower level elements, such as valence and arousal, give rise to specific behavioral, cognitive and physiological emotional states.

Studying the Stress Response in Patients

The stress response can be evaluated experimentally using psychosocial, pharmacological and physiological challenges that induce fluctuations in heart rate parameters and hormone release.

Trier Social Stress Test

The Trier Social Stress Test (TSST) is a well-established acute psychosocial stressor which has been used in diverse populations (with slight modifications) and activates the HPA axis with well-defined endocrine, immune and central nervous system stress responses. The TSST combines a public speaking task with challenging mental arithmetic (serial subtraction) to reliably induce a moderate stress response associated with a subjective negative experience (Allen et al., 2014; Kirschbaum et al., 1993). In response to the TSST, elevated proinflammatory cytokine production accompanies HPA activation and glucocorticoid release, along with gastrointestinal effects via autonomic innervation. Parasympathetic nervous system activity can be assessed using physiological heart rate parameters, including RSA, whereas sympathetic nervous system activity can be characterized using alpha-amylase, a salivary enzyme which rapidly increases following stress exposure, the galvanic skin response, and plasma catecholamine concentration (Nater et al., 2005). Alternatively, the Montreal Imaging Stress Test (MIST) is an fMRI compatible psychosocial stressor incorporating negative feedback and mental arithmetic. Increased deactivations in hippocampus and increased amygdala activation have been reported following MIST exposure (Allen et al., 2014). These psychosocial stressors have demonstrated utility in elucidating

the stress response in clinical populations, including schizophrenia (Brenner et al., 2009; Ciufolini et al., 2014; Foley and Kirschbaum, 2010).

Cortisol Collection Parameters

During a stress manipulation, cortisol is typically collected at distinct intervals to capture the characteristic stress-induced cortisol response curve. While cortisol can be assayed from cerebral spinal fluid (CSF), urine, and plasma, salivary cortisol is the preferred measurement of bioavailable cortisol, primarily because it is non-invasive and easily collected in patient populations (Allen et al., 2014). Cortisol has a natural diurnal rhythm which peaks 30 minutes upon awakening and plateaus in the early afternoon. Taking the natural fluctuations into consideration, experimental assessments of cortisol are typically conducted during the early afternoon hours to most accurately evaluate HPA function and stress reactivity. In response to an experimental stressor, cortisol peaks approximately 20 minutes following the introduction of stress, and recovers back to baseline levels about 70 minutes after the termination of the stress manipulation (Allen et al., 2014; Foley and Kirschbaum, 2010). Schizophrenia patients have demonstrated a blunted cortisol response in reaction to the TSST (Brenner et al., 2009; Jansen et al., 1998, 2000).

Heart Rate Parameters

The balance of parasympathetic and sympathetic nervous systems and autonomic flexibility can be evaluated using heart rate variability measurements, including parasympathetic mediated HRV or RSA (Appelhans and Luecken, 2006; Porges, 2007). TSST stress exposure elicits increased heart rate and blood pressure while reducing HRV, consistent with reduced HRV supporting mobilization behaviors in healthy individuals. Despite reports of resting acute atypical heart rate variability, HRV has not been examined in SCZ patients in reaction to the TSST.

Alternative Stress Induction Protocols

The TSST is widely used for reliably activating the HPA axis and capturing the stress response; however, alternative pharmacological and physiological challenges have also been utilized to induce a stress response experimentally. In particular, dexamethasone (dex), a synthetic glucocorticoid, can be

administered to study negative feedback to the HPA axis and suppression of cortisol and adrenocorticotropic hormone (ACTH) secretion (Allen et al., 2014; Carroll, 1982). The dex test can also be combined with corticotrophin releasing hormone (CRH) application for a more sensitive experimental approach to elucidate HPA axis function in neuropsychiatric disorders (Heuser et al., 1994). While a large release of cortisol and ACTH is prevented following the dex/CRH test in healthy individuals, indicating appropriate HPA axis activity, an abnormal dex/CRH test would suggest a failure to suppress cortisol, therefore indexing deficiencies in negative feedback mechanisms (Heuser et al., 1994). Additionally, the physiological stress response can be examined using the short Synacthen test which involves ACTH stimulation to assess HPA axis function at similar time intervals to TSST, and inhaling carbon dioxide is used to induce panic attacks and study physiological stress (Abdu et al., 1999). Furthermore, the cold pressor task is often used to induce a stress response by submerging the hand in cold water for a couple of minutes; however, it has a relatively short stress exposure, assesses pain tolerance in addition to stress, and is less efficient at inducing cortisol changes (McRae et al., 2006). Alternatively, a social evaluation component can be added to the cold pressor task, or the cold pressor task can be combined with the mental arithmetic component of the TSST (e.g., the Maastricht Acute Stress Test) to elicit a more robust stress response (Allen et al., 2014).

Challenging computerized cognitive tasks, including the Stroop task, along with distractors such as noise, have also been found to stimulate a stress response (Allen et al., 2014). While public speaking tasks and disturbing video clips are reported to elicit a reliable stress response, the combination of public speaking and other cognitive challenges or emotion induction procedures are suggested to be more effective at maximizing stress reactivity (Allen et al., 2014). Accordingly, the Mannheim Multicomponent Stress Test was designed to combine noise, cognitive performance, emotional induction, and the threat of losing financial compensation to elicit a stress response. Participants view aversive images while they perform serial subtraction test with the threat of reduced payment and increasingly louder levels of white noise (Reinhardt et al., 2012). Considering all of the available methods of stress induction, the TSST is arguably the most popular psychosocial stressor for it achieves a robust stress outcome without exposing the participant to physical discomfort or administering pharmacological manipulations.

Stress Cascade and the Affective Pathway to Psychosis

Effect of Stress on the Brain

Chronic exposure to stress and associated elevations in cortisol has detrimental effects on neural structural and functional integrity. Prefrontal cortical and hippocampal brain regions, which are fundamental to the neuropathology of schizophrenia, are disproportionally effected by the deleterious effects of stress exposure (Arnsten, 2009). Stress-induced neurotoxicity in the hippocampus and PFC causes cell atrophy and loss of glucocorticoid receptors, resulting in impaired cognitive functions reliant on these brain regions (Fuchs and Flügge, 2003). Furthermore, rodents with heightened glucocorticoids (corticosterone) exhibited diminished neurogenesis (Cameron and Gould, 1994) and weakened long-term potentiation (LTP) in the dentate gyrus of the hippocampus (Pavlides et al., 1993), and demonstrated behavioral deficits in hippocampal-dependent spatial memory (Luine, 1994). Additionally, endogenous (i.e., Cushing's disease) or exogeneous (experimenter-delivered) high levels of cortisol are associated with reduced hippocampal volume and memory function (Belanoff et al., 2001; Lupien et al., 2007), which can be reversed with the normalization of cortisol levels (Starkman et al., 1999). The effect of stress on volumetric changes observed in neuropsychopathology is further supported by the fact that mental disorders with stress as a defining feature, such as post-traumatic stress disorder (PTSD), present with reduced hippocampal volume, similar to schizophrenia patients (Bremner et al., 1995). Developmental insults may subserve hippocampal dysfunction leading to HPA dysregulation and impaired negative feedback, further exasperating stress-induced hippocampal impairment. Stress is also proposed to stimulate hyperresponsivity of subcortical dopamine activity through impaired PFC-inhibition and disrupted frontal connections with stress-related circuitry (Moghaddam, 2002).

HPA Dysfunction in Schizophrenia

Converging evidence points to a relationship between the HPA axis and psychosis, with SCZ patients exhibiting elevated baseline diurnal cortisol levels (Garner et al., 2011) and volumetric reductions in brain regions important for HPA regulation, including the hippocampus (Mondelli et al., 2010). Furthermore, cortisol levels have been associated with SCZ symptom severity (Garner et al., 2011; Walder et al., 2000) and high doses of exogenous corticosteroids can promote psychotic symptoms

(Buchman, 2001; Warrington and Bostwick, 2006). An impaired stress response may result in chronically elevated cortisol levels and heightened negative emotional reactivity, as well as promote cognitive deficits and increased symptom severity by modulating vulnerable fronto-limbic circuitry, and associated neural synchrony. Schizophrenia patients report greater subjective levels of stress (Horan et al., 2005; Renwick et al., 2009), heightened stress sensitivity (Yuii et al., 2007) and emotional reactivity to stressful events (Docherty et al., 2009), and appraise positive and negative events as being less well managed and less controllable than healthy individuals (Horan et al., 2005). Previous research has established that symptom severity and inferior coping tendencies are related to an aberrant stress response (Belvederi Murri et al., 2012; Corcoran et al., 2003; Quirin et al., 2011; Walder et al., 2000; Walker et al., 2013), and symptom severity has been associated with abnormalities in frontal and limbic brain activation (Goghari et al., 2010).

Stress Influences on Neurophysiology

Acute stress exposure compromises PFC function, disrupts network connectivity and impairs PFC-dependent working memory and underlying neural oscillatory activity. Oscillations underlying fronto-limbic connectivity, including theta and beta, appear to be most affected by the deleterious effects of stress. Frontal theta activity elicited during working memory (Gärtner et al., 2014) and mental arithmetic (Gärtner et al., 2015) tasks has been shown to diminish following stress induction using disturbing videos with aversive content. Disruptions in frontal theta, and associated frontal neural deficiencies following stress exposure, may interfere with the suppression of DMN during cognitive tasks (Broyd et al., 2009; Qin et al., 2009). However, stress has also been found to stimulate an increase in theta activity, with enhanced theta activity following sleep deprivation (Alonso et al., 2015) and with stressful task complexity (Jensen and Tesche, 2002). The differential effects of stress on theta activity may be explained by the type of stress exposure, and discrepancies in the analysis of theta oscillatory activity (e.g., whether it was time or phase-locked to task events). Furthermore, exposure to acute noise-induced stress impacts EEG indices of feedback processing and performance monitoring during a gambling task, with reduced ERP amplitudes (feedback-related negativity (FRN) and P3), a smaller increase in theta in response to feedback, and a sex-dependent increase in beta activity during the stress condition (Banis et al., 2014).

Beta activity has also been found to increase during a stressful Stroop task (Alonso et al., 2015). Consistent with enhanced beta activity during stress, Chapotot and colleagues (1998) propose a significant coupling between natural cortisol fluctuations and beta power that could potentially coordinate the regulation of arousal and alertness. Moreover, the relationship between resting state slow wave (theta) and fast wave (beta) oscillatory activity is proposed to underlie PFC network efficiency and be useful as a biomarker for PFC-mediated attentional control. Exaggerated limbic activity and weakened frontal control is reflected in an increased theta/beta ratio (relatively greater theta than beta activity), and is related to a greater decline of subjectively experienced attentional control following an acute psychosocial stressor (Putman et al., 2014). Additionally, stress is reported to shift resting frontal EEG asymmetry from greater left frontal alpha to predominately right frontal alpha during the high stress condition (Lewis et al., 2007), further demonstrating stress induced disruptions of oscillatory activity. Fronto-limbic oscillatory indices provide valuable information about the integrity of the fronto-limbic circuitry and the resiliency of the system in response to stress.

Interaction of Stress and Affective Processing

Emotion regulation strategies rely on fronto-limbic brain regions, which are disproportionately susceptible to the deleterious effects of stress (i.e., hippocampus, amygdala, PFC), indicating a critical role of stress in modifying emotional responses. Stress exposure interferes with emotion regulation and working memory processing by disrupting fronto-limbic circuitry engagement, causing an exaggerated recruitment of ventral affective regions and diminished dorsal frontal control (Oei et al., 2012). The shift towards a ventral affective dominated response may explain why it is more difficult to disengage from emotional images (Kinner et al., 2014) and to utilize emotion regulation strategies to minimize conditioned fear responses following stress exposure (Raio et al., 2013). Additionally, the amplified amygdala response to negative emotional stimuli, in particular negative facial emotion, may be associated with the elevated levels of norepinephrine and cortisol observed during stress (Kukolja et al., 2008). Furthermore, chronic stress exposure, such as childhood poverty, may interfere with emotion regulation and underlying neural circuitry in adulthood, causing inefficient frontal engagement and suppression of amygdala activity during an emotion regulation task (Kim et al., 2013). The interaction of stress and affective processing may be modulated by sex, as stress enhances the ability to regulate negative emotions in females

(Kinner et al., 2014), who also demonstrate increased limbic, amygdala, and superior temporal gyrus (mediating attention) recruitment during stress relative to males (Kogler et al., 2014). However, the threat of an acute stressor has also been found to disrupt sensitivity in facial emotion identification to a greater extent in females relative to males (DeDora et al., 2011).

The heightened cortisol levels that accompany stress exposure may aid in suppression and reappraisal emotion regulation approaches, and relieve some interference by emotional distractors on working memory performance (Lam et al., 2009; Oei et al., 2012). Yet, the advantageous role of cortisol in emotion regulation and working memory appears to be sex-dependent (Kinner et al., 2014; Kogler et al., 2014; Smeets et al., 2009). Cortisol levels following stress exposure had opposing effects on social cognition performance in males and females, as elevated cortisol associated with superior social cognition in males and weaker social cognition in females (Smeets et al., 2009).

While emotion regulation strategies are more difficult to implement under stressful conditions, they are essential for controlling the negative reaction to stress. Accordingly, the successful implementation of emotion regulation strategies, including attentional control and cognitive reappraisal, can promote heightened resilience following stress exposure to protect against the negative outcomes of stress (Troy and Mauss, 2011). Considering that subjective ratings of stress can be relieved using cognitive strategies reliant on the enhanced engagement of regions involved in working memory (middle frontal gyrus) and attention (superior temporal gyrus), and reduced activation of the hippocampus (Kogler et al., 2014), the deleterious effects of stress may be ameliorated by improving emotion regulation strategies and attentional control.

CHAPTER 2: SALIENCE AND AFFECTIVE PROCESSING IN SCHIZOPHRENIA PATIENTS AND FIRST-DEGREE RELATIVES

2.1 Context

Despite intact electrophysiological responses to attended evocative, emotional stimuli, it is unclear whether schizophrenia patients respond appropriately to extraneous task information or motivationally relevant distractor emotional stimuli (Dichter et al., 2010; Horan et al., 2010, 2012). This study examined differential electrophysiological responses to task-relevant and irrelevant emotional images in schizophrenia patients, first-degree relatives and healthy controls to determine whether patients are more susceptible to task interference from irrelevant, salient emotional stimuli.

Elucidating the pathophysiological mechanisms underlying familial risk for neuropsychiatric disorders is critical for identifying potential biomarkers for psychosis. Accordingly, the P3 component has demonstrated valuable utility as a biological trait or intermediate phenotype, as reduced P3 amplitudes are observed for medication naïve first episode schizophrenia patients along with first-degree family members (Kidogami et al., 1991). However, the P3 amplitude does not necessarily distinguish schizophrenia patients from other neuropsychiatric disorders, and may instead represent a trait marker for more general cognitive symptom pathologies shared among psychiatric disorders (Bestelmeyer et al., 2009; Johannesen et al., 2012). This is the first study to examine the LPP component in response to task-irrelevant emotional distractors as a biomarker for schizophrenia. Investigating the electrophysiological correlates of affective processing in schizophrenia and first-degree relatives may facilitate the discovery of genetic vulnerability markers and biological traits that represent pathophysiological mechanisms and cognitive dysfunctions evident in schizophrenia, and aid in the investigation of novel genes of interest (Meyer-Lindenberg and Weinberger, 2006).

2.2 Electrophysiological Correlates of Aberrant Motivated Attention and Salience Processing in Unaffected Relatives of Schizophrenia Patients[1]

Introduction

Schizophrenia (SCZ) is characterized by symptoms spanning psychological, cognitive, and behavioral domains. Disturbances in attentional and affective processing are particularly debilitating (Keefe and Harvey, 2012), considered core deficits (Nuechterlein et al., 2004), are associated with poor functional outcomes (Green et al., 2004; Keefe and Harvey, 2012; Williams et al., 2008), and remain difficult symptoms to treat (Erhart et al., 2006). Affective symptoms, including avolition and anhedonia, and attentional deficiencies, including impaired vigilance and sustained attention, are not mutually exclusive, and collectively rely on frontal and limbic distributed neural networks (Anticevic and Corlett, 2012). External salience, such as task-relevance, and internal salience, such as emotional or motivational aspects of stimuli, compete for frontolimbic engagement to orient attention and facilitate the processing of context-appropriate goal-relevant information, while disengaging from salient but task-irrelevant distractors. Affective information is particularly salient, and the inability to disengage from emotionally salient stimuli may lead to the over-allocation of sustained attention to, and impaired filtering of, irrelevant affective stimuli. Similarly, the inability to process external salience may lead to a bias towards affective yet task-irrelevant stimuli, further compromising the ability to orient attention to task-relevant stimuli and initiate goal-oriented behaviors (Anticevic and Corlett, 2012). Accordingly, the system is left more susceptible to interference from salient emotional stimuli. Imbalance in the dynamic interface between complementary affective and attention systems may affect numerous aspects of functioning, including social engagement, motivation, and overall quality of life (Anticevic and Corlett, 2012).

There is considerable evidence of aberrant information filtering deficits in SCZ, which potentially contribute to aberrant salience detection and an over-evaluation of task-irrelevant information, resulting in an inability to stay on task. Reported information filtering deficits in SCZ range from impairments in early sensory gating (Patterson et al., 2008), to disruptions in attention orienting (Laurens et al., 2005), to

[1]This chapter previously appeared as an article in the *Clinical EEG and Neuroscience* journal. The original citation is as follows: Andersen, E.H., Campbell, A.M., Schipul, S.E., Bellion, C.M., Donkers, F.C., Evans, A.M., Belger, A., 2016. Electrophysiological Correlates of Aberrant Motivated Attention and Salience Processing in Unaffected Relatives of Schizophrenia Patients. *Clinical EEG and Neuroscience*, Vol. 47(1), pp.11-23. http://journals.sagepub.com/doi/abs/10.1177/1550059415598063

abnormalities in higher order, goal-directed, and context-driven information processing (Barch and Dowd, 2010; Heerey and Gold, 2007). Aberrant orienting to task-relevant target information and salience detection have also been demonstrated across multiple processing domains in first-degree relatives (FDRs), including aberrant working memory (Krabbendam et al., 2001), episodic memory (Toulopoulou et al., 2003), executive functioning (Sitskoorn et al., 2004; Staal et al., 2000), and attention (Cornblatt and Keilp, 1994), suggesting that deviations in cognitive processing precede psychosis onset and may represent vulnerability markers. Elucidating the neurophysiological properties of attentional disturbances in patients with SCZ and individuals at familial high risk is critical for advancing our understanding of treatment-resistant attentional and affective symptoms, and for identifying novel biomarkers of SCZ to facilitate early intervention approaches and treatment strategies.

The goal of this study was to elucidate the neural correlates underlying the convergence of task-directed attention and automatic motivated attention to salient emotional distractors in patients with SCZ, clinically unaffected FDRs, and healthy control participants. Because of its high temporal resolution, electroencephalography (EEG), particularly event-related potentials (ERPs), can differentiate between perceptual and cognitive stages of information processing (Hajcak et al., 2010; Luck, 2005; van der Stelt and Belger, 2007). As such, ERP measures enable the isolation of distinct attentional and affective processing components, including novelty detection and motivated and sustained attention, and can inform whether impaired sensory filtering and ineffective salience detection and attribution are associated with specific clinical dimensions of SCZ.

An oddball detection ERP paradigm, combining a target detection task with infrequent emotional distractor stimuli, is useful for distinguishing between attentional processing domains, such as directed attention to task-relevant events (P3b), novelty detection (P3a), motivated attention to salient stimuli (late positive potential [LPP]), and sustained attentional processing (continued late positivity). The P3a component is a midline frontal positive waveform peaking at approximately 400 ms following the presentation of novel, infrequent stimuli, reflecting attentional capture by salient information (Katayama and Polich, 1998; Polich, 2007). Reduced P3a amplitudes have been reported in patients with SCZ, reflecting deficits in stimulus orientation, evaluation, discrimination, and salience detection (Turetsky et

al., 2009; van der Stelt et al., 2004), and have been related to enhanced positive symptom severity (Fisher et al., 2010; Turetsky et al., 2009). A parietally distributed P3b is elicited in response to task-relevant stimuli, indexing directed attention to "target" events (Falkenstein et al., 1999; Johnson, 1984; Katayama and Polich, 1998; Polich, 2007; Snyder and Hillyard, 1976; Squires et al., 1975). Diminished P3b amplitudes in auditory (Duncan, 1988; Kidogami et al., 1991; Mathalon, 2000; Roth and Cannon, 1972) and visual paradigms (van der Stelt et al., 2004) are among the most consistent findings in SCZ research (Duncan, 1988; Ford, 1999; Kidogami et al., 1991; Mathalon, 2000; Pritchard, 1986; Roth and Cannon, 1972; van der Stelt et al., 2004), and have been associated with abnormalities in directed attention, response selection, inhibition, and in aberrant salience attribution to task-relevant stimuli (Hajcak et al., 2010; Luck, 2005; Polich, 2007; Squires et al., 1975; van der Stelt and Belger, 2007). Reduced P3b (Kidogami et al., 1991; Price et al., 2006; van der Stelt et al., 2005) and auditory P3a amplitudes (Jahshan et al., 2012) have also been observed for individuals at clinical and familial high risk, suggesting that P3 components may be useful as endophenotypes and clinical state markers, as they can track fluctuations in clinical symptom severity (Mathalon et al., 2000). To our knowledge, P3a responses elicited in the visual modality have not been studied in individuals at familial high risk. Despite consistent findings of reduced P3 amplitudes in SCZ, similar effects have also been found in other neuropsychiatric disorders and may represent a trait marker for a central deficit in higher order processing of salient stimuli shared across psychopathologies (Bestelmeyer et al., 2009; Johannesen et al., 2012).

Whereas P3 components have been associated with directed attention and novelty detection, motivated and sustained attention to salient stimuli can be indexed by the LPP component. The LPP is elicited approximately 400 to 1000 ms post–stimulus onset and may be sustained well past the duration of the stimulus (Cuthbert et al., 2000; Hajcak et al., 2010; Hajcak and Olvet, 2008; Horan et al., 2012; Matsuda and Nittono, 2015; Schupp et al., 2000). Emotional stimuli evoke larger LPP amplitudes than neutral stimuli (Hajcak et al., 2009; Olofsson et al., 2008), suggesting that the LPP indexes sustained allocation of attentional resources to, and cognitive elaboration of, emotional, salient events. Recent studies have further suggested that early phases of the LPP may be associated with short-latency momentary directed attention to affective salient stimuli, whereas a later "sustained" LPP may reflect a

prolonged allocation of attention and maintenance of emotional salient information, critical for higher order cognitive processing (Hajcak et al., 2010).

Difficulty disengaging from negative stimuli, impaired sensory filtering, and elevated reactivity to irrelevant information may contribute to the relentless heightened negative affect observed in SCZ. Negative symptoms, marked by blunted affect, anhedonia, avolition, and enhanced experience of aversive emotion, are core clinical symptoms of SCZ, yet most patients express relatively preserved aspects of affective processing in experimental settings, including appropriate "in-the-moment" emotional responses to affective stimuli (Cohen and Minor, 2008; Horan et al., 2010; Kring and Moran, 2008; Strauss and Gold, 2012), and intact LPP valence discrimination between task-irrelevant emotionally salient stimuli (Horan et al., 2012) Nevertheless, patients show decreased performance on emotion maintenance tasks (for both positive and negative emotion) that were found to be related to deficits in motivated behavior (Gard et al., 2011), and deficits in downregulating the LPP response to aversive stimuli using cognitive change strategies (Horan et al., 2013; Strauss et al., 2013), suggesting selective deficiencies in affective processing. The discrepancy between intact emotional responding in experimental settings and clinically relevant negative symptoms in SCZ motivates the investigation of neural correlates of salience processing, especially because of its importance in effectively filtering irrelevant emotional stimuli to prioritize directed attention and goal-directed, motivational behaviors. This is the first study to examine the LPP response in familial risk participants, in addition to patients, and to explore its value as a novel biomarker for psychosis.

We evaluated directed and sustained attentional processing in SCZ and FDR participants relative to healthy controls using an oddball detection paradigm, focusing on directed attention to targets (P3b), novelty detection of aversive and neutral distractors (P3a), and the motivated (early-LPP) and sustained (late-LPP) cognitive elaboration of salient stimuli. We expected both SCZ and FDR to show deficits in the P3b responses to targets, as previously demonstrated (Kidogami et al., 1991; Sponheim et al., 2006), with FDR participants exhibiting reduced P3b amplitudes at an intermediate level between controls and patients. In addition, we predicted that aversive distractors would elicit smaller P3a amplitudes in SCZ and FDR relative to controls, reflecting aberrant attention allocation to non-target emotional stimuli (van

der Stelt et al., 2004). Consistent with previous studies, we hypothesized that SCZ and FDR participants would demonstrate intact affective valence processing, with increased LPP amplitudes for aversive compared to neutral stimuli, similar to controls. However, we predicted that the LPP (early, middle, late) would be reduced in SCZ and FDR participants relative to controls, indicating aberrant motivated and sustained attention to salient stimuli. Furthermore, we investigated the association between the P3a, P3b, and LPP amplitudes, symptom severity, and neurocognitive measures to further elucidate the electrophysiological correlates of behavioral and cognitive symptoms of SCZ. We expected the P3a, P3b and LPP amplitudes to all be inversely related to symptom severity, especially negative and disorganized symptom dimensions, and that performance on attentional, executive, and emotional neurocognitive assessments would predict target-P3b and aversive early-LPP amplitudes.

Method

Participants

Thirty-one adults diagnosed with SCZ within the past five years (recent-onset), 28 FDRs, and 47 healthy controls participated in the study (Table 1). Patients were referred by their treating clinicians, or recruited along with FDR and control participants from the community. Patients with SCZ met the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (*DSM-IV*) criteria for schizophrenia (n = 18), schizoaffective (n = 12), or schizophreniform (n = 1) disorder and had stable symptoms. The majority of patients were medicated with first-generation (n = 22) or second-generation (n = 1) antipsychotics; however, 8 participants were not medicated due to their recent diagnosis. FDR participants had a first-degree relative with a diagnosis of a schizophrenia-spectrum illness, no past or current Axis I disorders, and were not currently taking antipsychotic medications. Three FDR participants were taking antidepressants. Control participants had no history of a *DSM-IV* Axis I diagnosis and no first-degree relatives diagnosed with schizophrenia-spectrum illness. All participants spoke English, were 18 to 48 years old, had normal or corrected vision, and no history of neurological disorders. Participants were allowed to smoke and consume caffeine up until 40 minutes prior to the experiment in accordance with their habitual smoking and drinking patterns. Participants provided informed consent in accordance with the University of North Carolina at Chapel Hill Institutional Review Board.

Procedures

The testing session included clinical screening, neurocognitive testing, and an EEG session. Clinical screening included the Scale of Prodromal Symptoms (SOPS) (McGlashan et al., 2001; Miller et al., 1999), the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and the Premorbid Adjustment Scale (Cannon-Spoor et al., 1982), among others. Participants completed a neurocognitive test battery, including the Facial Emotion Identification Test (FEIT) (Kerr and Neale, 1993), Baron-Cohen "Reading the Mind in the Eyes" Test–Revised (BCAET) (Baron-Cohen et al., 2001), Continuous Performance Test-Identical Pairs (CPT-IP) (Cornblatt et al., 1989), and Delis-Kaplan Executive Function System–Color-Word Interference Test (DKEFS-CWIT) (Lippa and Davis, 2010). IQ was estimated using the North American Adult Reading Test (NAART) (Uttl, 2002).

ERP Emotional Oddball Task

EEG was recorded while participants performed a forced-choice oddball detection task with infrequent animal target images (n = 70; 6.3%) embedded among frequent standard scrambled images (n = 900; 81.1%), and infrequent novel neutral (n = 70; 6.3%) and aversive (n = 70; 6.3%) distractor images. Colored images were selected from the International Affective Picture System (IAPS) database (Lang et al., 2008). Average arousal and valence ratings for the neutral stimuli (common household objects, activities) were 3.28 (SD = 2.01) and 5.24 (SD = 1.39), respectively, aversive stimuli depicting scenes of human violence, mutilation, and disease were ($M_{arousal}$ = 6.44, SD = 2.17) and ($M_{valence}$ = 2.32, SD = 1.53), and nonthreatening target animal images were ($M_{arousal}$ = 4.21, SD = 2.2) and ($M_{valence}$ = 7.01, SD = 1.6). The task consisted of 10 blocks, three minutes each. Stimuli were pseudorandomized to ensure that the novel targets, aversive, and neutral images were followed by at least two standard images. Stimuli were presented for 500 ms, with variable interstimulus intervals between 1300 and 1700 ms during which a fixation cross appeared. Participants responded with their right middle finger for targets and their index finger for all other stimulus types.

EEG Recording and Processing

EEG was continuously recorded using a NeuroScan 4.3 SynAmps2 amplifier and a 32-electrode ECI Electro cap. AFz served as ground and right mastoid as reference. Vertical and horizontal

electrooculogram (VEOG/HEOG) were measured using bipolar recordings. Data were sampled at 500 Hz in AC acquisition mode, bandpass filtered online between 0.15 and 70Hz, with a 60-Hz notch filter, and impedances were maintained below 10 kohm. Analyses were conducted with SCAN 4.4 Edit Software (*Compumedics Neuroscan, Charlotte, NC*.). Ocular artifacts, including eye movements and blinks, were corrected with an algorithm implemented in Neuroscan (Semlitsch, 1986). Major artifacts were manually rejected, and data corresponding with incorrect behavioral responses were removed. Epochs of 200-ms prestimulus to 1000-ms poststimulus were segmented, artifact rejected (±100 μV at any electrode), baseline corrected (−200ms), averaged, and 15-Hz low-pass filtered offline for each stimulus type.

ERP Data Analysis

The P3 amplitude was defined as the average amplitude within the 350 to 500 ms window post–stimulus onset; target-P3b was analyzed from the mid-parietal Pz electrode (Comerchero and Polich, 1999; Horan et al., 2012; Polich, 2007; Turetsky et al., 2009), and P3a was analyzed from the mid-frontal Fz electrode (Comerchero and Polich, 1999; Jahshan et al., 2012; Polich, 2007), consistent with previous studies. To encapsulate the early and late LPP peaks observed in the grand average waveforms for novel stimuli, the LPP was analyzed in 3 distinct windows (early, 350-500 ms; middle, 500-650 ms; late, 650-800 ms) from Pz electrode (Hajcak et al., 2010). There were no differences between groups for the number of accepted trials for standard (M = 582.0, SD = 84.1), aversive (M = 55.7, SD = 10.7), neutral (M = 59.0, SD = 9.9) and target stimuli (M = 50.5, SD = 10.3).

Statistical Analyses

Statistical analyses were performed using PASW Statistical Software, version 18.0 (*SPSS Inc*, 2009). Demographic and clinical data were analyzed using analyses of variance (ANOVAs) for continuous variables and chi-square tests for categorical variables. Behavioral and EEG results were analyzed using repeated-measures (rm) ANOVAs, with age and sex entered as covariates. A Group (SCZ, FDR, control) × Stimulus (standard, neutral, target, aversive) rm-ANOVA was performed separately for reaction time (RT) and accuracy. P3a was assessed using a Group × Stimulus (aversive, neutral, standard) rm-ANOVA, and the target-P3b was analyzed using a Group × Stimulus (target, standard) rm-ANOVA. LPP was evaluated with a Group × Valence (aversive, neutral) × Window (early, middle, late) rm-ANOVA. Post

hoc pairwise comparisons were Bonferroni corrected for multiple comparisons and Greenhouse-Geisser epsilon corrections were used when the sphericity assumption was violated.

The relationship between SOPS (positive, negative, and disorganization) scores for FDR and SCZ, and neurocognitive measures of executive functioning (scaled DKEFS-CWIT inhibition/switching score), attentional (d-prime for a 3-digit CPT-IP test) and emotional (BCAET and FEIT) processing for all participants, were correlated with target-P3b, aversive and neutral P3a, and early- and late-LPP components using Spearman's rank correlation analysis.

Results

Demographics and Clinical Assessments

Groups differed on age, $F(2, 103) = 5.39$, $P < 0.05$; sex, $\chi(2) = 25.73$, $P < 0.001$; and education, $F(2, 102) = 4.27$, $P < 0.05$, with a younger, predominately male patient group and an older, female-dominated FDR group. Age and sex were therefore entered as covariates in subsequent analyses. Patients exhibited a lower educational level than controls ($P < 0.05$). SCZ patients differed from controls on IQ and FEIT measures ($P < 0.05$), and differed from controls and FDR participants on BCAET ($P < 0.05$), DKEFS ($P < 0.05$), CPT-IP ($P < 0.05$), and all SOPS scores ($P < 0.001$). FDR participants were equivalent to controls on all SOPS and neurocognitive assessments ($P > 0.05$ for all; Table 2.1).

Behavioral Results

There was a main effect of Stimulus for both RT, $F(3, 300) = 9.38$, $P < 0.001$, $\eta_p^2 = 0.09$, and accuracy, $F(1.62, 162.23) = 11.36$, $P < 0.001$, $\eta_p^2 = 0.10$, such that responses to standard images were faster and more accurate for all groups, and participants were slower and less accurate for target stimuli. A Stimulus $\times$ Group interaction, $F(6, 300) = 57.99$, $P < 0.001$, $\eta_p^2 = 0.54$, was found for RT, revealing that while FDRs and controls had similar RTs, patients with SCZ demonstrated slower RTs for neutral stimuli than controls ($t = 4.16$, $P < 0.001$) and FDR participants ($t = 3.49$, $P < 0.05$), and faster responses for aversive stimuli relative to control ($t = 8.28$, $P < 0.001$) and FDR participants ($t = 6.56$, $P < 0.001$). A Group effect, $F(2, 100) = 5.55$, $P < 0.05$, $\eta_p^2 = 0.10$, for accuracy indicated that SCZ patients had lower accuracy for neutral ($t = 2.99$, $P < 0.05$) and aversive stimuli ($t = 2.53$, $P < 0.05$) relative to controls. RT

and accuracy for target stimuli did not differ between groups ($P > 0.05$ for all). No additional effects or interactions were found (Table 2.2).

ERP Results From Oddball Paradigm

Target Detection–P3b. A Group main effect, $F(2, 101) = 17.83$, $P < 0.001$, $\eta_p^2 = 0.26$, was observed for target-P3b, indicating that controls demonstrated significantly greater target-P3b responses compared with FDR ($t = 2.47$, $P < 0.05$) and SCZ ($t = 5.67$, $P < 0.001$) participants. A significant main effect of Stimulus, $F(1, 101) = 18.32$, $P < 0.001$, $\eta_p^2 = 0.15$, confirmed that the response to target stimuli was greater than that for standard stimuli for control ($t = 15.67$, $P < 0.001$), FDR ($t = 8.43$, $P < 0.001$), and patients with SCZ ($t = 6.31$, $P < 0.001$). Additionally, a Group × Stimulus interaction, $F(2, 101) = 10.24$, $P < 0.001$, $\eta_p^2 = 0.17$, revealed that the difference between responses to target and standard stimuli was less for patients with SCZ relative to controls and FDR participants (Table 2.2; Figure 2.1).

Novelty Processing–P3a. No significant main effects or interactions were found for novel-P3a ($P > 0.64$; $F < 0.39$ for all). To verify that the amplitude responses for novel stimuli were greater than responses for standard stimuli, as expected for P3a, planned pairwise comparisons were performed and indicated that all groups demonstrated increased P3a amplitudes for aversive (CON, $t = 4.93$, $P < 0.001$; FDR, $t = 2.78$, $P < 0.05$; SCZ, $t = 3.59$, $P < 0.05$) and neutral (CON, $t = 3.75$, $P < 0.05$; FDR, $t = 2.68$, $P < 0.05$; SCZ, $t = 2.79$, $P < 0.05$) stimuli compared with standard stimuli (Table 2.2; Figure 2.1). The P3a was initially analyzed from Fz, FCz, and Cz electrodes to account for the understood frontocentral distribution of the component. While there was a group effect at Cz, with patients demonstrating reduced P3a amplitudes relative to controls, this analysis is not included because it is possible that the enhanced amplitude at Cz is attributable or simply carried over from the early-LPP response from Pz. P3a is typically assessed from frontal electrodes, as it is understood to underlie a predominately frontal process (Daffner et al., 2000; Friedman and Simpson, 1994; Knight, 1997).

Motivated Attention and Salience Processing–Late Positive Potential. A significant Group effect, $F(2, 101) = 12.38$, $P < 0.001$, $\eta_p^2 = 0.20$, demonstrated that SCZ patients exhibited reduced LPP responses overall compared with control ($t = 4.77$, $P < 0.001$) and FDR ($t = 3.94$, $P < 0.001$) participants. No main effects of Window or Valence were found. A Window × Group interaction, $F(3.02, 152.27) = 7.34$,

$P < 0.001$, $\eta_p^2 = 0.13$, indicated that patients had reduced LPP amplitudes in the early and middle windows compared with controls (early, t = 5.53, $P < 0.001$; middle, t = 2.81, $P < 0.05$) and all three windows with FDR (early, t = 2.68, $P < 0.05$; middle, t = 2.72, $P < 0.05$; late, t = 3.40, $P < 0.05$), and that FDR participants demonstrated greater LPP amplitudes compared with control participants during the late LPP window (t = 2.73, $P < 0.05$). A significant Valence × Window × Group interaction, F(3.74, 188.81) = 3.00, $P < 0.05$, $\eta_p^2 = 0.06$, suggested that FDR participants uniquely exhibited a greater positivity for aversive and neutral stimuli relative to control (aversive, t = 2.55, $P < 0.05$; neutral, t = 2.54, $P < 0.05$) and SCZ (aversive, t = 3.00, $P < 0.05$; neutral, t = 3.37, $P < 0.05$) participants during the late window only. During the early window, controls demonstrated greater LPP amplitudes in response to aversive stimuli relative to FDR (t = 2.50, $P < 0.05$) and SCZ participants (t = 5.46, $P < 0.001$), and greater LPP amplitudes for neutral stimuli compared with SCZ patients (t = 5.13, $P < 0.001$). FDR participants exhibited greater LPP responses during the early window for neutral stimuli relative to SCZ patients (t = 2.93, $P < 0.05$). Unlike controls and SCZ patients, FDR participants did not show valence discrimination during the early window, as the LPP response to aversive and neutral stimuli did not differ (t = 1.63, $P > 0.05$). During the middle LPP window, SCZ patients demonstrated reduced LPP responses for aversive and neutral stimuli compared with controls (aversive, t = 2.75, $P < 0.05$; neutral, t = 2.52, $P < 0.05$) and FDR participants (aversive, t = 2.45, $P < 0.05$; neutral, t = 2.69, $P < 0.05$) (Table 2.2; Figure 2.2).

Relationship Between Clinical and Neurocognitive Assessments and ERP Components

Spearman's rank correlations revealed that reduced target-P3b and aversive early-LPP amplitudes were associated with increased positive (P3b, $r_s = -0.27$, $P = 0.04$; early-LPP, $r_s = -0.35$, $P = 0.01$) and negative symptom severity (P3b, $r_s = -0.29$, $P = 0.03$; early-LPP, $r_s = -0.33$, $P = 0.01$), reduced aversive late-LPP amplitudes were related to increased negative symptoms ($r_s = -0.39$, $P = 0.00$), and reduced aversive P3a amplitudes ($r_s = -0.28$, $P = 0.03$) were related to increased positive symptoms, across FDR and SCZ participants. Additionally, greater target-P3b and aversive early-LPP amplitudes were associated with increased performances on executive functioning (DKEFS-CWIT; P3b, $r_s = 0.30$, $P = 0.00$; early-LPP, $r_s = 0.28$, $P = 0.01$), attentional processing (CPT-IP; P3b, $r_s = 0.29$, $P = 0.00$; early-LPP, $r_s = 0.32$, $P = 0.00$), and affective processing (BCAET; P3b, $r_s = 0.27$, $P = 0.01$; early-LPP, $r_s = 0.31$,

P = 0.00) neurocognitive tasks, and greater aversive late-LPP and neutral P3a amplitudes were correlated with increased attentional (late-LPP, r_s = 0.27, P = 0.01; P3a, r_s = 0.22, P = 0.03) and affective processing (late-LPP, r_s = 0.26, P = 0.01; P3a, r_s = 0.25, P = 0.01) performances, across all participants. Refer to Supplementary Table 1 (available at http://eeg.sagepub.com/content/by/supplemental-data) for additional information (selected correlations presented in Figure 2.3).

Discussion

Results from the present study suggest that deficits in multiple stages of information processing map onto specific disruptions in attention and affective salience detection in SCZ patients and FDR individuals. During an early stage of attention orienting and novelty detection, both SCZ and FDR participants showed intact novelty detection (P3a), yet exhibited deviations in neural correlates of directed attention to task-relevant stimuli (target-P3b), and motivated attention to salient distractors (early-LPP). Diminished P3b amplitudes for target stimuli and aberrant LPP responses for salient distractors may reflect disruptions in attentional tuning in SCZ and FDR participants, and an overall reduction in signal-to-noise discrimination. Impaired sensory filtering and salience processing may interfere with cognitive processes essential for social interactions and goal-directed behaviors. In this study, the neural correlates of attentional processing for FDR participants were found to be intermediate to the SCZ patients and controls, suggesting that P3b and early-LPP components may represent neurophysiological markers for psychosis, and may potentially facilitate the identification of vulnerable individuals in younger populations.

In contrast to the earlier directed attention responses, FDR participants exhibited a unique enhancement of the late-LPP amplitude, suggesting sustained motivated attention to emotional (albeit task-irrelevant) information. While the neurocognitive and behavioral significance of this enhanced processing of task-irrelevant affective information remains unclear, it may reflect a compensatory mechanism that engages “alternate” salience systems to compensate for loss of signal at earlier stages of processing. Conversely, the distinct augmentation of the late positivity could reflect maintenance of the salient representation for later and higher order cognitive processes, therefore enabling FDR participants to achieve a behavioral performance comparable to controls. Elevated sustained processing of salient stimuli may promote superior allocation of attention, thereby minimizing symptom manifestation in

vulnerable individuals. Alternatively, enhanced sustained motivated attention may reflect an inability to switch off erroneous salience signals. Future research should examine the utility of the LPP component in the detection and prediction of psychopathology, as a distinct risk marker for aberrant salience and attentional processing, and its potential value in distinguishing between psychotic disorders.

The electrophysiological abnormalities underlying attentional processing in SCZ and FDR participants may represent disruptions in frontolimbic circuitry, critical for maintaining an effective interaction between frontal executive and limbic affective processing networks. Dichter et al (2010) reported a disrupted balance between a dorsal executive network and a ventral affective system responsible for attention and emotion regulation in patients with SCZ, resulting in the disproportionate recruitment of limbic regions. The exaggerated limbic response may promote greater affective interference (Anticevic and Corlett, 2012; Dichter et al., 2010; Fichtenholtz et al., 2004) and result in attentional disturbances manifested in the reduced directed attention ERP responses to task-relevant target events and novel distractors. Future research could employ parallel functional magnetic resonance imaging and EEG to elucidate atypical circuitry underlying discrepancies in LPP amplitudes between groups.

SCZ participants demonstrated intact novelty detection, indexed by the P3a amplitude, and valence discrimination, as LPP amplitudes were larger for aversive than neutral stimuli. In contrast to previous studies reporting reduced P3a amplitudes in patients with SCZ (Turetsky et al., 2009; van der Stelt et al., 2004), the present study found novelty orientation undisturbed in patients and relatives. Inconsistent results could be attributed to differences in task design (content of novel stimuli), sensory modality, or discrepancies in the electrode(s) (Fz, Pz) used in the analysis. While P3a is understood to be a frontocentral component, it has also been found to be maximal at parietal locations in novel oddball variants (van der Stelt et al., 2004), muddling the distinction between early-LPP and P3a. Intact novelty detection and valence discrimination observed in the present study support previous research suggesting that SCZ patients' emotion-dependent attention was relatively undisturbed (Horan et al., 2012). Despite intact novelty detection, FDR participants uniquely exhibited aberrant salience processing, indicated by

the indistinguishable early-LPP response for neutral and aversive stimuli, additional evidence for atypical salience processing in FDR.

While patients demonstrated intact behavioral accuracy and reaction times for target stimuli, they exhibited longer reaction times for neutral stimuli, and shorter reaction times for aversive stimuli. This finding provides evidence in support of aberrant salience processing in psychosis, whereby patients attribute inappropriate salience and motivational significance to irrelevant stimuli, potentially accompanying dysregulated dopamine release (Kapur, 2003). FDR participants did not differ from controls on behavioral performance, and appropriately exhibited slower responses to emotional stimuli, potentially reflecting deeper processing of these events, along with control participants. SCZ patients additionally demonstrated reduced accuracy for aversive and neutral images, indicating that SCZ patients are biased toward target responses. In contrast to prior evidence of intact overt, "in-the-moment" emotional processing in SCZ, these findings suggest atypical processing of salient, emotional distractors and disruptions in frontolimbic engagement (Laurens et al., 2005; Liu et al., 2012).

Severity of negative, positive, and disorganized symptoms was associated with reduced neutral and aversive early-LPP amplitudes across FDR and SCZ participants, suggesting that the early-LPP may offer a method for tracking fluctuations in clinical state. Deficits in attention orienting, reflected in reduced auditory P3a amplitudes, have been reported to be associated with increased negative symptoms in individuals at clinical risk for psychosis (Jahshan et al., 2012). While there was no relationship between P3a and negative symptoms in this study, severity of negative symptoms was found to be related to reduced early-LPP and target-P3b amplitudes, also suggestive of potential impairments in attentional processing promoting negative symptom pathology. More profound deficits in P3b amplitude have also been reported in patients with more severe negative symptoms (Liu et al., 2004), further supporting a critical role for P3b in targeting treatments for especially debilitating negative symptoms, and for its utility as a biomarker for neuropsychopathology. Furthermore, executive functioning, attentional processing and the ability to identify emotional facial expressions were associated with higher target-P3b and early-LPP amplitudes, suggesting that cognitive behavioral therapy or other intervention techniques may be effective in addressing affective and attentional processing impairments, and subsequently enhancing P3 and LPP

amplitudes in affected individuals. Additionally, superior attentional processing, reflected in the CPT sensitivity index, was related to novelty detection (P3a) and salience processing (late-LPP), indicating that novelty orienting, sustained attention to salience and maintaining motivational significance may be associated with improved performance on attentional tasks. This finding provides additional support for the LPP underlying a potential compensatory mechanism in FDR participants.

Although FDR participants did not demonstrate observable affective or attentional deficiencies, as measured by clinical assessments and neurocognitive testing, they shared deviant neurophysiological correlates of directed (target-P3b) and motivated attention (early-LPP) with SCZ patients. While SCZ and FDR participants were able to detect novel distractor stimuli appropriately, they demonstrated aberrant motivated attention, possibly attributable to disturbances in sensory filtering or early stages of attention orienting, which contributed to a reduced distinction between the signal response to task stimuli and background EEG "noise." Furthermore, FDR participants displayed atypical sustained salience processing reflected in the elevated late-LPP response for aversive and neutral stimuli, indicating reduced network efficiency relative to healthy controls. To perform equivalently to controls behaviorally, it appears that FDR participants prioritize salience processing by engaging a compensatory neural mechanism to overcome deficits in cognitive functioning. Without the compensatory recruitment of neural circuitry and resulting elevation of late positivity, SCZ patients may be unable to perform at the same level as control and FDR participants. These findings suggest that first-degree relatives of SCZ patients have aberrant attentional neural processing (P3b and LPP), which does not lead to clinical symptoms, perhaps because of compensatory neural processing, reflected in the elevated late positivity. These findings may have implications for targeting salience processing to improve cognitive deficits and clinical symptom severity, as they suggest that the LPP component may be used as a neurophysiological marker for assessing directed and motivated attention deficits in individuals at risk for psychosis.

There are several limitations to the current study. Valence and arousal ratings of the aversive stimuli from this set of participants were not available and would have been necessary to compare the experience of unpleasant stimuli between patients with SCZ, FDR participants, and controls. While limited medication exposure could interfere with accurate interpretation of patients' results (Coburn et al., 1998;

Gonul et al., 2003), we purposely recruited recently diagnosed patients to minimize chronic pharmacological effects. Even though age and sex were entered as covariates in the analyses, it should be noted that the FDR group was largely made up of older, female individuals and it is known that females respond differently to emotional stimuli (Stevens and Hamann, 2012; Whittle et al., 2011). Balanced experimental groups, or studies restricted to male participants, would be necessary to elaborate on the sex contributions to the current results. The study was intended to examine familial high risk, and not promote predictions for disease onset; however, future studies assessing adolescent FDRs with prodromal symptoms would offer valuable insight for the use of this paradigm in assessing risk for SCZ.

The goal of the current study was to investigate directed and sustained motivated attention to salience in SCZ patients and FDR participants to determine whether deterioration of the complementary affective and attention systems potentially underlies abnormalities in cognitive and behavioral functioning, and negative symptom pathology. This is the first study, to our knowledge, to explore the neurophysiological correlates of early and late motivated attention and salience processing in FDR individuals, and provides promising evidence for a compensatory neural mechanism, which allows FDR participants to perform behaviorally equivalent to healthy controls. Results suggest that early and late LPP responses may reflect novel vulnerability markers of aberrant attentional processes in individuals at risk for psychosis.

2.3 Future Directions

Preliminary analyses evaluating the oscillatory activity underlying directed and sustained motivated attention to salient stimuli during the emotional oddball paradigm found additional evidence for a compensatory mechanism in FDR and aberrant salient processing in SCZ patients. Consistent with the elevated LPP amplitude, FDR participants (N = 26) additionally exhibited a unique enhancement of beta oscillatory activity (16-30 Hz) in response to aversive stimuli relative to a control group matched on age and sex [$t=2.2$, $p<0.05$)] (*Figure 2.4*). Additionally, SCZ patients (N = 30) demonstrated reduced evoked power (EP) [($t=2.4$, $p<0.05$] and intertrial (phase) coherence (ITC) [$t=3.1$, $p<0.05$] in the theta frequency range (4-8 Hz) in response to aversive stimuli. Disrupted theta activity potentially reflects impaired fronto-limbic connectivity involved in the evaluation of emotional stimuli (Aftanas et al., 2001; Ertl et al., 2013;

Lesting et al., 2011), and is consistent with previous research from our lab demonstrating reduced theta in adolescents at high-risk for SCZ (Donkers et al., 2011). Furthermore, deficits in delta EP [SCZ: $t=2.6$, $p<0.05$; FDR: $t=2.4$, $p<0.05$] and ITC [SCZ: $t=2.6$, $p<0.05$; FDR: $t=2.4$, $p<0.05$] for SCZ and FDR participants may underlie impairments in the suppression of affective networks responsible for adaptive gating of emotionally salient distractor stimuli. Controls demonstrated increased delta EP for targets compared with aversive stimuli, suggesting that delta may be involved in the inhibition of affective networks during target processing to allow for appropriate task-relevant electrophysiological responses. In contrast, the delta response did not distinguish stimulus type in SCZ patients and FDR participants (Andersen et al, *in preparation, Figure 2.5*).

2.4 Significance

Investigating the neurophysiological correlates of motivated attention and salience processing in SCZ patients and first-degree relatives advanced the understanding of familial risk, and identified potential biomarkers for core symptom domains of schizophrenia. The unique affective response pattern found for FDR participants may represent a compensatory engagement of affective circuitry that allows the clinically unaffected FDR individuals to achieve a behavioral performance equivalent to controls. Disruptions in P3 and LPP responses for aversive stimuli may serve as neurophysiological markers of SCZ, and aid in the detection and prediction of psychopathology. Despite patients' intact valence discrimination and cognitive elaboration of emotional stimuli in a simple oddball paradigm, it is unclear whether SCZ patients will be able to utilize a cognitive framing strategy to alleviate the electrophysiological response to aversive stimuli and maintain the capacity for valence discrimination following a stress manipulation.

These preliminary results suggest that SCZ patients and FDR participants demonstrate aberrant neural correlates of attentional processing, and FDR participants additionally exhibit a unique deviation in sustained affective processing. The next experiment described in Chapter 3 further elucidates the neural mechanisms governing affective processing in SCZ, and characterizes the mechanisms by which affective regulation is influenced by psychosocial stress, both reliant on the appropriate engagement of fronto-limbic circuitry.

Chapter 2.2 Tables

Table 2.1. Demographics

	Controls (n = 47)	FDR (n = 28)	SCZ (n = 31)	Statistic
Age in years, mean (SD)	26.8 (7.0)	30.7 (8.5)	24.8 (5.2)	$F(2, 105) = 5.4$*
Sex (% male)	53.2	17.9	83.9	χ^2 (2, 105) = 25.7**
Ethnicity (%)				
White/Caucasian	70.2	57.1	58.1	
African American	29.8	25	35.5	
Asian	0	3.6	3.2	
Multiple	0	10.7	0	
Other	0	3.6	3.2	
Education, mean (SD)[a]	3.2 (1.4)	3.2 (1.8)	4.2 (1.6)	$F(2, 104) = 4.3$*
Average SES, mean (SD)[b]	15.2 (2.2)	15.0 (2.3)	15.1 (2.4)	$F(2, 103) = 0.07$
Duration of illness, mean (SD)			2.3 (1.8)	
SOPS, mean (SD)				
Total positive	1.0 (1.6)	1.7 (2.0)	11.0(6.0)	$F(2, 104) = 81.3$**
Total negative	0.8 (1.3)	1.9 (2.5)	14.1 (7.2)	$F(2,104) = 103.3$**
Total disorganized	0.3 (0.7)	1.0 (1.6)	5.2 (4.3)	$F(2,104) = 37.1$**
Total general	0.7 (1.2)	2.3 (2.5)	5.4 (4.4)	$F(2,104) = 26.4$**
Neurocognitive measures, mean (SD)				
Estimated IQ[c]	113.6 (7.0)	112.2 (8.6)	107.9 (10.6)	$F(2, 100) = 4.0$*
D-KEFS:IS	11.1 (2.6)	11.1 (2.3)	8.6 (3.5)	$F(2, 97) = 8.5$**
CPT-IP:d’	3.7 (.7)	3.7(.7)	3.0 (.9)	$F(2,94) = 8.0$*
FEIT	13.0 (2.9)	13.0 (2.4)	11.5 (2.3)	$F(2, 99) = 3.5$*
BCAET	27.3 (4.0)	27.2 (3.8)	24.4 (4.1)	$F(2, 99) = 5.4$*

Abbreviations: SCZ, patients with schizophrenia; FDR, first-degree relatives; SES, socioeconomic status; SOPS, Scale of Prodromal Symptoms; FEIT, Facial Emotion Identification Test; D-KEFS:IS, Delis-Kaplan Executive Function System–Color-Word Interference Test–inhibition/switching scaled score; CPT-IP:d′, Continuous Performance Test–Identical Pairs Sensitivity Index; BCAET, Baron-Cohen “Reading the Mind in the Eyes” Test.

[a]1 = graduate training, 2 = college graduate, 3 = at least 1 year of college, 4 = high school graduate/GED, 5 = did not finish high school, 6 = elementary school, 7 = less than 8 years of school.

[b]Average years of parental education serves as a proxy for SES.

[c]IQ estimated using North American Adult Reading Test (NAART).

*$P < .05$. **$P < .001$.

Table 2.2. Results for Oddball Detection Paradigm

Latency (ms)	Controls (n = 47)	FDR (n = 28)	SCZ (n = 31)	Post Hoc *t* values CON vs FDR	SCZ vs FDR	CON vs SCZ
Behavioral results						
Standard	342.7 (52.5)	356.1 (83.4)	367.1 (61.8)	0.5	1.0	1.8
Neutral	502.5 (72.6)	511.9 (63.5)	560.5 (68.1)	0.2	3.5*	4.2**
Aversive	536.1 (70.3)	547.7 (65.7)	383.0 (78.7)	0.0	6.6**	8.3**
Target	571.1 (88.5)	593.4 (63.6)	562.2 (69.0)	0.2	0.8	0.7
	F values					
Stimulus (df = 3, 300)	9.4**					
Group (df = 2, 100)	0.2					
Stimulus × Group (df = 6, 300)	58**					
Accuracy (%)						
Standard	97.9 (2.5)	96.3 (8.1)	94.6 (5.1)	2.2	0.4	1.9
Neutral	95.3 (4.3)	95.2 (7.7)	87.9 (13.1)	0.8	1.7	2.9*
Aversive	92.4 (4.4)	91.2 (9.4)	84.5 (16.2)	1.3	0.9	2.5*
Target	81.1 (13.0)	83.0 (10.4)	72.2 (13.8)	0.4	1.4	2.2
	F values					
Stimulus (df = 1.6, 162.2)	11.4**					
Group (df = 2,100)	5.6*					
Stimulus × Group (df = 3.2, 162.2)	0.8					
ERP results						
Target P3b amplitude (Pz)						
Target	14.3 (4.7)	11.4 (4.7)	8.2 (3.6)	2.5*	2.4	5.7**
Standard	3.5 (1.6)	3.5 (2.6)	2.2 (2.0)	0.6	1.3	2.3
	F values					
Stimulus (df = 1, 101)	18.3**					
Group (df = 2, 101)	17.8**					
Stimulus × Group (df = 2, 101)	10.2**					
Average P3a amplitude (Fz)						
Aversive	3.6 (2.2)	4.2 (2.5)	3.4 (2.8)	0.2	0.1	0.4
Neutral	3.1 (2.0)	3.9 (2.4)	3.1 (2.6)	0.8	0.3	0.5
Standard	1.9 (1.1)	2.4 (1.4)	2.1 (1.7)	1.2	0.4	0.8
	F values					
Valence (df = 1.7, 168.4)	0.4					
Group (df = 2, 101)	0.4					
Valence × Group (df = 3.3, 168.4)	0.1					
Late positive potential (Pz)						
Aversive (350-500 ms)	11.1 (4.4)	8.7 (3.7)	6.0 (3.1)	2.5*	2.2	5.5**
Neutral (350-500 ms)	9.2 (3.7)	7.7 (4.0)	5.0 (2.6)	1.4	2.9*	5.1**
Aversive (500-650 ms)	7.1 (3.7)	7.4 (3.4)	5.0 (3.3)	0.3	2.5*	2.8*
Neutral (500-650 ms)	5.5 (2.7)	6.0 (2.9)	3.9 (2.9)	0.8	2.7*	2.5*
Aversive (650-800 ms)	4.6 (2.8)	6.6 (3.4)	3.8 (3.0)	2.6*	3.0*	1.1
Neutral (650-800 ms)	3.3 (1.8)	4.6 (2.7)	2.5 (2.4)	2.5*	3.4*	1.6
	F values					
Valence (df = 1, 101)	0.0					
Window (df = 1.5, 152.3)	2.3					
Group (df = 2, 101)	12.4**					
Valence × Group (df = 2, 101)	0.7					
Valence × Window (df = 1.9, 188.8)	0.1					
Window × Group (df = 3.0, 152.3)	7.4**					
Valence × Window × Group (df = 3.7, 188.8)	3.0*					

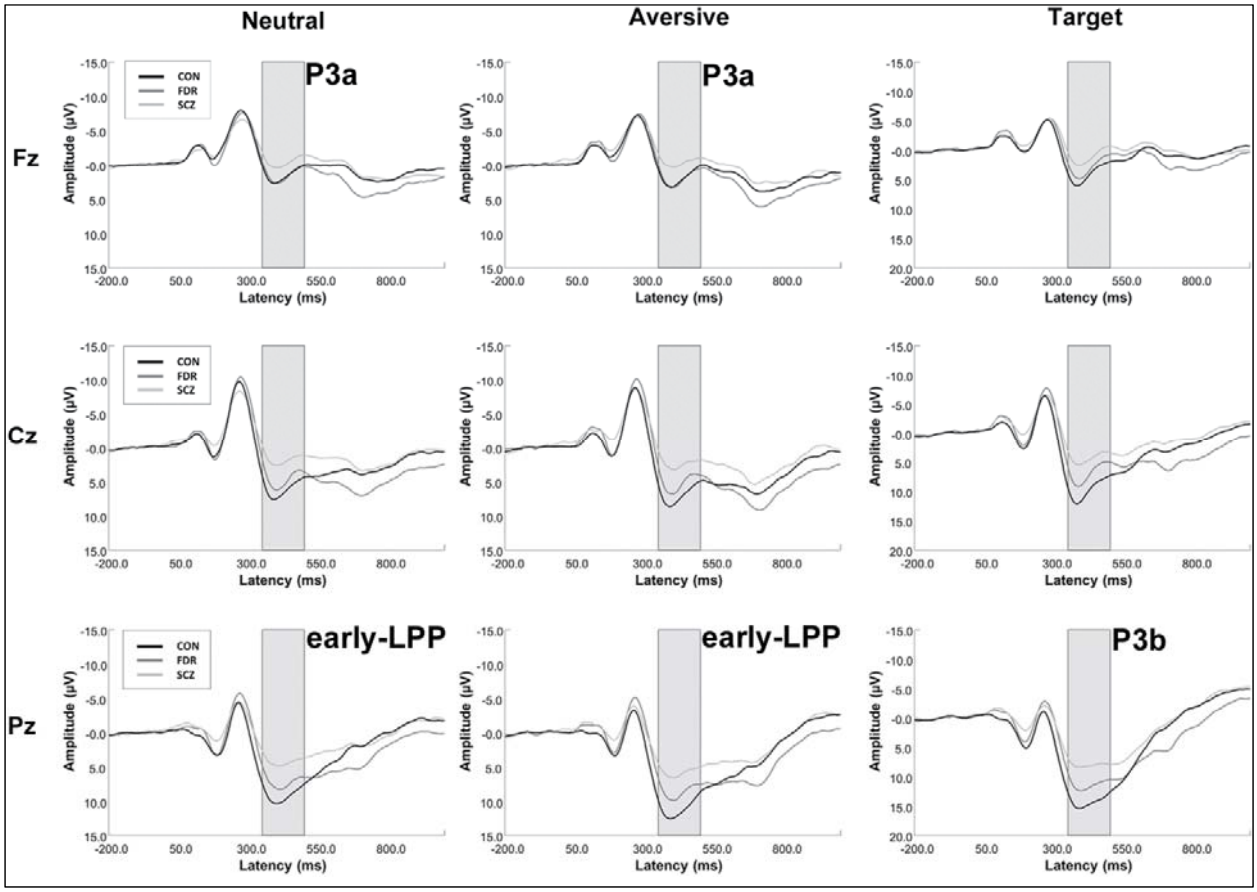
Abbreviations: CON, controls; SCZ, patients with schizophrenia; FDR, first-degree relatives; ERP, event-related potential.

[a]Mean amplitudes (μV) recorded from Pz. Standard deviations are presented in parentheses. Controls missing 1 participant's behavioral data (n = 46). Post hoc comparisons are Bonferroni corrected for multiple comparisons. Sex and age were entered as covariates.

*P < .05. **P < .001.

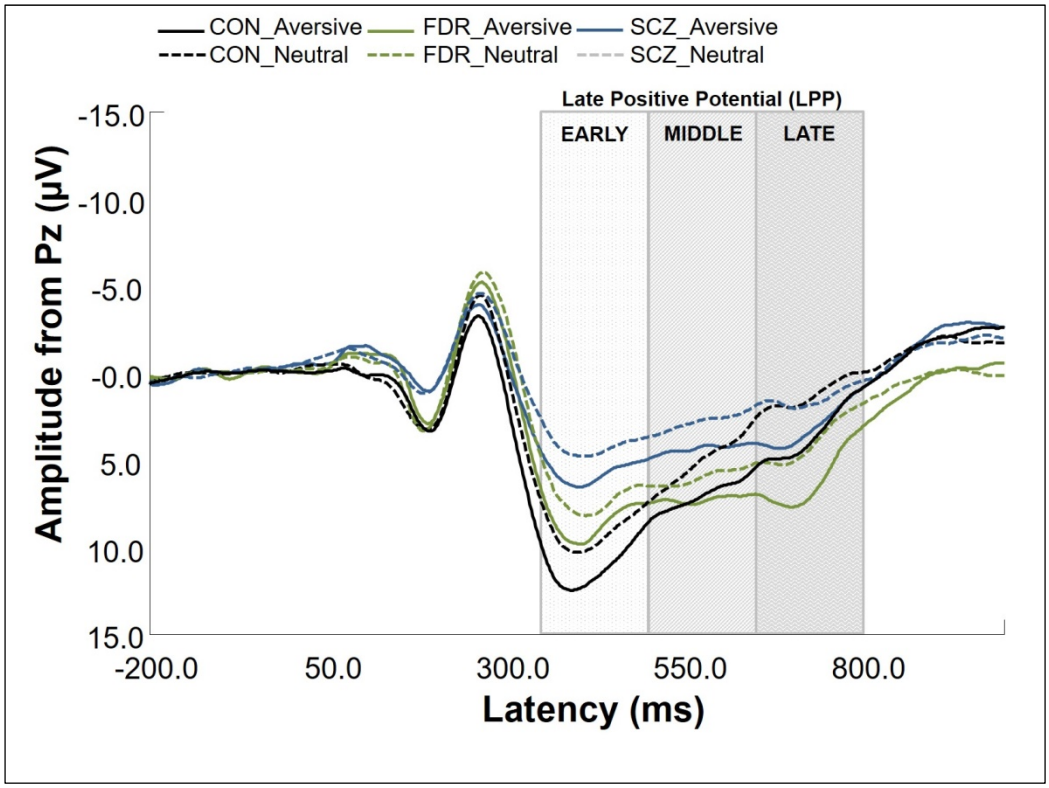
Chapter 2.2 Figures

Figure 2.1. Novelty Detection of Novel Distractor Stimuli and Directed Attention to Targets



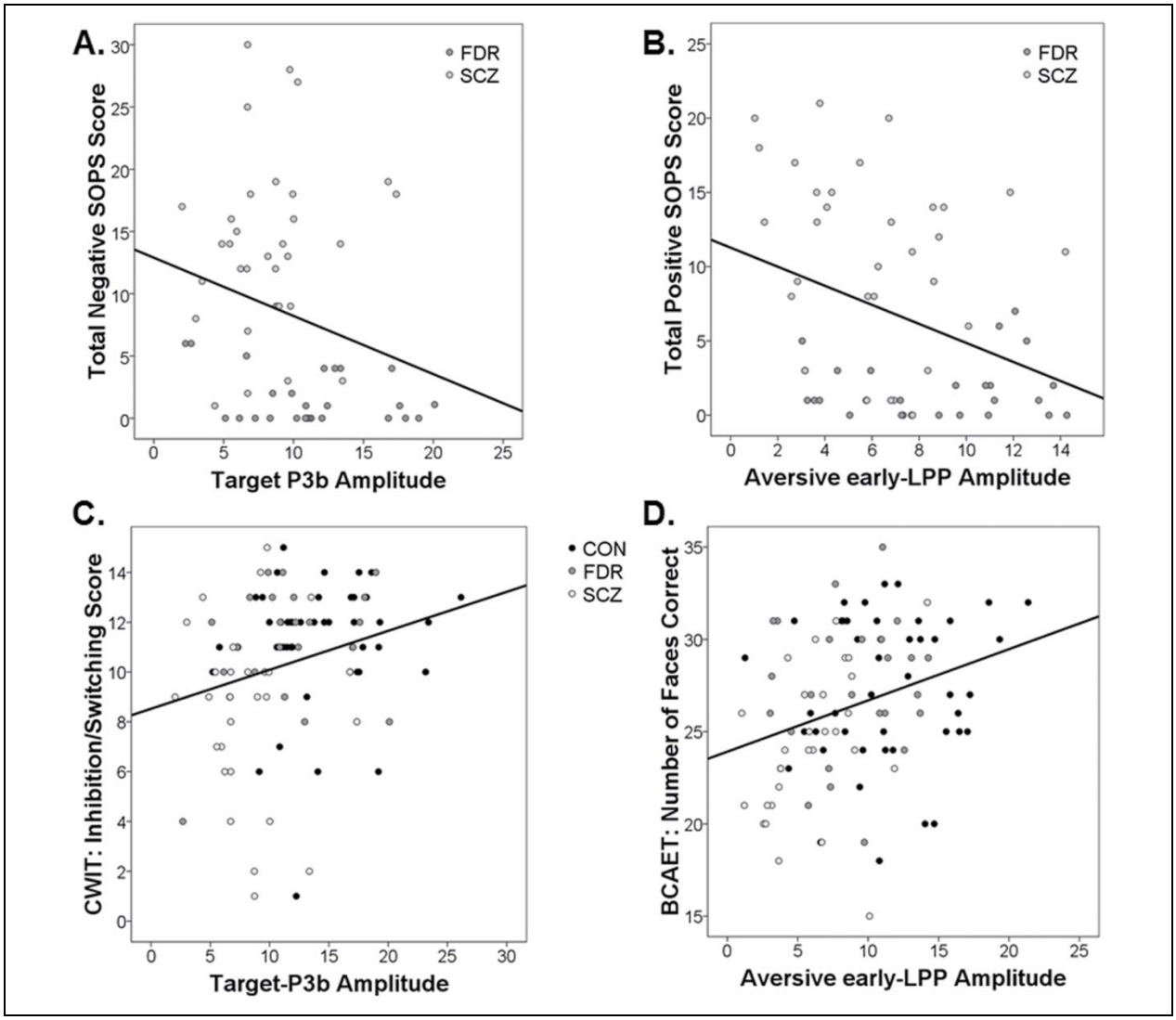
Grand average waveforms for neutral, aversive, and target stimuli recorded from Fz, Cz, and Pz electrodes for SCZ, FDR, and controls. Gray boxes indicate the analysis window (350-500 ms). P3a was analyzed from Fz, early-LPP and P3b were analyzed from Pz. SCZ, patients with schizophrenia; FDR, first-degree relatives; LPP, late positive potential.

Figure 2.2. Late Positive Potential (LPP) Underlying Motivated Attention and Salience Processing



The LPP grand average waveforms elicited from Pz in response to neutral and aversive stimuli for SCZ, FDR, and controls. Gray boxes indicate the early (350-500 ms), middle (500-650 ms), and late (650-800 ms) analysis windows. SCZ, patients with schizophrenia; FDR, first-degree relatives.

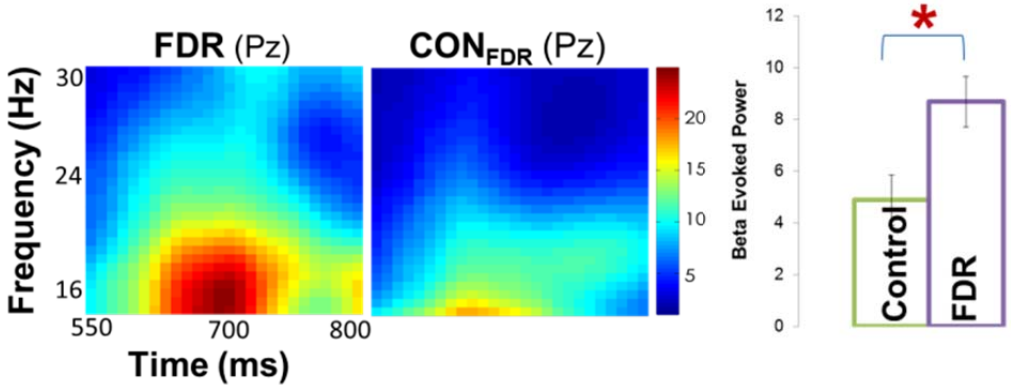
Figure 2.3. Relationship between SOPS, Neurocognitive Assessments, and Oddball ERP Amplitudes



A. More severe negative symptoms are related to reduced target-P3b. B. More severe positive symptoms are associated with reduced aversive early-LPP. C. Superior attentional processing is related to greater target-P3b. D. Increased aptitude for facial emotion identification is associated with greater aversive early-LPP. ERP, event-related potential; LPP, late positive potential; SOPS, Scale of Prodromal Symptoms; CWIT, Color-Word Interference Test; BCAET, Baron-Cohen “Reading the Mind in the Eyes” Test.

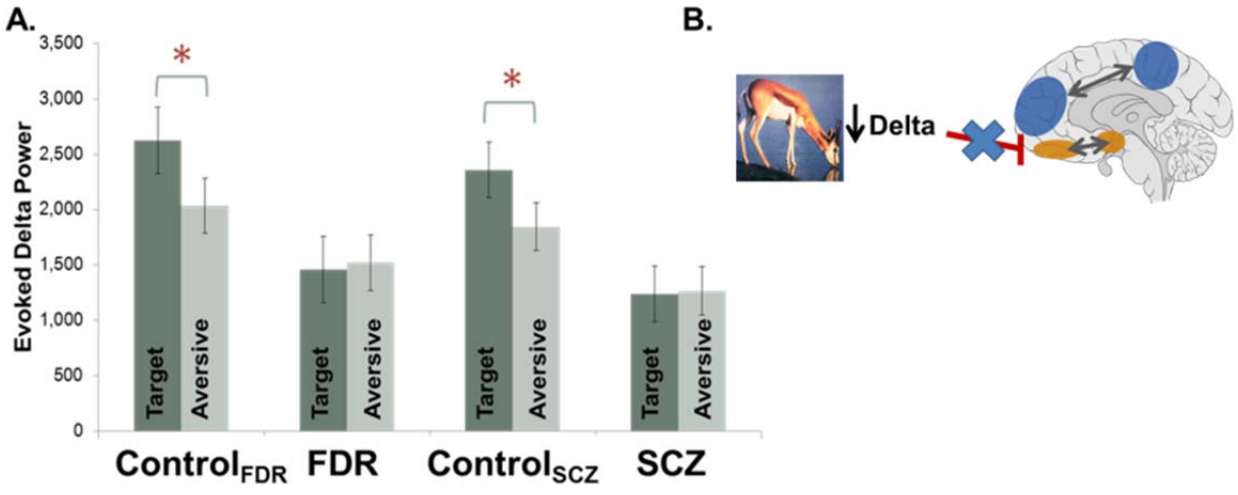
Chapter 2.3 Figures

Figure 2.4. Enhanced Beta Activity in FDR in Response to Aversive Stimuli



Evoked power in beta frequency range (16-30 Hz) from mid-parietal electrode (Pz) during the LPP window (550-800 ms) for first-degree relatives and healthy controls.

Figure 2.5. Disrupted Neural Oscillatory Activity in SCZ and FDR



A. Delta evoked power for target vs. aversive stimuli. B. Theoretical model depicting impaired delta inhibition in response to target animal stimuli for SCZ and FDR promoting affective interference.

CHAPTER 3: STRESS EFFECTS ON EEG CORRELATES OF AFFECTIVE PROCESSING

3.1 Context

SCZ patients and first-degree relatives demonstrated aberrant electrophysiological correlates of affective processing, with reduced ERP indices of motivated attention and salience processing. First-degree relatives additionally revealed exaggerated LPP and beta oscillatory responses for aversive stimuli, possibly indicating a compensatory engagement of neural circuitry. To advance the understanding of the electrophysiological correlates of aberrant affective and salience processing in SCZ patients, the next experiment used an emotional oddball framing task to probe the integrity of fronto-limbic circuitry, and then challenged the circuitry with a psychosocial stressor to see how well it adapted to and recovered from stress exposure. The study design combined electrophysiological measures of affective framing, assessing a key aspect of emotion regulation, peripheral stress physiology, and clinical and neurocognitive assessments in SCZ patients and healthy controls. This is the first study to examine respiratory sinus arrhythmia (RSA) in reaction to a psychosocial stressor in patients with schizophrenia and identify associated electrophysiological indices of aberrant arousal and stress reactivity. Results from this study have the potential to inform novel treatment approaches targeting the stress response to modify fronto-limbic oscillatory activity and consequently, improve the effectiveness of cognitive behavioral therapy which is reliant on successful emotion regulation strategies.

3.2 Stress Modifies the Electrophysiological Correlates of Affective Processing in Patients with Schizophrenia and Healthy Controls

Introduction

Emotion regulation (ER) is fundamental to the development, maintenance and treatment of neuropsychiatric disorders, and plays a significant role in social, cognitive, and interpersonal functioning (Livingstone et al., 2009; Phillips et al., 2008). The emotional response is malleable and subject to change with cognitive context. Accordingly, ER refers to the ability to cognitively adjust physiological and emotional arousal to aversive events to appropriately meet situational demands. Along with negative

symptoms of anhedonia, avolition, apathy, and blunted effect, patients with schizophrenia exhibit debilitating deficits in cognitive functioning and ER which are generally resistant to pharmacotherapy, are associated with the poorest functional outcome, and are exacerbated by stress (Horan et al., 2013; Strauss et al., 2013). ER is fundamental for treatment efficacy, as cognitive behavioral therapy (CBT) and coping mechanisms rely on successful ER strategies (Papa et al., 2012). Implementation of ER strategies is critical during stressful situations; however, altering the nature of emotional responses is more challenging under stress, as the regulation of stress and affective systems similarly rely on fronto-limbic circuitry (Raio et al., 2013). While it is understood that stress interferes with ER by disrupting the dynamic balance of frontal executive and affective limbic circuitry, it is unclear how this processing disruption is reflected in peripheral physiology and neurophysiological correlates of affective network efficiency in patients with schizophrenia.

Neuroimaging research has established that ER involves the recruitment of frontal executive networks to suppress affective limbic activity in order to control the emotional response and promote an adaptive functional outcome (Goldin et al., 2008; Ochsner et al., 2002, 2004; Phan et al., 2005). Electroencephalography (EEG) offers a powerful method for probing network level neural activity, as oscillations and their synchronization support interneuronal communication and the integration of information processing in neural networks (Roach and Mathalon, 2008). The successful execution of ER strategies has been shown to alter electrophysiological correlates of affective processing, including the late positive potential (LPP) and theta oscillatory activity, to support a more adaptive behavioral response (Ertl et al., 2013; Goldin et al., 2008; Hajcak et al., 2010; Kisley et al., 2011; Phillips et al., 2008). The LPP is an event-related potential (ERP), a voltage deflection elicited by motivationally salient stimuli, and serves as an index for the cognitive elaboration of aversive stimuli, as the LPP amplitude is greater for unpleasant stimuli relative to pleasant or neutral stimuli (Ito et al., 1998). It is possible to suppress the heightened LPP response to aversive stimuli by introducing cognitive framing strategies, assessing a key aspect of ER (Kisley et al., 2011). A novelty P3 ERP component is also elicited in response to novel and salient stimuli, especially during oddball paradigms which require discrimination between infrequent and frequent stimuli (Polich, 2007). While SCZ patients generally exhibit appropriate reports of emotional valence and arousal in response to unpleasant stimuli in laboratory settings (Cohen and Minor, 2008;

Horan et al., 2010; Strauss and Gold, 2012), they demonstrate heightened negative emotion for neutral and positive stimuli (Cohen and Minor, 2008; Horan et al., 2008; Strauss and Herbener, 2011), impaired LPP correlates of ER (Horan et al., 2013; Strauss et al., 2013), deficiencies in P3 (Andersen et al., 2016; van der Stelt et al., 2004, 2005), and a disturbance in the frontal executive control over affective limbic systems (Dichter et al., 2010; Javanbakht, 2006).

Schizophrenia patients express profound disruptions in brain dynamics including many cortical areas and their connectivity, and substantial oscillatory deficiencies (Friston, 1999; Moran and Hong, 2011; Roach and Mathalon, 2008; Uhlhaas et al., 2008; Uhlhaas and Singer, 2014). Abnormalities in the salience neural network are consistently reported in schizophrenia patients, including structural and connectivity disturbances of the anterior insula, and are associated with cognitive and negative symptoms (Liddle et al., 2016). Neural oscillations and their synchronization subserve the coordination and integration of information among brain regions and support a wide range of cognitive, perceptual and sensorimotor functions. In particular, theta and beta oscillations and their synchronization are fundamental to proficient salience and affective processing, and interact with neurotransmitter systems to regulate global cortical state (Ertl et al., 2013; Liddle et al., 2016). Increased theta oscillations and coherence between frontal and limbic regions has been demonstrated during fear conditioning and extinction behaviors in animals (Lesting et al., 2011; Narayanan et al., 2011), and memory processing in humans (Anderson et al., 2010), suggesting a crucial role for theta activity in mediating affective fronto-limbic interactions (Javitt et al., 2008; Uhlhaas et al., 2008). Accordingly, disruptions in theta oscillatory activity may produce impairments in long-distance functional connectivity between frontal and limbic brain regions critical for affective processing (Lesting et al., 2011). Furthermore, increases in theta oscillatory activity, localized to frontal scalp locations, have been reported to accompany successful reappraisal of emotional events, representing enhanced frontal recruitment (Ertl et al., 2013). Deficiency in theta activity is proposed to be of particular interest in patients, as theta oscillations are prominent in the hippocampus, a brain region that demonstrates volumetric reductions in SCZ (Mondelli et al., 2010), and because of theta's involvement in prefrontal-dependent working memory and executive function, which are impacted in SCZ (Uhlhaas et al., 2008).

Less is understood about the contributions of beta oscillations to cognitive function. Though traditionally thought of as a sensorimotor signal, beta oscillatory activity has been linked with novelty, salience detection, arousal, sensory gating, reward evaluation, personal distress, and aberrant levels of beta are associated with neural excitability and insula connectivity (Hong et al., 2008; Kisley and Cornwell, 2006; Liddle et al., 2016; Uhlhaas and Singer, 2014). Absent of environmental influences, patients exhibit a disruption in response hierarchy with exaggerated dopaminergic guided limbic responses to irrelevant stimuli (Kapur, 2003) and disproportionate neural excitability and inhibition (Inan et al., 2013), which promotes salience and motivated attention deficiencies (Andersen et al., 2016). Through interactions with dopaminergic and GABAergic systems, beta oscillatory activity plays a pivotal role in regulating the intricate balance of excitability and inhibition, and supports appropriate salience attribution. Understanding aberrant electrophysiological correlates of salience and affective processing in SCZ patients is crucial for identifying novel endophenotypes for psychosis and to assist in developing innovative therapeutic interventions with improved efficacy.

Stress exposure interferes with frontal engagement and enhances recruitment of limbic regions, especially the amygdala, which in turn heightens the emotional salience and arousal for aversive stimuli, and promotes adaptive response selection (Oei et al., 2012). The integrity of fronto-limbic circuitry and network construction, and underlying oscillatory activity, is disproportionately affected by the deleterious effects of acute stress exposure. Stress impairs frontal-dependent processing, reflected in diminished frontal theta activity during working memory (Gärtner et al., 2014) and mental arithmetic (Gärtner et al., 2015) tasks following disturbing videos with aversive content. Theta and beta activity have also been shown to increase following stress exposure, with enhanced theta activity following sleep deprivation (Alonso et al., 2015) and with stressful task complexity (Jensen and Tesche, 2002), and increased beta activity during a stressful Stroop task (Alonso et al., 2015). Furthermore, Chapotot and colleagues (1998) propose a significant coupling between natural cortisol fluctuations and beta power, suggesting a critical interaction between beta and stress systems in regulating arousal and alertness. Additionally, resting frontal EEG asymmetry is proposed to shift from greater left frontal alpha to predominately right frontal alpha during high stress situations (Lewis et al., 2007), further demonstrating stress induced disruptions in oscillatory activity.

The exaggerated affective limbic engagement following stress exposure makes it more challenging to disengage from emotional images (Kinner et al., 2014) and to utilize emotion regulation strategies to minimize conditioned fear responses following a stress manipulation (Raio et al., 2013). Furthermore, heightened cortisol levels during stress may support emotion regulation strategies, including suppression and reappraisal, and relieve some interference by emotional distractors on working memory performance (Lam et al., 2009; Oei et al., 2012); however, the advantageous role of cortisol is potentially sex-dependent (Kinner et al., 2014; Kogler et al., 2014; Smeets et al., 2009). Effective implementation of ER strategies can promote heightened resilience following stress exposure to protect against the negative outcomes of stress (Troy and Mauss, 2011). Therefore, the deleterious effects of stress may be ameliorated by improving emotion regulation strategies and attentional control reliant on efficient fronto-limbic oscillatory activity.

An appropriate stress response relies on the elaborate convergence of neural regulation and autonomic nervous systems. The neural regulation of the autonomic nervous system conforms to a phylogenetical response hierarchy, with the phylogenetically newer myelinated vagal influence on the heart supporting social communication and calm, non-arousing behavioral states, incompatible with the sympathetic and unmyelinated dorsal vagal complex (Porges, 2007). The delicate balance of opposing inhibitory parasympathetic (vagus) and excitatory sympathetic autonomic systems determine variability in heart rate and physiological adaptation. Respiration influences parasympathetic vagal influence on the heart, generating high-frequency rhythmic heart rate oscillations associated with spontaneous breathing, or RSA (Porges, 2007). Frontal and limbic regions comprising the central autonomic network (CAN) interact with visceral afferents to modify arousal state and regulate emotion expression though the autonomic nervous system (Appelhans and Luecken, 2006). As emotion regulation relies on appropriate physiological arousal states to promote adaptive behaviors, autonomic function plays a pivotal role in the development and maintenance of symptom pathology. SCZ patients exhibit heightened emotional reactivity to stressful events (Docherty et al., 2009), and appraise positive and negative events as being less well managed and less controllable than controls (Horan et al., 2005). In addition to elevated stress sensitivity, SCZ patients demonstrate acute hyperarousal with reduced parasympathetically mediated HRV (RSA), heightened peripheral autonomic output (Boettger et al., 2006; Chang et al., 2009), and

prolonged HRV recovery in reaction to a mental arithmetic stressor (Castro et al., 2009). However, this is the first study, to my knowledge, to determine changes in RSA and heart rate parameters elicited by an acute experimental psychosocial stressor in SCZ patients, and to connect peripheral physiology with neurophysiological correlates of affective processing.

The current study employed a multimodal experimental approach, incorporating neurocognitive and clinical assessments, EEG, and physiological measures of stress to elucidate affective fronto-limbic network efficiency before and after a stress manipulation. While source localization is limited, EEG offers a valuable tool for investigating functional brain networks by directly measuring oscillations and their synchronization, which represent important neurophysiological mechanisms for neuronal communication (Roach and Mathalon, 2008; Uhlhaas et al., 2008). The purpose of the study was to probe the integrity of fronto-limbic neural circuitry, indexed by theta and beta oscillatory activity, in SCZ patients and healthy volunteers using an emotional framing paradigm, assessing a key aspect of ER, and challenge the circuitry using a psychosocial stress manipulation, reliant on the interaction of frontal and limbic brain regions, to see how well the affective system adapts to, and recovers from, stress exposure. The study investigated the effect of stress on modulating the LPP amplitude and oscillatory indices of ER to aversive stimuli, and established the relationship between stress, electrophysiological correlates of ER, and clinical symptoms.

Patients are expected to exhibit deficits in emotional framing and cognitive control over affective circuitry, with difficulty alleviating the LPP response to aversive stimuli following positive framing and reduced frontal theta activity during the positive framing condition, which requires additional cognitive resources to modulate the emotional response. In addition, enhanced beta activity is expected to accompany patients' reported inability to suppress the limbic system during ER. Psychosocial stress exposure is predicted to disrupt oscillatory and ERP indices of ER in patients and control participants, with difficulty reducing the LPP response to aversive stimuli and divergent reductions in theta and enhanced beta oscillatory activity. The electrophysiological response in controls following stress is predicted to mimic SCZ patients' electrophysiological profile before stress. However, stress is expected to have a more profound effect on EEG correlates in patients relative to controls. Consistent with previous

literature, patients are expected to exhibit overall heightened stress reactivity relative to controls with greater heart rate and reduced RSA and heart period, a blunted stress response with less physiological fluctuation during and following stress exposure, and a longer recovery of amplified stress levels. Furthermore, symptom severity and heightened stress reactivity is predicted to associate with aberrant neural synchrony, indexed by diminished frontal theta and enhanced parietal beta.

Method

Participants

Participants consisted of 21 patients diagnosed with a schizophrenia-spectrum illness (SCZ) and 21 healthy control (CON) individuals, all male between the ages of 18 to 35 years. Recruitment was restricted to males to prevent gonadal hormone interactions with HPA activity (Foley and Kirschbaum, 2010; Kirschbaum et al., 1992), and because women exhibit distinct neural correlates of affective processing (Gardener et al., 2013; Stevens and Hamann, 2012; Whittle et al., 2011). Patients were recruited from the Outreach and Support Intervention Services (OASIS) clinic in Carrboro, North Carolina, and referred to the study by their treating psychiatrist, who judged them stable and fit to volunteer in the study. CON participants were recruited from the Orange County community via flyers. Patients met criteria for schizophrenia (n = 14), schizoaffective (n = 4), or schizophreniform (n = 3) disorder as assessed by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (SCID DSM-IV), and diagnoses were confirmed using diagnostic criteria outlined in DSM-V (American Psychiatric Association, 2013; First et al., 1995). All patients were medicated with first-generation (n = 2) or second-generation (n = 19) antipsychotics and had stable symptoms. Control participants had no DSM-IV Axis I diagnosis, were not taking antipsychotic medications, and did not have first-degree relatives with a schizophrenia-spectrum illness diagnosis. All participants spoke English, had normal or corrected vision, and no history of neurological disorders. Participants received $20.00 per hour for their participation, amounting to $100.00 total. Informed consent was provided in accordance with the University of North Carolina at Chapel Hill Institutional Review Board.

Measures

Clinical Assessments

Along with the SCID, all participants were given the Clinical Assessment Interview for Negative Symptoms (CAINS) to assess motivation, pleasure and emotional expression (Kring et al., 2013), and the Alcohol Use Scale/ Drug Use Scale (AUS/DUS) (Drake et al., 1989). Patients were additionally administered the Structured Interview for Positive and Negative Syndrome Scale (SCI-PANSS) to assess symptom severity along positive, negative and general symptom subscales (Opler et al., 1992).

Neurocognitive Tests

Participants performed a computerized battery of neurocognitive assessments, including the North American Adult Reading Test (NAART) (Uttl, 2002) to estimate intelligence, the Continuous Performance Test- Identical Pairs test (CPT-IP) (Cornblatt et al., 1989) to measure effort and attention, Auditory Verbal Learning Test (AVLT) (Geffen et al., 1994) to evaluate learning and memory, Visuospatial Sequencing Test (VST) to assess working memory, and the Stroop Test to evaluate executive functioning (van Erp et al., 2015). Neurocognitive assessments were administered through the Computerized Multiphasic Interactive Neurocognitive DualDisplay System (CMINDS) (O'Halloran et al., 2008).

Stress and Affect Questionnaires

Self-report ratings of stress and affect were collected using the Daily Stress Inventory (DSI) (Brantley et al., 1987) to evaluate frequency and content of daily stress, the Perceived Stress Scale (PSS) (Cohen et al., 1983) to examine experienced levels of stress, the Emotion Regulation Questionnaire (ERQ) (Gross and John, 2003) to evaluate cognitive reappraisal and expressive suppression behaviors, and subjective levels of stress and affect were measured concurrently with saliva collections using 10-point Likert scales on the Subjective Stress/Affect Rating form (SSR). Additionally, the Positive and Negative Affect Schedule (PANAS) was administered at the beginning and end of the session to assess current state of affect (Watson and Clark, 1999).

Stress Protocol

The acute psychosocial stressor, Trier Social Stress Test (TSST), was implemented by combining the preparation and delivery of a speech with challenging mental arithmetic performance in front of a committee (Kirschbaum et al., 1993). After a three-minute preparation period, the participants were asked to give a five-minute mock job interview, followed by five minutes of challenging serial subtraction in front of an intimidating committee. The committee was introduced as "academic experts" trained in evaluating nonverbal behavior, and were instructed to refrain from providing any feedback. The participants were told that they were being video recorded to later evaluate their performance. Six saliva samples were collected from each participant to assess both salivary cortisol (sCORT) and salivary alpha amylase (sAA): a baseline sample before the experiment begins, before and after the onset of the stressor, at 25 minutes post stressor and two additional samples collected 45 and 80 minutes following stress onset to capture the recovery of the stress response. Saliva was collected using a salivary cotton swab (Salivette-Sarstedt, Germany) which the participant inserted under their tongue for two minutes. Experimenter instructed participants to saturate the cotton swab with as much saliva as possible. sCORT and sAA analyses are not included in the current report. Electrocardiogram (ECG) was collected simultaneously with each task and the stressor. In addition to the saliva samples, participants completed SSR forms for 5 different adjectives (stressed, happy, irritated, unhappy, overwhelmed) at each of the six saliva collection time-points to further validate the stress manipulation.

Emotional Oddball Framing Paradigm

An emotional oddball framing paradigm, modeled after Kisley and colleagues (2011), was employed while EEG was recorded (*Figure 3.1*). A series of five images selected from the International Affective Picture System (IAPS) database comprised a block. IAPS images are complex images with standardized ratings from adults on a scale of 1-9 for valence and arousal, with higher numbers reflecting more positive valence and higher arousal (Lang et al., 2008). The average (SD) valence and arousal ratings for the aversive stimuli, with images of mutilation, disease, and human violence, were 2.2 (1.5) and 5.8 (2.3), respectively, whereas neutral images depicting household items and neutral human faces had average (SD) valence and arousal ratings of 4.7 (1.4) and 3.6 (2.0), respectively. Each block

consisted of a target stimulus, which depicted aversive or neutral emotional content, embedded among four neutral, non-arousing stimuli. Target stimuli were located in the third, fourth or fifth image slot to ensure that target images were followed by at least two neutral "fillers". Neutral and aversive blocks were matched for human content. Images were presented for 1000 ms, followed by a framing cue instructing the participant to respond on a button box to indicate whether the image presented previously was either "positive" or "negative" according to the condition. The framing cue was presented until the participants made a response (up to 5000 ms), and had variable interstimulus intervals between 400-600 ms. A neutral framing condition was performed first, and required participants to determine whether there was an animal in the image presented previously. Animals were depicted in both neutral and negative contexts. Each condition lasted approximately 10 minutes and contained the random selection of 30 neutral blocks and 30 aversive blocks. A total of four emotional framing conditions (positive and negative before and after stressor) were administered to each participant and the order of conditions was counterbalanced between participants. Participants used self-assessment manikins (SAMs) to rate 20 representative images on valence and arousal at the end of the EEG session.

Resting State Recordings

Participants were instructed to focus (eyes open) on a fixation cross for three minutes and remain relaxed and still as possible while resting state EEG and ECG measurements were performed. Resting state recordings were administered at the beginning of the EEG session, directly before the stressor, immediately following the stressor and at the conclusion of the EEG session.

Procedure

The experiment included a clinical and neurocognitive assessment session and an EEG recording session, primarily scheduled on separate days. Refer to *Figure 3.2* for a diagram of the study design. The EEG 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), whereas the clinical session occurred at variable times throughout the day. Participants were allowed to smoke and consume caffeine up until two hours prior to the experiment in accordance with

their habitual smoking and drinking patterns. After providing informed consent during the clinical and neurocognitive session, clinical interviews and computerized neurocognitive tests were performed for approximately two hours.

Participants first completed a urinary toxicology screen upon arrival at the EEG session and had their head measured for an EEG net, followed by the first saliva collection and SSR and PANAS ratings. After the EEG net and ECG electrode placement, the participants performed a resting state and the neutral framing condition. The TSST was introduced between two sets of positive and negative framing conditions. After the final framing condition, participants completed a collection of questionnaires and used SAM to provide valence and arousal ratings for 20 select images (15 aversive, 5 neutral) (Bradley and Lang, 1994). The EEG session lasted approximately three hours.

Electrophysiological and ECG Recording Parameters

The EEG was acquired using a 128-channel Hydrocel Geodesic Sensor Net (Electrical Geodesics Inc., Eugene, OR). Placement of electrodes conformed to the International 10-20 System (Klem et al., 1999). Net Station 4.5.1 software on an iMac computer, along with a Net Amps 300 (1.0.1) amplifier, were used for EEG recordings. 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 a central electrode (Cz). Impedances were maintained below 50 KΩ for the duration of the session. E-Prime 2.0 with E-Studio 2.0.8.74 was used to program the tasks and events were synchronized with the EEG data using an 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).

Three self-adhering electrodes (Ultratrace) were hand placed directly below collar bone, over rib cage and above hip bone to monitor ECG with Biopac (Biopac Systems, Inc., CA) and sampled at 1000 Hz by Acq*Knowledge* acquisition software (Biopac Systems, Inc., CA).

Neurocognitive Data Analysis

Neurocognitive scores were standardized using a z-transform to generate composite scores for memory and executive function to use in further analyses. A description of outcome variables and composite score calculations are presented in *Figure 3.3*. NAART was used to estimate verbal intellectual ability by taking the total number of correctly identified words.

Behavioral Data and Self-Assessment Manikin (SAM) Ratings Analysis

SAM valence and arousal ratings for 20 representative images were averaged separately for aversive (15 images) and neutral (5 images) stimulus types. Response latency (reaction time (RT) measurements of the framing categorization were averaged across condition for each stimulus type, collapsed over correct and incorrect trials. Accuracy (percent correct) for the correct categorization of aversive images during the negative framing conditions (before and after stress) was also assessed.

ERP Data Analysis

EEG datasets were down-sampled to 250 Hz, high pass filtered at 0.1 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. Bad channels were detected and removed using the EEGLAB processing extension, *trimOutlier* (Lee & Miyakoshi, SCCN, INC, UCSD), and channels were interpolated before manually rejecting segments of data with major artifacts. EEG data were re-referenced to the average and continuous EEG data from 56 selected channels (emitting electrodes toward the edge of the net) were subsequently segmented into epochs spanning from 200 ms before to 1200 ms post stimulus onset using the ERPLAB toolbox (Luck and Lopez-Calderon, UC Davis). Epochs containing amplitudes exceeding ±150 μV or contained abnormally distributed data were excluded. ERPs were obtained by averaging the baseline corrected (-200 to 0 ms) epochs for each participant for each stimulus type. The average number of accepted trials was 24.84 (SD = 2.24) and did not differ by group ($F(1,41) = 0.67$, $P = 0.42$). Grand average waveforms were generated and low pass filtered at 15 Hz. A cluster of four parietal channels were averaged together to represent the region of interest (electrodes: Pz = 62,71,72,76; *Figure 3.4*), approximating clusters that have been used in a previous study (McEvoy et al., 2015). The P3

component was defined as the average amplitude between 250 and 500 ms, and the LPP was analyzed between 400 and 1000 ms following stimulus onset, averaged over the parietal cluster.

EEG Data Analysis

For time-frequency analyses, EEG data were down-sampled to 250 Hz, and high and low pass filtered between 1 and 55 Hz (as described above). Raw data were cleaned and bad channels were removed using the 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. An independent component analysis was performed, followed by the interpolation of the removed bad channels. Epochs spanning 1 second before and 2 seconds after stimulus onset were generated for each stimulus type and epochs with amplitudes exceeding ±500 μV (does not capture blinks) and containing abnormally distributed data were rejected. Cleaned, epoched data for each condition and stimulus type for all participants 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). 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. Peak event-related spectral perturbation (ERSP) in theta (4-8 Hz) and beta (13-30 Hz) frequency bands was then extracted from the pre-computed matrices between 100-500 ms and 600-1000 ms post stimulus onset from select electrodes (F3, F4, Fz, C3, C4, Cz, P3, P4, Pz).

ECG Data Analysis

Inter-beat-intervals (IBIs) were extracted from the raw ECG data using in-house software implemented through LabView2014 version 14.0f2 (developed by Maria Davila and Greg Lewis, UNC). IBIs were visually inspected and missed R-wave detections and errors were corrected using CardioEdit (Brain-Body Center, Chicago, IL). RSA was quantified using standard adult parameters that define RSA from frequencies between 0.12 to 0.40 Hz associated with spontaneous respiration, and analyzed using the Porges-Bohrer method of RSA analysis in CardioBatch (Brain-Body Center, Chicago, IL). Filtered time series were divided into 30 second epochs, the variance of each epoch was transformed with a natural

logarithm ($ln(ms^2)$) to calculate the RSA amplitude, and the average epoch value was used to estimate RSA and characterize individual differences. Average heart period (HP), interval between successive R-waves (ms) and heart rate (HR; bpm) were also calculated using CardioBatch software. While ECG was collected throughout the EEG session, RSA, HP and HR were specifically analyzed during the baseline resting state (rsb, 3 minutes), the resting state prior to stress exposure (rs1, 3 minutes), TSST (preparation (3 minutes), speech (5 minutes), math (5 minutes), the resting state following the stressor (rs2, 3 minutes) and during the final resting state recording (rs3, 3 minutes).

Statistical Analyses

Statistical analyses were performed using PASW Statistical Software, version 18.0 (*SPSS Inc*, 2009). Demographic, neurocognitive, clinical and self-report questionnaire data were analyzed using analyses of variance (ANOVAs) for continuous variables, and race was assessed using a chi-square test. SAM ratings of valence and arousal for neutral and aversive stimuli were analyzed using a Group X Stimulus (aversive, neutral) X SAM rating (valence, arousal) repeated-measures (rm) ANOVA, and PANAS affect ratings were assessed using a Group X Affect (positive, negative) X Time (beginning, end) rm-ANOVA.

Valence was evaluated during the neutral (animal) framing condition for ERP (P3, LPP) and EEG (theta, beta) variables separately using a Group (Controls, SCZ patients) X Stimulus (aversive, neutral) rm-ANOVA. The effect of framing on processing aversive and neutral stimuli before stress was examined using a Group X Framing (neutral, positive, negative) X Stimulus (aversive, neutral) rm-ANOVA, and the influence of stress reactivity on behavioral and EEG correlates of affective processing was evaluated by performing a Group X Framing (positive, negative) X Stimulus (aversive, neutral) X Stress (before stress, after stress) rm-ANOVA separately for ERP (P3, LPP), EEG (theta, beta) and reaction time (RT).

ECG measures were analyzed using a Group (Controls, SCZ patients) X Measure (6 time points) rm-ANOVA for RSA, HP and HR separately. Polynomial and repeated within subject contrasts were performed to evaluate linear and quadratic trends and the comparison of adjacent levels, respectively. While age did not differ between groups, there are physiological changes with age; therefore, age was

entered as a covariate for the ECG analyses (O'Brien et al., 1986). RSA, HR and HP were also assessed by generating averaged before stress (rsb, rs1), during stress (TSST) and after stress (rs2, rs3) composite scores and performing a Group X Measure (RSA, HR, HP) X Time (before stress, during stress, after stress) rm-ANOVA. Self-report affect/stress ratings were assessed using a Group X Affect (Happy, Stressed, Depressed, Overwhelmed, Irritated) X Time (baseline, before stress, after stress, recovery 1, recovery 2, recovery 3) rm-ANOVA with repeated within subject contrasts. Post-hoc pairwise comparisons were Bonferroni-corrected for multiple comparisons and Greenhouse-Geisser epsilon corrections were used when the sphericity assumption was violated for all rm-ANOVA analyses.

CAINS scores conformed to a bimodal distribution, therefore, correlation analyses were performed in SCZ patients only. The relationship between CAINS scores (motivation and pleasure, expression), neurocognitive measures (memory and executive function composite scores, NAART), physiological stress measures (RSA, HR, HP before, during and after stress), were correlated with the early frontal theta and late parietal beta ERSP responses for aversive stimuli (collapsed over positive and negative framing conditions) before and after stress using Spearman's rank correlation analysis. Additionally, positive, negative and general PANSS subscales were correlated with ECG measures (RSA, HR, HP) before, during and after stress and early frontal theta and late parietal beta activity for aversive stimuli before and after stress.

Results

Demographics, Neurocognitive and Clinical Assessments

Age, handedness, and average parental education did not differ between control and SCZ patients ($P > 0.05$); however, controls received more years of education than patients ($F(1,41) = 14.53$, $P < 0.001$) and groups marginally differed by race (X^2 (3, $n = 42$) = 7.13, $P = 0.07$). Patients expressed greater negative symptom severity measured by CAINS motivation and pleasure and expression scores compared with controls, and demonstrated an inferior performance on all neurocognitive assessments (Fs > 6, Ps < 0.05) (*Table 3.1*). Furthermore, groups did not differ on subjective measures of stress (DSI, PSS) and affect (PANAS, ERQ), or self-reported drug and alcohol use (AUS/DUS) ($P > 0.05$) (*Table 3.2*).

Stress Reactivity (SSR, ECG)

Subjective Stress/Affect Rating (SSR)

Main effects of Affect ($F(1.74, 60.73) = 58.00$, $P < 0.01$, $\eta_p^2 = 0.62$) and Time ($F(3.18, 111.37) = 17.43$, $P < 0.01$, $\eta_p^2 = 0.33$) and a Time X Affect interaction ($F(7.63, 267.20) = 14.89$, $P < 0.001$, $\eta_p^2 = 0.30$) indicated differential experiences of affect which fluctuated throughout the EEG session. Stress exposure elicited changes in subjective measures of affect, as planned contrasts demonstrated a significant linear increase in subjective affect rating between "before stress" and "after stress" ($F(1, 35) = 10.39$, $P < 0.01$, $\eta_p^2 = 0.23$), and "after stress" and "recovery 1" time-points ($F(1, 35) = 52.14$, $P < 0.001$, $\eta_p^2 = 0.60$). Pairwise comparisons revealed that ratings of "happy" deteriorated ($P < 0.001$) while ratings of "stressed" ($P < 0.01$) and "irritated" ($P < 0.01$) increased following stress. Additionally, SCZ patients exhibited greater levels of "unhappy" during the "recovery 2" time-point than controls ($P = 0.03$) (*Figure 3.5*).

Positive and Negative Affect Schedule

Ratings for positive affect were greater than for negative affect ($F(1, 35) = 48.95$, $P < 0.001$, $\eta_p^2 = 0.58$), and ratings significantly decreased following stress ($F(1, 35) = 18.69$, $P < 0.001$, $\eta_p^2 = 0.35$). Furthermore, stress exposure reduced positive affect disproportionately, reflected in a Affect X Time interaction ($F(1, 35) = 25.63$, $P < 0.001$, $\eta_p^2 = 0.42$).

Heart Period

Heart period (HP) decreased significantly during stress exposure ($F(2.48, 69.49) = 3.88$, $P = 0.02$, $\eta_p^2 = 0.12$) according to a quadratic trend ($F(1, 28) = 5.69$, $P = 0.02$, $\eta_p^2 = 0.17$), thus validating the stress manipulation. The pattern of HP variation differed significantly between groups ($F(1, 28) = 9.16$, $P = 0.01$, $\eta_p^2 = 0.25$), with patients demonstrating a blunted response to the acute stressor. Controls exhibited a stronger decrease in HP from "rs1" to "TSST_prep" compared with patients ($F(1, 28) = 7.49$, $P = 0.01$, $\eta_p^2 = 0.21$), represented in planned within-subject contrasts (*Figure 3.6a*).

Heart Rate

A main effect of heart rate was found ($F(2.83, 76.30) = 3.61$, $P = 0.02$, $\eta_p^2 = 0.12$) conforming to a quadratic trend ($F(1, 27) = 4.68$, $P = 0.04$, $\eta_p^2 = 0.15$), which differed by group ($F(1, 27) = 5.63$, $P = 0.03$, $\eta_p^2 = 0.17$). Planned within-subjects contrasts of heart rate over time did not produce any significant results (*Figure 3.6b*).

Respiratory Sinus Arrhythmia

Planned contrasts demonstrated a significant difference in the slop of RSA between groups ($F(1, 27) = 4.68$, $P = 0.04$, $\eta_p^2 = 0.15$), while within-subject contrasts suggest that the difference between RSA at baseline and the RSA measured at recovery 3 was greater for SCZ patients ($F(1, 27) = 11.10$, $P < 0.01$, $\eta_p^2 = 0.29$). No significant main effects of Group or RSA were found (*Figure 3.6c*).

Combined Physiological Measurements

Acute stress exposure induced changes in ECG (RSA, HP, HR) measurements ($F(1.70, 61.18) = 44.44$, $P < 0.001$, $\eta_p^2 = 0.55$) which differed significantly by group ($F(1.70, 61.18) = 6.30$, $P = 0.01$, $\eta_p^2 = 0.15$). Patients exhibited heightened stress reactivity with greater HR and reduced HP before (HR, $F(1, 36) = 8.73$, $P = 0.01$, $\eta_p^2 = 0.20$; HP, $F(1, 36) = 8.45$, $P = 0.01$, $\eta_p^2 = 0.19$) and after (HR, $F(1, 36) = 6.03$, $P = 0.02$, $\eta_p^2 = 0.14$; HP, $F(1, 36) = 6.25$, $P = 0.02$, $\eta_p^2 = 0.15$) stress, along with reduced baseline RSA levels ($F(1, 36) = 6.52$, $P = 0.02$, $\eta_p^2 = 0.15$) (*Figure 3.6d*).

Emotional Oddball Framing Task

Behavioral Results

Response latency was greater overall for neutral relative to aversive images before stress ($F(1, 37) = 9.83$, $P < 0.01$, $\eta_p^2 = 0.21$), except for the animal framing condition, in which a Framing X Stimulus interaction indicated reaction times (RTs) were greater for aversive stimuli ($F(1.45, 53.63) = 3.51$, $P = 0.05$, $\eta_p^2 = 0.09$). Increased RTs were observed during the negative condition compared with the animal and positive conditions before stress ($F(2, 74) = 8.46$, $P < 0.001$, $\eta_p^2 = 0.19$). While the same pattern of enhanced RTs for neutral stimuli persisted following the stress manipulation ($F(1, 33) = 11.96$, $P < 0.01$,

η_p^2 = 0.27), an overall reduction in RT (F(1, 33) = 11.80, P < 0.01, η_p^2 = .26), especially for the negative condition (F(1, 33) = 4.45, P = 0.04, η_p^2 = 0.12), was observed. Accuracy was greater for aversive stimuli during the negative framing condition compared with neutral stimuli (F(1, 37) = 6.98, P = 0.01, η_p^2 = 0.16); however, correct categorization of neutral stimuli during the negative condition became more challenging after stress exposure (F(1, 37) = 8.93, P = 0.01, η_p^2 = 0.19) (*Table 3.3*).

Self-Assessment Manikin (SAM) Ratings

A Stimulus X SAM rating interaction confirmed that aversive images were rated as more negative and arousing than neutral images (F(1, 35) = 70.66, P < 0.001, η_p^2 = 0.67). A Group X Stimulus interaction suggested that patients rated aversive images as being more negative, yet less arousing than control participants (F(1, 35) = 5.14, P = 0.03, η_p^2 = 0.13) (*Table 3.3*).

ERP

A significant main effect of Stimulus for P3 (F(1, 39) = 13.12, P < 0.01, η_p^2 = 0.25) and LPP (F(1, 39) = 6.51, P = 0.02, η_p^2 = 0.14) confirmed that the response to aversive stimuli was greater than that for neutral stimuli during the neutral (animal) framing condition (*Figure 3.7*). A Stimulus X Framing interaction indicated a unique enhancement of the P3 amplitude for aversive stimuli compared to neutral stimuli during the animal framing condition, which was not observed for negative and positive framing conditions before stress (F(2, 78) = 4.99, P = 0.01, η_p^2 = 0.11). A Stimulus main effect revealed the LPP amplitude for aversive stimuli was greater than the amplitude for neutral stimuli across animal, positive and negative framing conditions before stress (F(1, 39) = 9.28, P < 0.01, η_p^2 = 0.19), and positive and negative conditions after stress (F(1, 37) = 11.30, P < 0.01, η_p^2 = 0.23). No additional main effects or interactions were found, including group or stress effects for P3 or LPP components (Ps > 0.05) *(Figure 3.8)*.

EEG

A significant main effect of Group for theta was found indicating reduced early frontal theta ERSP for SCZ patients compared with controls before stress (F(1, 39) = 6.52, P = 0.02, η_p^2 = 0.14) and after stress (F(1, 37) = 5.15, P = 0.03, η_p^2 = 0.12). Planned pairwise comparisons demonstrated that patients exhibited significant reductions in theta ERSP specifically for aversive stimuli compared with controls

during positive (F(1, 39) = 6.33, P = 0.02, η_p^2 = 0.14) and negative (F(1, 39) = 7.30, P = 0.01, η_p^2 = 0.16) conditions before stress (*Figure 3.9*). An effect of Stress (F(1, 37) = 4.22, P = 0.05, η_p^2 = 0.10) and a Stress X Stimulus interaction (F(1, 37) = 5.05, P = 0.03, η_p^2 = 0.12) indicated that theta ERSP was greater after stress exposure, especially for aversive stimuli *(Figure 3.10)*.

A decrease in beta ERSP, or event-related desynchronization (ERD), was found for neutral and aversive stimuli across all conditions for SCZ patients and controls. A Stimulus effect for beta suggested that beta ERD was stronger for emotional stimuli before (F (1, 39) = 5.29, P = 0.03, η_p^2 = 0.12) and after stress (F(1, 37) = 16.43, P < 0.001, η_p^2 = 0.31). Pairwise comparisons revealed patients exhibited reduced beta ERD for aversive stimuli during the negative framing condition before stress (F(1, 39) = 4.78, P = 0.04, η_p^2 = 0.11) (*Figure 3.11*). A Stimulus X Stress interaction was found indicating reduced beta ERD for neutral stimuli after stress (F(1, 37) = 4.06, P = 0.05, η_p^2 = 0.10). No additional main effects or interactions were found (*Figure 3.12*).

Relationship Between Clinical, Neurocognitive, Stress and EEG Activity

Spearman's rank correlations revealed that reduced frontal theta for aversive stimuli before stress was associated with inferior memory performance (r_s = 0.47, P = 0.04, N = 19) and enhanced CAINS motivation and pleasure symptom severity (r_s = -0.65, P = 0.01, N = 17) in SCZ patients. Increased parietal beta activity (decreased beta ERD) for aversive stimuli before stress was related to decreased HP and RSA, and increased HR (indicative of greater stress levels) before (HP, r_s = -0.56, P = 0.01, N = 19; RSA, r_s = -0.58, P = 0.01, N = 19; HR, r_s = 0.56, P = 0.01, N = 19) and during stress (HP, r_s = -0.59, P = 0.01, N = 19; RSA, r_s = -0.59, P = 0.01, N = 19; HR, r_s = 0.56, P = 0.01, N = 19). PANSS symptom severity on the positive subscale was associated with decreased HP before (r_s = -0.67, P = 0.002, N = 19), during (r_s = -0.56, P = 0.01, N = 19) and after (r_s = -0.46, P = 0.05, N = 19) stress, and enhanced parietal beta for aversive stimuli after stress (r_s = 0.47, P = 0.05, N = 19) (selected correlations are presented in *Figure 3.13*).

Discussion

The effect of psychosocial stress on electrophysiological correlates of ER was investigated in patients with SCZ and healthy volunteers using a multimodal design. SCZ patients demonstrated deficiencies in employing frontal control mechanisms to dampen affective neural circuits, evident by a deficit in frontal theta and weakened beta desynchronization for aversive stimuli. Enhancement of theta and reduced beta ERD accompanied the stress manipulation, indicative of a shift to a more arousing, excitable state and a disruption in affective network efficiency. Along with a heightened stress profile at baseline, patients exhibited a maladaptive stress response which was associated with CAINS symptoms of expression and motivation and pleasure, positive symptom severity, and beta excitability. This is the first study to examine the effect of psychosocial stress on electrophysiological correlates of emotional framing in patients with schizophrenia and control individuals, and to correlate peripheral physiological measures of stress with oscillatory EEG indices of ER.

Validation of the psychosocial stress test (TSST) protocol to effectively elicit a stress response in all participants was established, as evident by contradictory shifts in subjective happiness and stress, and an autonomic profile of sympathetic activation and parasympathetic inhibition with increased HR, and decreased HP. Despite similar subjective ratings of stress and affect experience throughout the stress manipulation, patients exhibited enhanced baseline levels of stress, with reduced RSA and HP and increased HR. The aberrant physiological measures of stress at baseline in patients may reflect impaired parasympathetic input to the heart, consistent with a previous report of disrupted heart rate variability (HRV) in SCZ patients (Castro et al., 2008). Additionally, patients demonstrated blunted HP and HR response patterns to stress exposure, in accordance with hypotheses and previous reports of blunted cortisol and electrodermal responses in SCZ patients (Brenner et al., 2009). However, the unique progression in RSA from baseline to post-stress recovery in patients was unexpected and inconsistent with previous reports of a delayed recovery of HRV in patients (Castro et al., 2008). In contrast to Castro and colleagues' assessment of HRV during 14 minutes of stress and recovery, the current study tracked changes in RSA throughout the entire three-hour recording session, which along with differential analysis parameters for RSA and HRV, could account for the discrepancy in results. Controls exhibited successful RSA suppression during stress and following the stress manipulation, indicating appropriate vagal

withdrawal to concentrate mobilization and defensive efforts (Porges, 2007). Enhanced RSA and reliable RSA suppression have been associated with superior executive functioning and cognitive performance (Hansen et al., 2003, 2004), social engagement (Hamilton et al., 2014) and emotion regulation processes (Appelhans and Luecken, 2006; Lane et al., 2009). In patients, reduced baseline RSA levels and the inability to suppress RSA following stress may reflect a maladaptive stress response, and index deficient autonomic flexibility and neural regulation of visceral state. Consistent with the Jacksonian principle of dissolution, when higher order myelinated vagal motor pathways are ineffective at disinhibiting the vagal influence to support calm, social behaviors, an unmyelinated vagal component dominates, optimizing defensive, avoidance behaviors (Porges, 2007). Accordingly, a maladaptive stress response was found to correlate with inferior executive function and heightened symptoms of expression and positive symptom severity in patients, consistent with the association between autonomic dysregulation and psychiatric symptoms (Henry et al., 2010).

Emotional regulation strategies require frontal engagement to manipulate the perception of evocative stimuli and determine whether the image was consistent with the contextual framework provided, reflected in elevated frontal theta oscillatory activity (Ertl et al., 2013). Examining oscillatory activity underlying fronto-limbic-mediated ER processes is a valuable method for discerning network efficiency, as the synchronization of neural oscillations support the integration of information in neural networks. While the exact function of theta during ER is unclear, theta has been proposed to underlie PFC-dependent cognitive control and to be responsible for coordinating attentional resources for specific task demands (Cavanagh and Frank, 2014). The task employed was not sufficiently robust to demonstrate significant framing effects; however, framing appeared to modify the electrophysiological response to aversive and neutral stimuli, reflected in the reduced LPP amplitude during the positive condition compared to the negative condition before stress. Furthermore, frontal theta activity was greater during the positive framing of aversive stimuli in controls as predicted, despite not reaching significance. Accordingly, theta activity may support enhanced cognitive and attention demands required to down-regulate the emotional response. Neutral images and aversive images framed in the positive condition required additional attentional resources, as they were not consistent with the contextual frame, resulting in minimal increases in the P3 amplitude and increased behavioral response latency for neutral images

during the emotional framing tasks. The P3 component is more susceptible to changes in attentional demand relative to the LPP amplitude (Hajcak et al., 2007; Kleih et al., 2010; Polich, 2007), which could explain why marginal emotional framing effects were found for the LPP but not for the P3 component. An independent component analysis could be employed to further differentiate between P3 and LPP and underlying oscillatory activity. Without first establishing clear framing effects before stress, it was difficult to determine whether acute stress exposure disrupted the regulation of ERP amplitude in response to aversive stimuli. Thus, stress influences on the ERP correlates of emotional framing will require further investigation in SCZ patients.

Despite minimal framing modifications of the EEG signal in the emotional oddball framing paradigm, valence discrimination was intact. The animal framing paradigm resembled a traditional oddball paradigm with novel infrequent aversive targets and frequent neutral stimuli, and appropriately elicited enhanced P3 and LPP amplitudes for aversive stimuli relative to neutral stimuli. The greater ERP responses for aversive stimuli reflected the appropriate cognitive elaboration of aversive, emotional events. However, there was not a significant difference between the P3 response for aversive and neutral stimuli in the emotional framing conditions. Given these results, it is evident that valence discrimination diminished with the introduction of emotional framing cues, possibly indicating that the emotional context augmented the electrophysiological response to neutral images. Furthermore, the response latency for aversive stimuli was greater than that for neutral stimuli in the neutral condition, which was not found during the emotional framing tasks, further supporting the differential effect of emotional framing on the electrophysiological response to neutral stimuli.

Participants appropriately rated the aversive stimuli as being more negative and arousing than the neutral stimuli. However, compared to control participants, patients rated aversive images as being more negative, yet less arousing, indicating an aberrant arousal response. The elevated “in-the-moment” ratings of negative emotions when exposed to unpleasant stimuli is consistent with previous reports of valence attribution in SCZ patients (Cohen and Minor, 2008; Strauss and Gold, 2012), though it is unclear why patients experienced the aversive images as being less arousing. It is possible that stress exposure influenced the arousal rating, as the SAM assessment was completed at the end of the session. The low

subjective rating of arousal for aversive stimuli is consistent with the inability to suppress RSA observed in patients, further promoting maladaptive arousal and behavioral states. Future studies should determine whether SAM ratings are influenced by stress and framing condition.

SCZ patients exhibited an overall deficit in frontal theta activity, especially for aversive stimuli, before and after the stress manipulation. Reduced frontal theta oscillatory activity may indicate deficient neuronal participation and synaptic connectivity, and aberrant frontal connectivity, as slow-wave oscillations are critical for integrating information processed in remote brain regions (Uhlhaas and Singer, 2014). Additionally, reduced theta oscillations may indicate a global deficit in cortical communication, consistent with schizophrenia being a disconnection syndrome (Fitzsimmons et al., 2013; Friston, 1999). Frontal theta activity is proposed to underlie PFC and ACC engagement during working memory, cognitive control and performance monitoring (Gärtner et al., 2014; Gevins et al., 1997; Onton et al., 2005), and these regions have been reported to be functionally and structurally impaired in SCZ (van der Meer et al., 2014). Therefore, it is not surprising that deficiencies in theta activity were observed in SCZ patients, and is consistent with previous reports of aberrant theta oscillatory activity in recent onset SCZ patients (Andersen et al., *In preparation*) and adolescents at familial risk for SCZ (Donkers et al., 2011). Furthermore, the observed relationship between greater frontal theta activity in response to aversive stimuli during an emotional oddball framing task and superior memory performance, higher IQ and reduced symptoms of expression and motivation provide support for theta playing a fundamental role in PFC-dependent attentional processing and cognitive control. Consistent with these results, theta has previously been reported to be associated with superior working memory and executive functioning (Berger et al., 2016), to support higher working memory load (Jensen and Tesche, 2002), and to implement ER strategies (Ertl et al., 2013). Accordingly, theta oscillatory activity may be a critical neurobiological marker for frontal integrity and PFC-dependent cognitive symptoms of psychopathology. However, a spontaneous predominance of slow-wave (i.e., theta) activity relative to fast-wave (i.e., beta) has been proposed to underlie inferior cortical control over subcortical affective processes at rest (Morillas-Romero et al., 2015; Schutter et al., 2006). The inconsistent results most likely result from different theta measurements (i.e., induced phase-invariant or evoked phase-locked) and collection parameters (spontaneous activity at rest, or due to task manipulation).

Following stress exposure, frontal theta activity increased, especially for aversive stimuli. Heightened tonic theta activity has been proposed to underlie deficient regulation of brain arousal, indicating that greater frontal theta activity following stress may reflect the elevated arousal state and the weakened regulation of brain state (Arns and Kenemans, 2014; Morillas-Romero et al., 2015). Consistent with these results, enhanced theta activity is found to accompany increasing task demands (Jensen and Tesche, 2002), which are considered stressful in experimental settings (Allen et al., 2014), and to subserve cognitive reappraisal in emotion regulation paradigms (Ertl et al., 2013). Stress has been reported to reduce frontal midline theta oscillations during working memory tasks (Gärtner et al., 2014), yet the effect of stress on electrophysiological correlates of ER has not been previously reported. While PFC-dependent working memory is impaired and associated theta is reduced under stressful conditions, acute stress exposure heightens arousal state, possibly promoting exaggerated attention to, and cognitive processing of, emotional events, reflected in the increased theta observed in the current study. Consequently, stress may modify theta differently according to the task employed. However, it is also possible that the discrepancy in results could be accounted for by the method of extracting theta power. The current study examined non-phase locked changes in spectral power with respect to event onset, whereas, Gärtner and colleagues extracted phase-locked event-related changes in EEG power, which may explain the different results. Consistent with increased theta accompanying greater workload and successful ER, increased theta may also represent a compensatory mechanism to allow for the challenging implementation of ER strategies under stressful conditions and increased arousal states.

Along with frontal theta deficiencies, SCZ patients also expressed aberrant parietal beta activity, with weakened beta desynchronization in response to aversive stimuli, consistent with previous reports of beta ERD and emotional processing in SCZ (Csukly et al., 2016). The reduced beta ERD in patients possibly reflects impaired engagement and connectivity within the insula-centered salience network, and disruptions in the delicate balance of excitatory and inhibitory activity. Beta oscillatory activity signals the initial requirement for heightened attentional resources for novel or salient stimuli to prepare the shift to a gamma-dominated attention state (Wróbel 2000). Furthermore, beta activity is associated with stimulus-driven salience (Kisley and Cornwell, 2006), and increased beta activity has been found in response to negative valence high arousal eliciting images (Güntekin and Başar, 2010) and angry faces (Güntekin

and Basar, 2007) during a passive viewing task, and for relevant target images (Güntekin et al., 2013). The stronger beta ERD for aversive stimuli relative to neutral stimuli found in the current study may support appropriate stimulus attribution and motivated attention, and is consistent with previous research (Csukly et al., 2016). For control participants, enhanced parietal beta ERD for aversive stimuli in the emotional framing paradigm may have prevented alternative processes from interfering with the frontal engagement required to appropriately process the stimuli according to the framing context. Additionally, a magnetoencephalography (MEG) study found that SCZ patients revealed an atypical increase in beta activity in the insula for irrelevant stimuli, further supporting beta's imperative role in salience processing and dysfunction of the salience network in schizophrenia (Liddle et al., 2016). In SCZ patients, aberrant beta activity may disrupt the initial detection and attribution of salience, causing impaired perceptual integration, deficient evaluation of stimuli and inappropriate response selection.

Furthermore, neurotransmitter systems, including dopamine and GABA, are proposed to coordinate beta activity, suggesting that aberrant beta activity may reflect disruptions in neurotransmitter systems. Dopamine is of particular interest for its role in modifying beta activity to support coordination of neural activity in cortical-basal ganglia networks (Jenkinson and Brown, 2011; Leventhal et al., 2012). Consequently, hyperdopaminergic transmission in SCZ may influence beta activity, causing abnormal salience attribution and distorted perceptions of reality. Along with salience processing, beta is associated with inhibitory cortical transmission; therefore, the weakened beta desynchronization observed in the current study may indicate a disruption in the excitability-inhibitory balance, mediated by GABAergic interneuron transmission, resulting in heightened neural excitability (Liddle et al., 2016). Aberrant beta activity exhibited in patients may indicate inferior GABAergic transmission, as GABA is responsible for generating beta oscillations (Liddle et al., 2016).

Following stress exposure, neutral stimuli evoked reduced parietal beta ERD for both groups, indicating a disruption in salience attribution and arousal, and is consistent with aberrant limbic activation following stress in neuroimaging studies (Oei et al., 2012). Increased beta has been reported in response to sleep deprivation and the Stroop test when used as experimental stressors (Alonso et al., 2015), and during a noise stressor (Banis et al., 2014), which along with the current findings, implicate beta in

regulating arousal state. Impaired neural regulation of the vagal brake and the inability to alter visceral state, indexed by reduced RSA and HP and increased HR, was related to weakened beta ERD. The heightened beta excitability (reflected in reduced ERD) may be suggestive of a maladaptive arousal state before stress, which was further associated with increased motivation and pleasure symptoms, and positive symptom severity in SCZ patients. The relationship between RSA, executive function and social engagement has been demonstrated previously (Appelhans and Luecken, 2006; Hamilton et al., 2014; Hansen et al., 2003, 2004; Lane et al., 2009; Porges, 2007); however, to my knowledge, this is the first study to confirm a relationship between aberrant stress reactivity, clinical symptom severity and dysregulated electrophysiological correlates of affective processing. In addition to supporting inappropriate mobilization and defensive behaviors, a maladaptive stress response may subserve impaired oscillatory activity, which compromises the integration of neural information, shifts the excitatory-inhibitory balance, and ultimately results in network dysconnectivity and cognitive and behavioral interference. Aberrant beta activity may reflect a global brain state of heightened arousal, potentially caused by maladaptive stress regulation exhibited in patients in the absence of stress or in response to acute stress exposure, which interferes with top-down, slow-wave dominated frontal processes (Engel and Fries, 2010).

External representations of the environment are processed through the central autonomic network, comprised of frontal and limbic regions, including PFC, ACC, insula and amygdala, which interact with visceral afferents conveying information of internal physiological states to adjust arousal and select appropriate behavioral and emotional responses (Benarroch, 1993). Additionally, a significant coupling between natural cortisol perturbations and beta activity is reported, indicating an intricate relationship between the HPA stress system and oscillatory regulation of arousal state (Chapotot et al., 1998). The relationship between deficient frontal theta, aberrant parietal beta and maladaptive physiological measures of stress may reflect a compromised interface of the central autonomic network and visceral afferents to regulate autonomic flexibility. Furthermore, the insula has a proposed role in coordinating autonomic, visceral and homeostatic states, and the subjective experience of salience, providing additional evidence that beta abnormalities may subserve the atypical insula connectivity and

activation patterns found in schizophrenia (Palaniyappan et al., 2012b; Uddin, 2015; Wylie and Tregellas, 2010).

A number of limitations should be addressed in future studies. Notably, the current study restricted recruitment to males because of the significant interaction between gonadal and stress systems, sex differences in the psychosocial stress response (Foley and Kirschbaum, 2010; Kirschbaum et al., 1992), and sex disparities in the neural correlates of affective processing (Gardener et al., 2013; Stevens and Hamann, 2012; Whittle et al., 2011). Extensive sex differences in neural correlates of affective processing have been reported, including enhanced negative emotionality in females, thus representing the importance of considering sex in elucidating the neurobiological substrates of emotion (Gardener et al., 2013; Stevens and Hamann, 2012). Furthermore, it has been demonstrated that men and women differentially respond to emotion regulation strategies following stress exposure, suggesting that the interaction between stress and sex influences emotion regulation ability (Kinner et al., 2014; Kogler et al., 2014). Despite the profound interest in examining the interaction between sex, stress and emotion, the current study did not have sufficient subject numbers to control for sex, let alone menstrual cycle phase and contraceptive use. Elucidating sex differences in the interaction between stress and affective processing would be crucial for developing gender-unbiased, novel treatment approaches.

As mentioned previously, the emotional oddball framing paradigm did not produce a significant effect of framing. The emotional oddball framing paradigm has been reported previously to reliably down-regulate the LPP response to aversive stimuli with positive contextual cues in healthy college students (Kisley et al., 2011); however, there are several notable differences in the task design which could account for the discrepancy in results. The initial study (Kisley et al., 2011) was a between-subjects design, where the participants were either assigned to a positive or negative condition, and included positive images in the task design. I chose to eliminate the positive images because there are no significant framing effects found for positive stimuli and ER effects are stronger for aversive stimuli (Kisley et al., 2011). Additionally, the current study used 120 neutral and aversive target stimuli in contrast to the 30 (6 target) images used in the initial study, which could have contributed to the heightened P3 amplitude for neutral stimuli. Future studies could implement an alternative ER paradigm requiring more

cognitive effortful reappraisal strategies to regulate emotional response, such as the task used in Strauss et al., 2013. While there were no significant framing effects in the current study, differential responses to aversive and neutral stimuli before and after a stress manipulation were still examined. Additionally, SAM ratings were not given after each framing condition because of time constraints; however, this repeated SAM administration would be necessary to determine any differences in arousal and valence ratings due to the framing or stress manipulation.

Future studies examining stress effects on electrophysiological correlates of affective processing should include the analysis of intertrial phase coherence as an additional measure of neural synchrony. Source localization methods and concurrent fMRI-EEG studies could also be employed to further define the anatomical substrates of the EEG oscillatory activity. The effect of stress on resting EEG state is still being explored and will provide evidence for differential effects of stress on spontaneous and evoked theta and beta activity.

Finally, medication exposure, smoking and caffeine consumption, and body-mass-index are all thought to modify peripheral autonomic output. While participants were instructed to refrain from smoking and consuming caffeine prior to the study session, these behaviors could have influenced heart rate parameters of stress reactivity. Medication exposure is a common issue in studies with SCZ patients as it is challenging to disentangle the medication effects from the experimental results without restricting medication use. However, high-potency antipsychotics and novel agents used by the majority of patients have only minimal effects on heart rate parameters, consequently, it seems unlikely that the current physiological results are attributable to medication use (Bar et al., 2005; Boettger et al., 2006). Despite evidence that medication exposure alters ERP components (Coburn et al., 1998; Gonul et al., 2003), oscillatory dysfunction, at least in gamma frequency, seems to be maintained regardless of medication status (Gallinat et al., 2004). Future studies could look at first-episode psychosis with patients without chronic medication exposure to further understand the influence of anti-psychotic medications on oscillatory activity, or investigate first-degree relatives to determine vulnerability.

Oscillations and their synchronization are important mechanisms by which brain regions interact, therefore, providing a valuable tool for elucidating the efficiency of fronto-limbic circuitry in regulating

affective and stress responses. This is the first study, to my knowledge, to investigate electrophysiological correlates of affective network efficiency following a stress manipulation in patients with SCZ. Advancing the understanding of neural mechanisms underlying ER and the stress response and how they interact provides valuable insight on homogeneous symptom dimensions shared across neuropsychiatric disorders. The relationship between aberrant EEG indices of ER, impaired stress reactivity and enhanced symptom severity may motivate future studies to examine therapeutic and intervention approaches targeting stress and ER to alleviate symptom pathology 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 alleviate persistent negative and cognitive symptoms.

3.3 Future Directions

To further elucidate the effect of stress on the integrity of fronto-limbic oscillations and efficiency of the circuitry to respond and adapt to stress, future studies could analyze the resting state EEG recordings directly before and immediately after the stress manipulation and at the termination of the session. Using frequency decomposition to extract spontaneous theta and beta power, the slow wave – fast wave (theta/beta) ratio could be evaluated during the resting state recording before and after the stress manipulation, and compared to previous studies suggesting that high ratios may reflect a motivational imbalance in cortical control and subcortical affective networks (Morillas-Romero et al., 2015). Additional examination of cross-frequency coupling between slow and fast frequencies during resting state and during the emotional oddball framing paradigms would be informative in understanding the regulation of cortical state and maintenance of the dynamic excitatory-inhibitory balance. Furthermore, separating theta and beta frequencies into high and low components could also help refine the contribution of each band.

While the current project focused on the influence of stress on theta and beta oscillatory activity for their roles in salience and affective processing, it would be interesting to expand the research scope and investigate changes in alpha activity due to stress. Alpha has been related to inhibition of task-irrelevant processing and maximal over occipital cortex during relaxed state (Uhlhaas et al., 2008).

However, frontal alpha asymmetry has also been examined as an important index for affective state and efficient arousal and regulation. Goodman and colleagues (2013) found that elevations in alpha asymmetry were associated with weakened eye-blink startle response (proposed to underlie ER) during heightened stress situations. In addition to extracting ERSP, which is time-locked but not phase-locked, future studies could also evaluate phase-locked event-related evoked power and phase consistency or intertrial (phase) coherence (ITC), an additional measure of neural synchrony (Roach and Mathalon, 2008) to further characterize oscillations and their synchronization in patients with SCZ. Cross-channel coherence can be used to examine oscillatory consistency or connectivity between scalp locations, especially between frontal and parietal locations, or between cortical and subcortical sources of the EEG signal using source localization algorithms.

Salivary cortisol and alpha amylase were collected throughout the EEG session to monitor stress reactivity and HPA axis function; however, data were not analyzed because of financial limitations. Cortisol and alpha amylase would provide crucial information to characterize the stress response as cortisol is released in response to HPA stimulation and alpha amylase is an index of sympathetic system activity, not currently assessed with the physiological heart rate parameters.

Results from the current study provide valuable information about the oscillatory activity underlying affective and salience processing and how they are affected by stress in SCZ patients and healthy controls. However, the emotional oddball framing paradigm did not produce reliable neural regulation of the electrophysiological response to aversive stimuli. Future studies could employ a more robust cognitive reappraisal task, similar to Horan and colleagues (2013), to establish differences in ER and determine if acute psychosocial stress would influence the ability to utilize ER strategies and the electrophysiological correlates underlying ER. It would also be interesting to administer an emotional go-no-go task before and after the TSST stressor to elucidate the affective interference on cognitive processing and inhibition processes.

While this study was limited to males with schizophrenia, deficiencies in ER are not unique to schizophrenia and span multiple neuropsychiatric disorders. The current study protocol, with the stressor sandwiched between two ER tasks, could be applied to other neuropsychiatric disorders and during

pivotal stages of development to investigate the impact of stress on implementing emotion regulation strategies, integral to the effectiveness of cognitive behavioral therapy. Moreover, this protocol should be applied to women with schizophrenia in order to examine sex-dependent disparities in stress reactivity and its effect on electrophysiological correlates of affective processing. Despite the important revelations of the current study in demonstrating the deficiency of fronto-limbic neural oscillatory activity and maladaptive stress responses in patients with schizophrenia revealed in the current study, there are still many unanswered questions that excite further research exploration.

3.4 Significance

Cognitive behavioral therapy is a fundamental therapeutic approach for alleviating the persistent, debilitating negative and cognitive symptoms of SCZ, and it is reliant on emotion regulation strategies that are more difficult to implement under stress. This is the first study to elucidate the effects of stress on the electrophysiological correlates of emotional framing, assessing an important aspect of ER, in SCZ patients and controls to identify therapeutic targets for improving treatment efficacy. The study advances the understanding of neural mechanisms underlying ER and the stress response and how they interact, and it provides valuable insight on homogenous symptom dimensions shared across multiple neuropsychiatric disorders. Furthermore, the study confirmed that theta oscillatory dysfunction is a potential biomarker for frontal impairment, while beta activity may index an excitatory-inhibitory imbalance promoting aberrant salience processing. These neurophysiological biomarkers may be useful in future studies examining innovative therapeutic and intervention approaches targeting stress and ER to alleviate symptom pathology and prevent the precipitation of symptoms in vulnerable individuals. Specifically, results suggest that therapeutic approaches targeting the stress response, including mindfulness training and stress mediation therapy, may restore fronto-limbic oscillatory activity to facilitate cognitive therapies, and may be valuable in combating resistant negative and cognitive symptoms of schizophrenia. Oscillations at different frequencies reflect global cortical state, suggesting that transcranial magnetic stimulation (TMS) or transcranial current stimulation (TCS) may manipulate oscillatory activity to encourage effective neural processing. Targeting theta and beta activity therapeutically may improve fronto-limbic efficiency and support the cognitive therapies reliant on ER to ameliorate symptom severity.

Chapter 3.2 Tables

Table 3.1. Demographic and Clinical Characteristics of Study Groups

Demographic Information	**SCZ Patients** (N=21)	**CON group** (N=21)	**Statistic**
Age	25.81 ± 4.25	23.81 ± 4.61	F(1,41) = 2.14
Handedness (r/l)	17/4	18/3	F(1,41) = 0.16
Education (years)	13.24 ± 1.76	15.24 ± 1.64	F(1,41) = 14.53**
Avg parental education (years)	15.38 ± 2.38	15.89 ± 2.71	F(1,33) = 0.34
Race			$X^2(3) = 7.13$
White	9	11	
Black	11	4	
Asian	1	5	
Hispanic	0	1	
Clinical			
CAINS-MAP	10.53 ± 5.94	2.39 ± 3.20	F(1,34) = 25.89**
CAINS-EXP	2.82 ± 3.11	0.44 ± 0.78	F(1,34) = 9.90*
Illness Duration	6.11 ± 5.23		
PANSS (total score)	57.90 ± 14.80		
Positive subscale	15.05 ± 5.07		
Negative subscale	14.05 ± 4.63		
General subscale	28.8 ± 7.72		
Drug & Alcohol Use (AUS/DUS)			
Tobacco	1.0 ± 1.10	0.58 ± 0.84	F(1,34) = 1.66
Alcohol	1.10 ± 1.24	1.84 ± 1.38	F(1,34) = 3.03
THC	0.94 ± 1.73	0.79 ±1.23	F(1,34) = 0.09

Abbreviations: CAINS-MAP: Clinical Assessment Interview for Negative Symptoms- Motivation and Pleasure Scale; CAINS-EXP: CAINS-Expression Scale; PANSS: Positive and Negative Syndrome Scale

*$P < 0.05$. **$P < 0.001$.

Table 3.2. Neurocognitive Assessments and Questionnaires

	SCZ Patients	CON Group	Statistic
Neurocognitive Assessments			
CPT-IP (Avg D-Prime)	2.73 ± 0.96	3.38 ± 0.64	F(1,37) = 6.00*
NAART (# of words)	29.55 ± 11.88	45.2 ± 6.99	F(1,39) = 25.80**
Visuospatial Sequencing Test (tot. correct)	15.38 ± 3.07	18.81 ± 2.68	F(1,41) = 14.86**
Auditory Verbal Learning Test (tot. recalled)	21.16 ± 5.95	28.89 ± 5.17	F(1,37) = 18.31**
Auditory Verbal Learning Test (tot. rec. after delay)	11.67 ± 3.00	14.05 ± 1.07	F(1,41) = 11.693*
Stroop Interference Score[a]	9.40 ± 7.73	3.71 ± 2.53	F(1,41) = 10.27*
Questionnaires			
Perceived Stress Scale[b]	17.50 ± 7.01	15.05 ± 4.96	F(1,38) = 1.62
Daily Stress Inventory[c]	2.83 ± 1.30	2.67 ± 0.84	F(1,38) = 0.21
ERQ Reappraisal[d]	27.05 ± 7.62	29.95 ± 6.45	F(1,39) = 1.70
ERQ Suppression[e]	14.79 ± 3.60	13.86 ± 5.85	F(1,39) =0.36

Abbreviations: CPT-IP: Continuous Performance Test- Identical Pairs, Average Sensitivity Index (D') for 2,3, and 4 digit trials; NAART: North American Adult Reading Test; ERQ: Emotion Regulation Questionnaire

[a] Stroop interference score = colored words – colored squares
[b] Perceived Stress score reflects sum of all scale items
[c] Daily Stress score is the average impact rating of endorsed events
[d] ERQ Suppression items: 2,4,6,9
[e] ERQ Reappraisal items: 1,3,5,7,8,10

*$P < 0.05$. **$P < 0.001$.

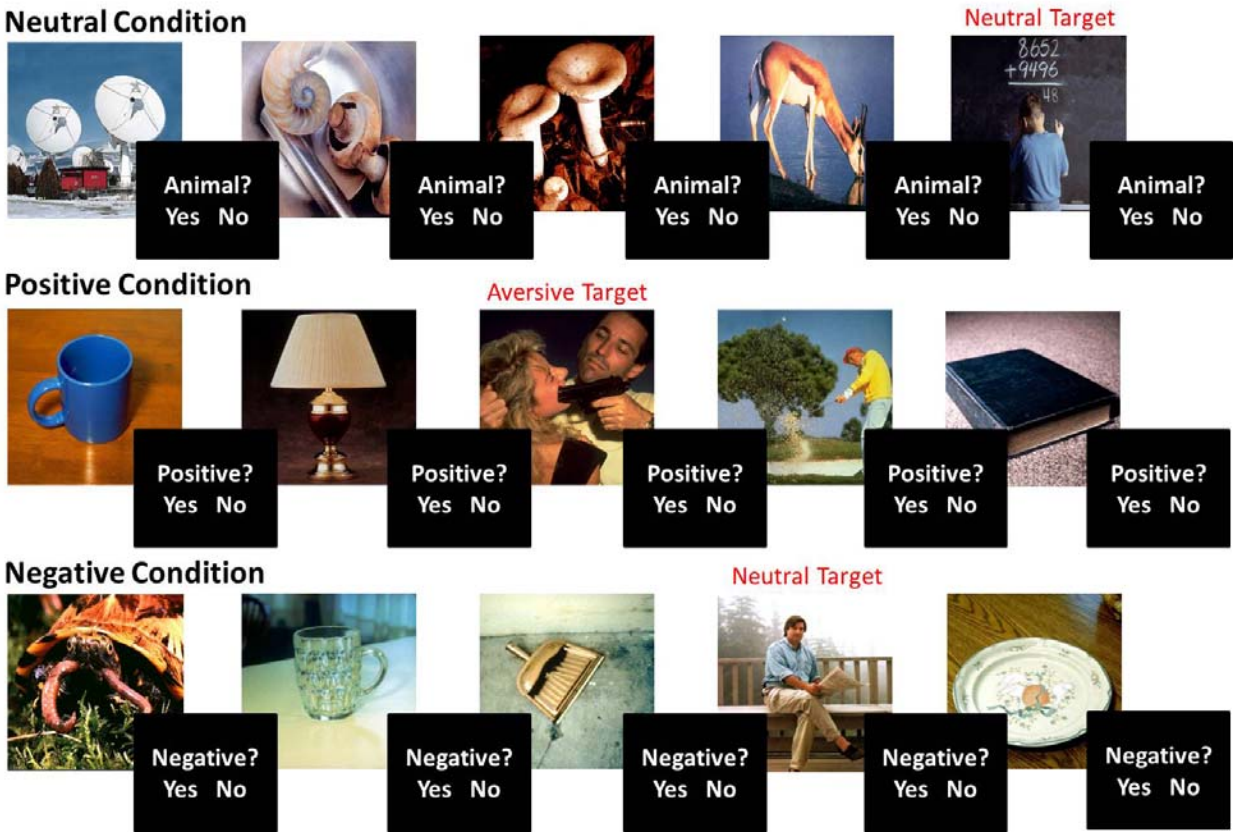
Table 3.3. Emotional Oddball Framing Paradigm: Behavior and SAM ratings

	SCZ Patients		Controls	
	Aversive	Neutral	Aversive	Neutral
Behavior				
Latency (ms)(Mean ± SD)				
Neutral Framing Condition	535.65 ± 226.18	534.40 ± 202.04	468.61 ± 280.58	428.58 ± 287.74
Negative Framing Before Stress	645.50 ± 334.92	756.32 ± 464.93	500.65 ± 305.93	614.51 ± 459.50
Positive Framing Before Stress	550.69 ± 276.20	702.27 ± 305.42	385.39 ± 243.13	535.49 ± 253.15
Negative Framing After Stress	477.37 ± 313.61	517.81 ± 286.63	401.14 ± 232.05	405.21 ± 166.89
Positive Framing After Stress	520.97 ± 373.40	546.12 ± 304.91	386.36 ± 302.93	449.17 ± 175.32
Accuracy (% correct)				
Negative Framing Before Stress	85.00 ± 14.34	82.59 ± 13.79	88.84 ± 10.00	84.60 ± 8.27
Negative Framing After Stress	85.19 ± 17.54	79.07 ± 10.28	90.79 ± 7.67	77.94 ± 10.08
SAM Rating *(Mean ± SD)*				
Valence	2.30 ± 0.96	4.99 ± 1.41	2.84 ± 0.85	4.99 ± 0.68
Arousal	3.63 ± 1.41	3.20 ± 1.77	4.63 ± 1.82	3.22 ± 1.71

Abbreviations: SAM: Self-assessment manikin

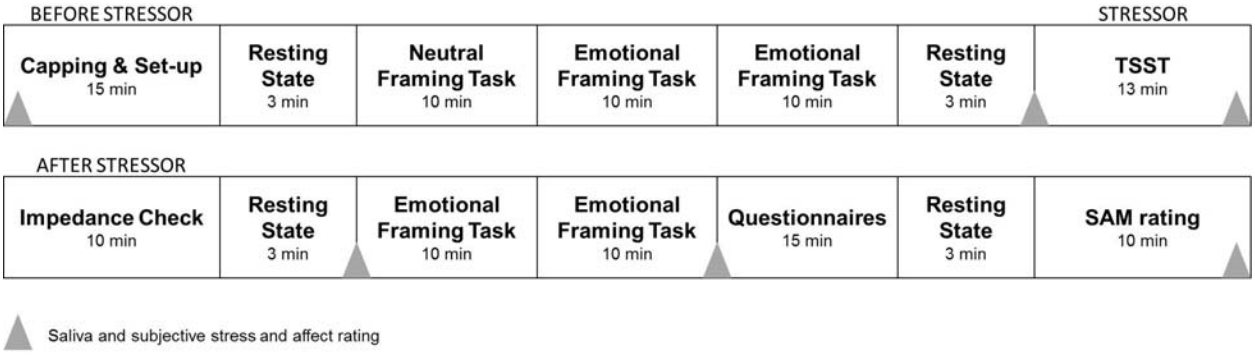
Chapter 3.2 Figures

Figure 3.1. Emotional Oddball Framing Paradigm



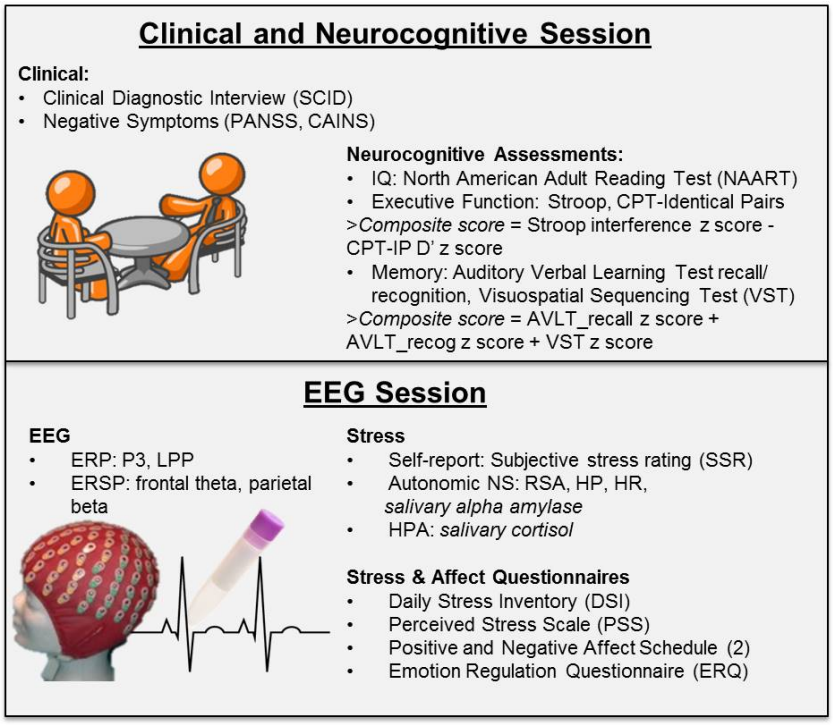
Schematic diagram showing a representative block from each of the three framing conditions with a neutral or aversive target embedded among four neutral stimuli. Each stimulus was presented for 1000 ms followed by a framing cue. Participants were instructed to categorize the image according to the framing cue using a button box.

Figure 3.2. Diagram of Study Design



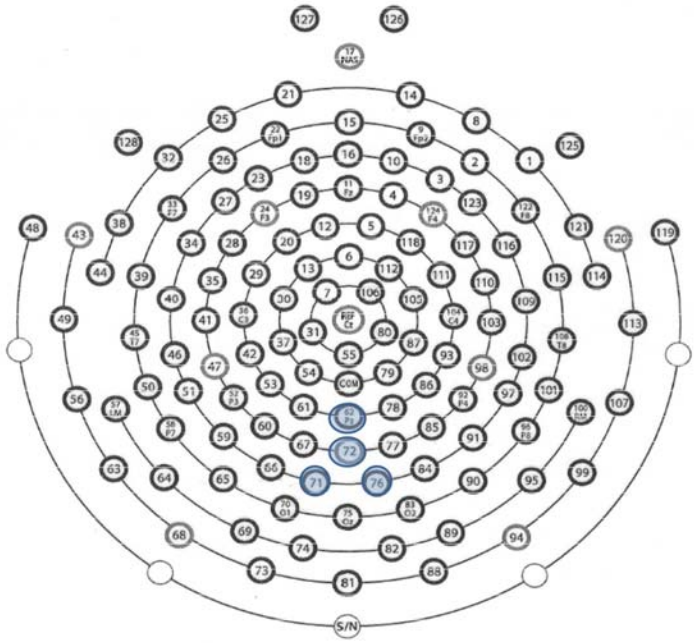
Timeline of the EEG session. Session started at 1:00 PM for all participants. Order of emotional framing tasks was counterbalanced between participants. TSST: Trier Social Stress Test; SAM: Self-assessment manikin

Figure 3.3. Summary of Neurocognitive and Clinical Measures



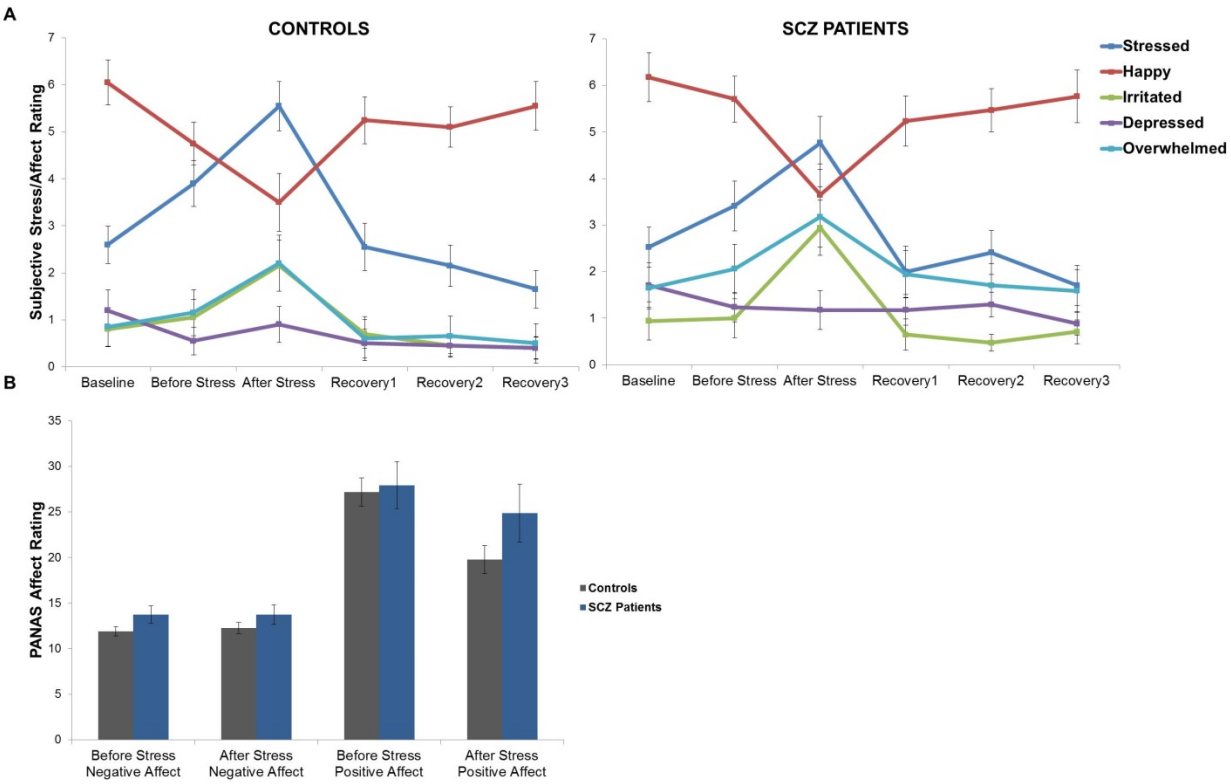
Summary of the outcome variables collected at the clinical and neurocognitive and EEG sessions. Calculation of composite scores is described.

Figure 3.4. Electrode Map of Parietal Montage



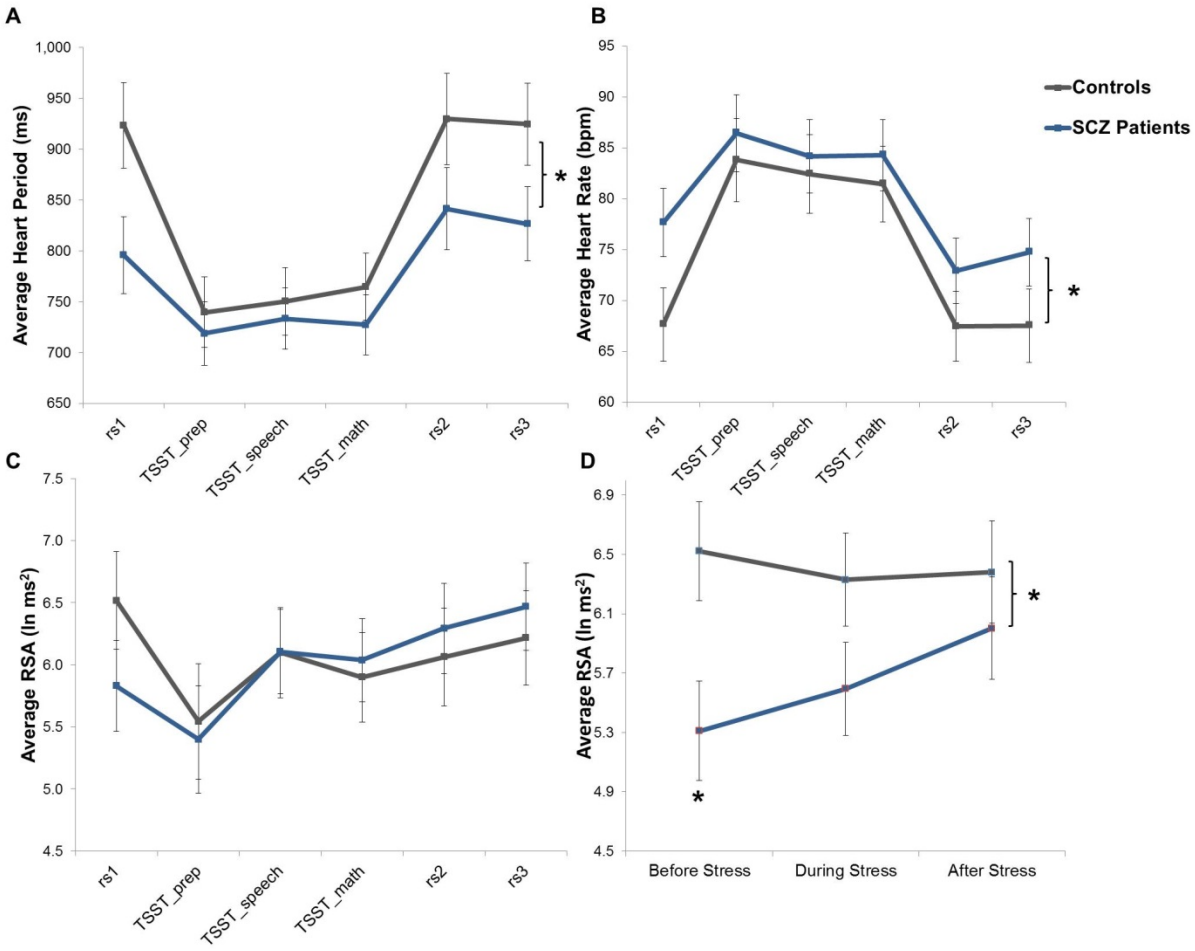
Electrode map highlighting the four parietal electrodes (Pz (62), 71, 72, 76) comprising the parietal cluster that was used to analyze average ERP amplitudes.

Figure 3.5. Subjective Stress and Affect Ratings



A. Subjective stress and affect ratings (SSR) collected at six time-points throughout the EEG session to monitor changes in affect following the stress manipulation. Five affect categories were assessed (Stressed, Happy, Irritated, Depressed, Overwhelmed). Controls on the left, SCZ patients on the right. B. PANAS affect ratings collected at the beginning (Before Stress) and end (After Stress) of EEG session to look at changes in negative and positive affect. Controls are represented by the gray bars and SCZ patients are represented in blue.

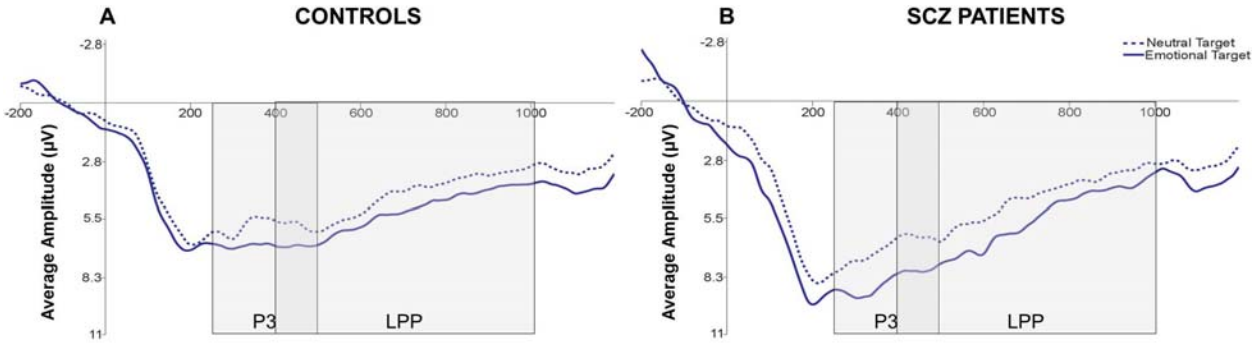
Figure 3.6. Physiological Measures of Stress



Heart rate parameters collected before (rs1), during (TSST-prep, TSST-speech, TSST-math) and following stress exposure (rs2, rs3). Controls are represented in gray, SCZ patients in blue. A. Average heart period measured in ms. SCZ patients exhibited a blunted heart period response relative to controls. B. Average heart rate measured in beats per minute (bpm). Group difference in quadratic contrast was found. C. Respiratory Sinus Arrhythmia (RSA) measured in ln ms^2. D. RSA before stress, during stress and after stress. SCZ patients revealed reduced RSA before stress and a significant group difference in slope was observed.

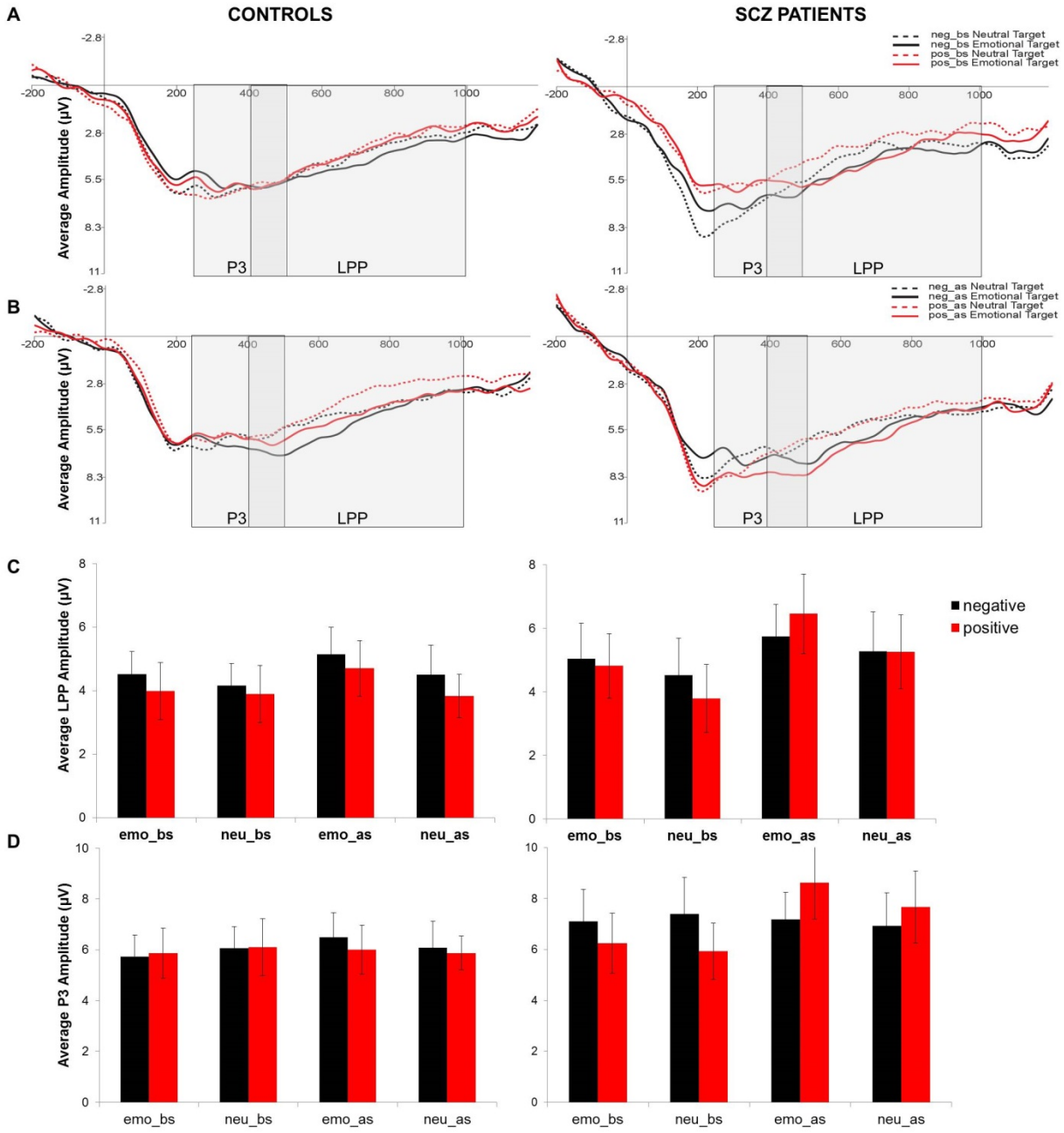
*$P < 0.05$.

Figure 3.7. Valence Discrimination during Neutral (Animal) Framing Condition



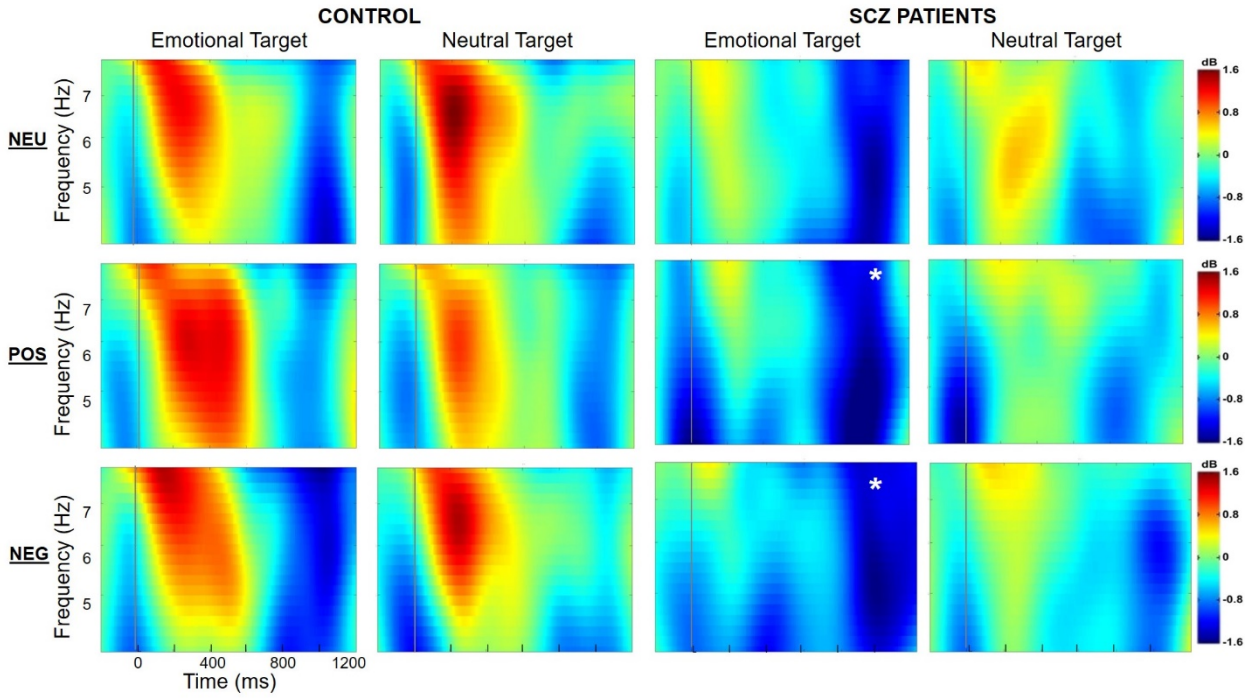
Grand average waveforms for control participants (A) and SCZ patients (B) averaged across the parietal electrode cluster in response to neutral targets (dashed blue line) and emotional targets (solid blue line). Gray boxes indicate analysis window for P3 (250-500 ms) and LPP (400-1000 ms). Average P3 and LPP amplitudes for aversive stimuli were greater than neutral stimuli, indicating intact valence discrimination.

Figure 3.8. ERP Amplitudes Elicited During the Different Framing Conditions Before and After Stress



Grand average waveforms from the parietal cluster for control participants (left) and SCZ patients (right) during negative (black) and positive (red) framing conditions for neutral (dashed lines) and emotional (solid) target stimuli. Gray boxes indicate analysis windows, P3 (250-500 ms) and LPP (400-1000 ms). A. P3 and LPP waveforms before stress. B. P3 and LPP waveforms after stress. C. Graphical representation of framing effects on average LPP amplitude. Black is negative framing condition and red is positive framing condition, with controls on the left and SCZ patients on the right. D. Framing effects on average P3 amplitude.

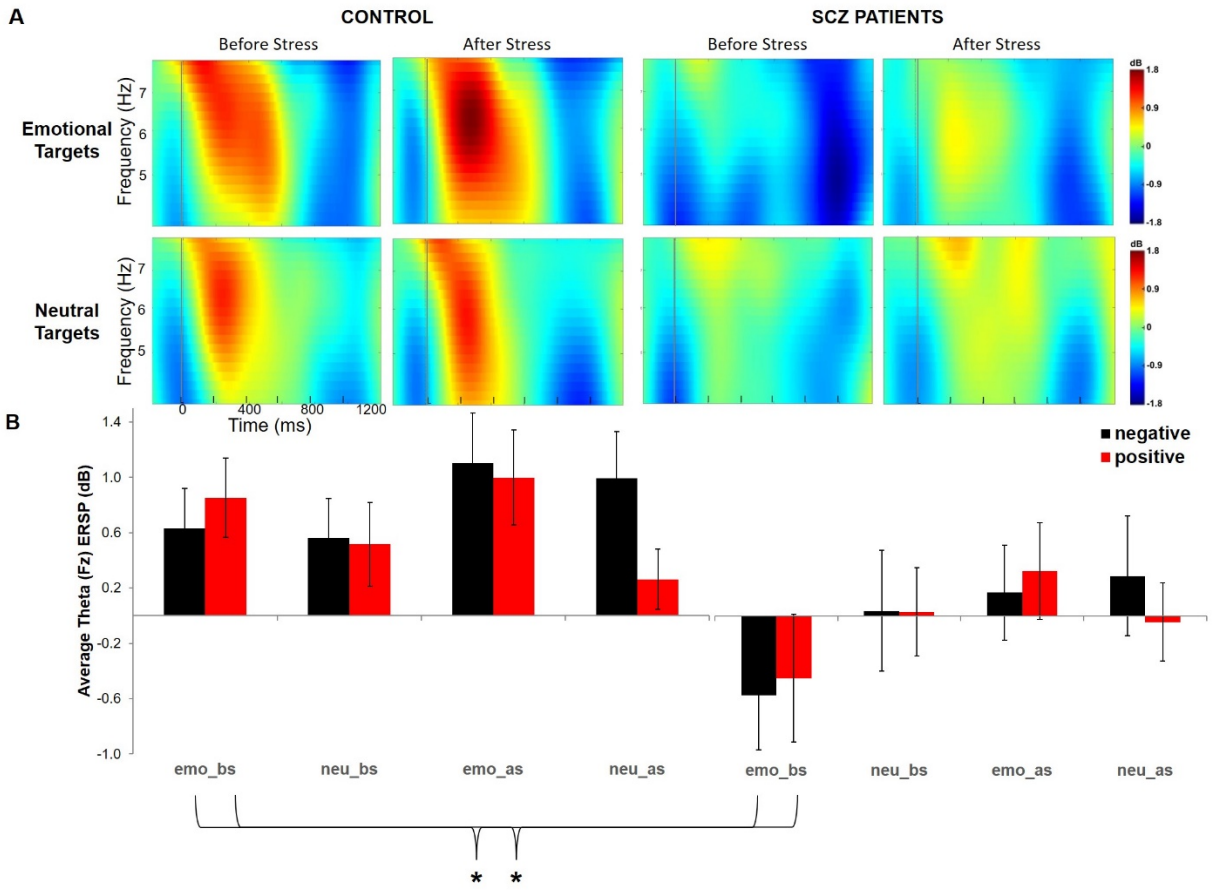
Figure 3.9. Early Frontal Theta Activity Before Stress



Time-frequency spectrograms show event-related changes in theta (4-8 Hz) ERSP (event-related spectral perturbation, dB) at Fz electrode following emotional and neutral targets during neutral, positive and negative framing conditions before stress (stimulus onset = time 0 ms). Controls are on the left and SCZ patients are on the right. SCZ patients exhibited significantly reduced theta activity for emotional targets during the positive and negative framing conditions.

*$P < .05$.

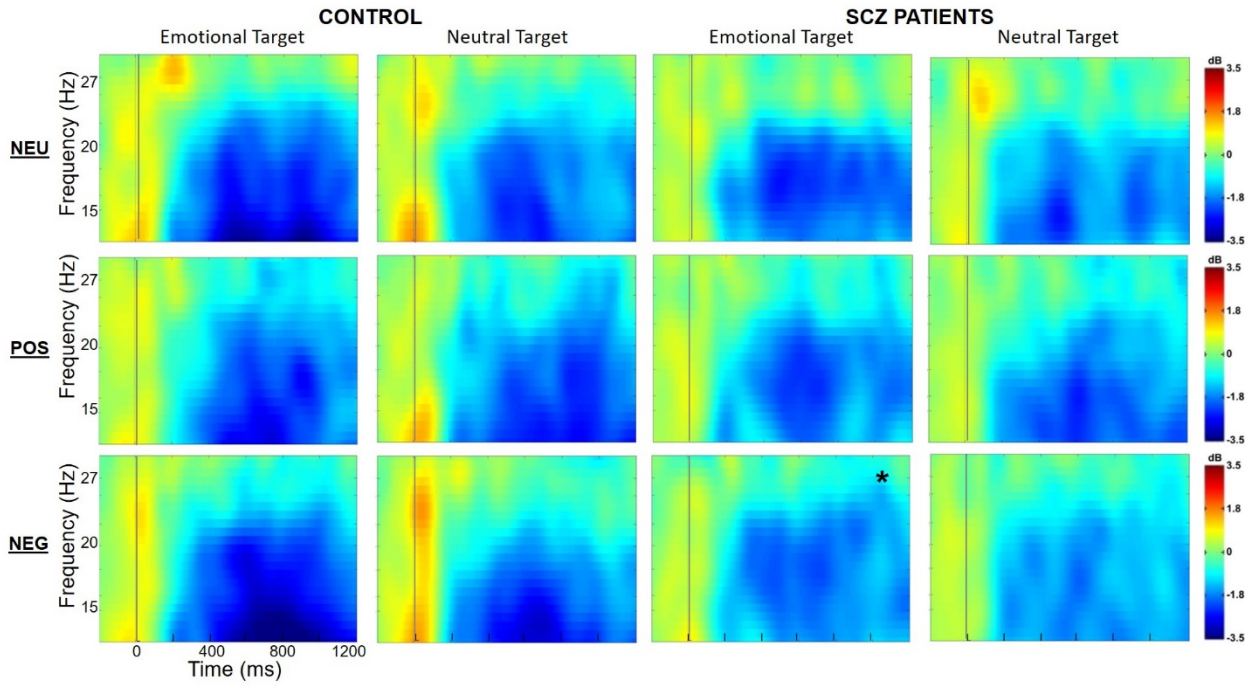
Figure 3.10. Stress Reactivity Induced Changes in Early Frontal Theta ERSP



A. Time-frequency spectrograms depict frontal midline (Fz) theta (4-8 Hz) ERSP (event-related spectral perturbation, dB) for emotional and neutral targets collapsed across emotional framing condition before and after stress. Stress exposure increased theta activity, especially for emotional stimuli. B. Graphical representation of negative (black) and positive (red) framing effects on average early theta (100-500 ms) measured from Fz electrode. Controls on the left, SCZ patients on the right.

*$P < 0.05$.

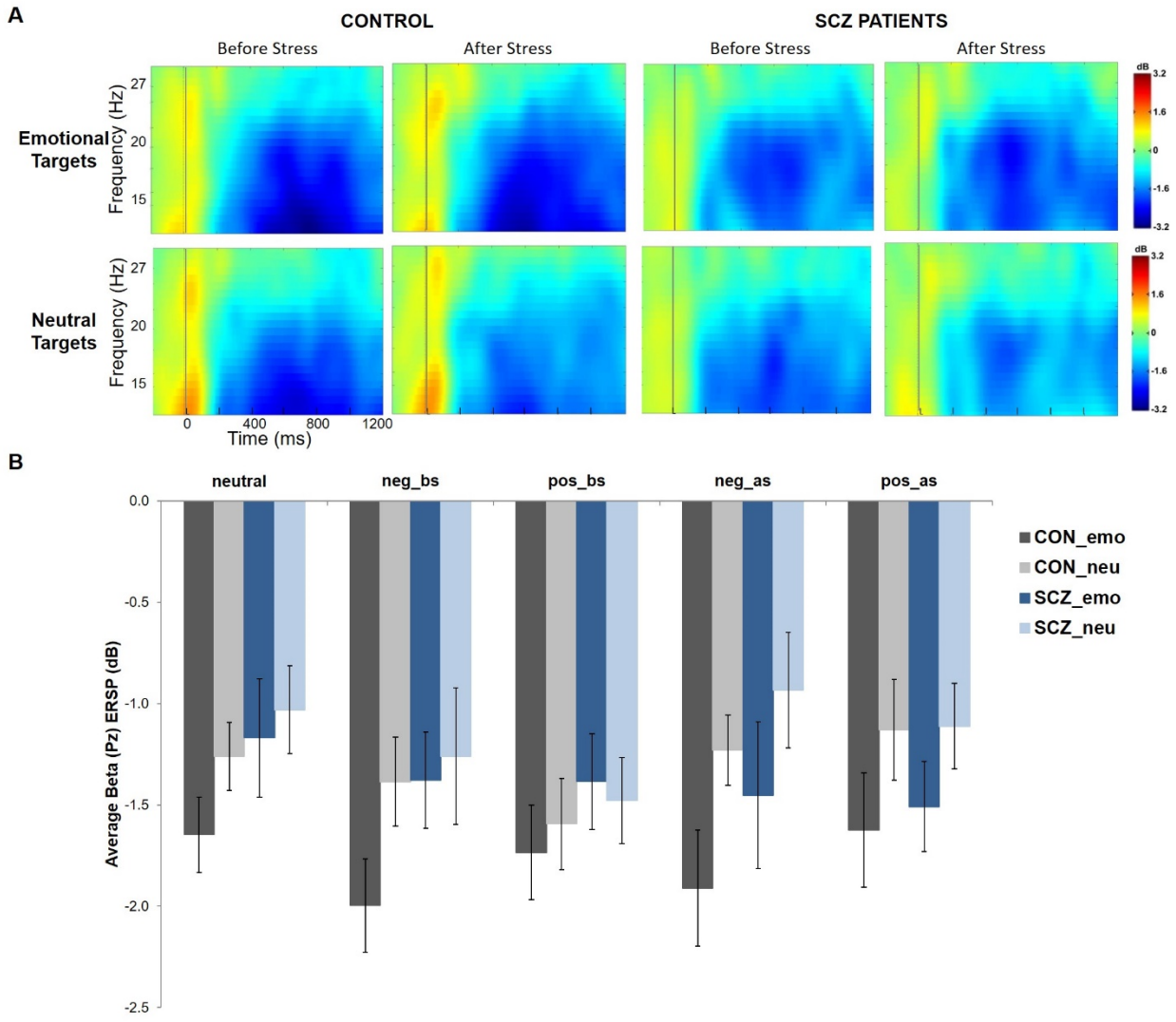
Figure 3.11. Late Parietal Beta Activity Before Stress



Time-frequency spectrograms show parietal (Pz) beta (13-30 Hz) ERD (event-related desynchronization, dB) for emotional and neutral targets during neutral, positive and negative framing conditions before stress (stimulus onset = time 0 ms). Controls on the left, SCZ patients on the right. Beta ERD was stronger for aversive stimuli relative to neutral stimuli. SCZ patients demonstrated weakened beta ERD for emotional stimuli compared to controls.

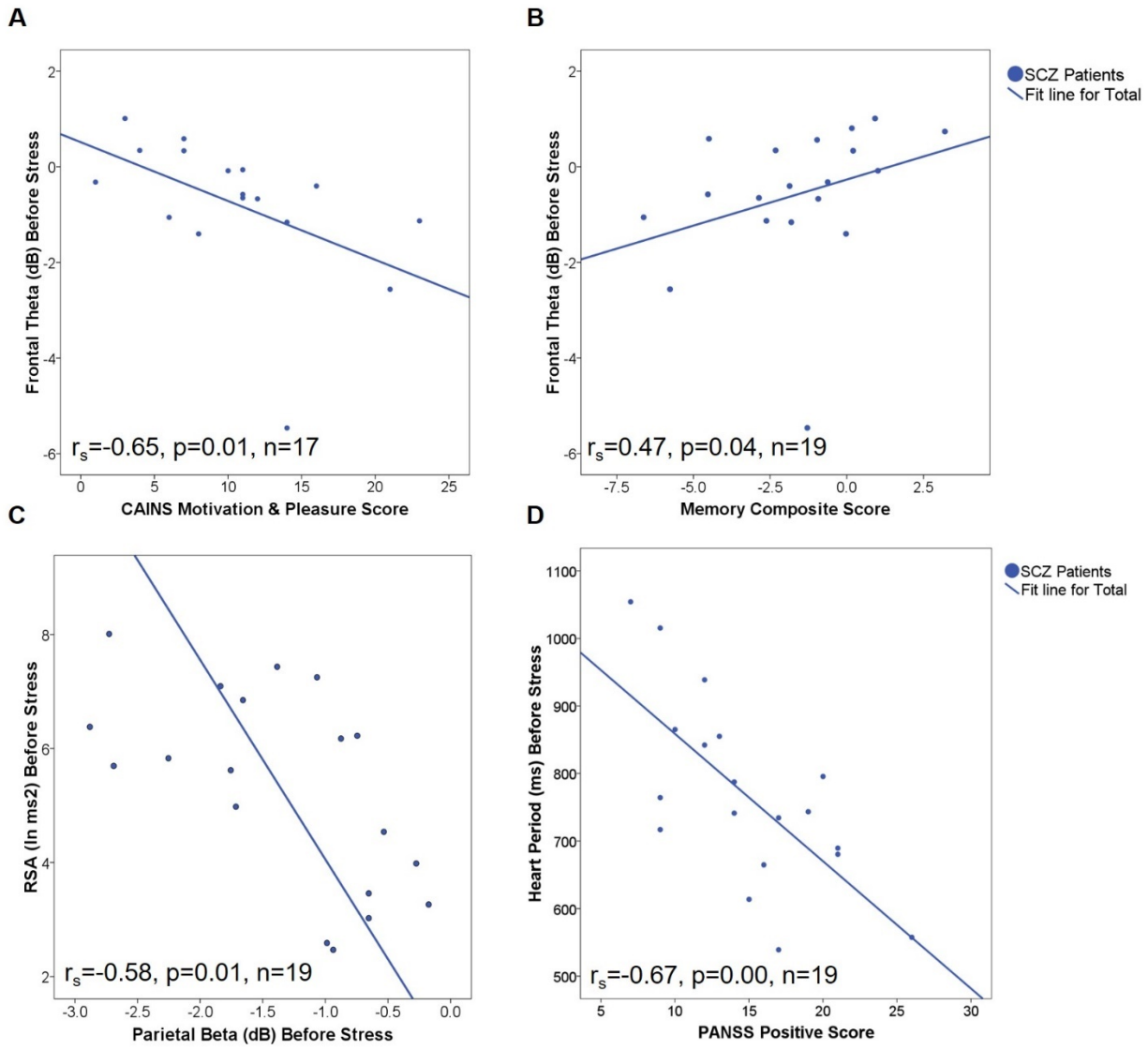
*$P < 0.05$.

Figure 3.12. Changes in Late Parietal Beta Activity Following Stress



A. Time-frequency spectrograms show average parietal (Pz) beta (13-30 Hz) activity for emotional and neutral targets collapsed across emotional framing conditions before and after stress. B. Graphical representation showing average late (600-1000 ms) parietal beta ERD (event-related desynchronization) for neutral, and negative and positive framing conditions before and after stress. Beta ERD was stronger for aversive stimuli before and after stress. Beta ERD was reduced for neutral stimuli following stress. Controls are represented in gray, SCZ patients are in blue. Light colors represent neutral stimuli and dark colors represent emotional stimuli.

Figure 3.13. Relationship between Physiological Measures of Stress, Clinical and Neurocognitive Assessments, and EEG Activity in SCZ Patients.



Spearman's rank correlations for SCZ patients demonstrate relationships between clinical, neurocognition, stress and neurophysiology. A. Reduced frontal theta activity before stress is associated with increased CAINS motivation and pleasure symptom severity. B. Reduced frontal theta activity before stress is related to inferior memory performance. C. Reduced RSA before stress is associated with greater parietal beta. D. More severe positive symptoms were related to lower heart period before stress. RSA: Respiratory Sinus Arrhythmia; CAINS: Clincial Assessment Interview for Negative Symptoms; PANSS: Positive and Negative Syndrome Scale.

CHAPTER 4: CONCLUSIONS

Maladaptive stress and arousal regulation and exaggerated limbic recruitment in patients with schizophrenia may interfere with effective frontal engagement, promoting aberrant perceptual integration, inappropriate salience attribution, deficient cognitive control and devastating symptom pathology. Results from the current study suggest that neural connectivity dysfunction and compromised fronto-limbic circuitry are further exacerbated by stress in patients with schizophrenia. Important findings from Experiment 1 and 2 are summarized in the following sections, including a discussion of the aberrant salience, fronto-limbic deficiencies and dysregulated stress reactivity observed in schizophrenia patients and how these affective and stress systems interact to promote symptomatology.

4.1 Support of Schizophrenia as a Salience Syndrome

The debilitating disruptions in salience processing observed in patients with SCZ is reflected in aberrant beta activity, which interacts with neurotransmitter systems including dopamine, to regulate cortical state and support the integration of information in the salience network. Heightened beta activity, observed in patients for task-relevant aversive stimuli, and for irrelevant salient stimuli in individuals at familial high-risk, may indicate deficiencies of the salience network to support the attentional resources necessary for processing evocative stimuli, resulting in reduced electrophysiological correlates of motivated attention to salient distractors (early LPP) and reduced frontal theta. Interestingly, symptom naïve first-degree relatives (FDR) exhibited a unique enhancement of the late LPP amplitude and beta activity in response to irrelevant aversive distractors, possibly representing a compensatory mechanism which recruits alternative salience regions to enhance the allocation of attention, and allows FDR participants to achieve a behavioral performance equivalent to controls. Additionally, patients with SCZ demonstrated paradoxical behavioral responses for neutral and aversive stimuli, with increased latency responses for neutral stimuli and reduced latency for aversive stimuli, further indicative of inappropriate salience and attribution of motivational significance to irrelevant, neutral stimuli. Beta oscillations are thought to be generated by GABAergic transmission, suggesting a pivotal role of GABA-derived beta

activity in maintaining an appropriate excitatory-inhibitory balance. Therefore, weakened beta desynchronization may reflect enhanced neural excitability, which in turn, interrupts attentional tuning and signal to noise discrimination which are reflected in the reduced early LPP amplitudes in patients and FDR. Thus, beta oscillatory activity, along with early LPP, may be important neurophysiological markers for psychosis. Salience dysfunction interferes with cognitive processes essential for social engagement and goal-oriented behaviors, and may underlie positive and negative symptoms of schizophrenia.

4.2 Insights into Fronto-Limbic–Dependent Affective Processing Impairments in Patients with Schizophrenia

The disproportionate recruitment of limbic activity observed in patients with schizophrenia subserves heightened affective interference, further blunting frontal engagement and disrupting response selection. Despite intact novelty detection in schizophrenia and FDR (P3a) and appropriate valence discrimination (greater neural correlates for aversive relative to neutral stimuli), patients exhibit aberrant attentional processing of affective information, reflected in the reduced early LPP and theta activity during the emotional oddball paradigm, and reduced theta activity during the processing of aversive stimuli during the emotional framing paradigms. Theta activity plays a critical role in coordinating attentional resources and provides a foundation for frontal mediated function (Ertl et al., 2013; Gärtner et al., 2014). Furthermore, the successful integration of neural information processed in remote brain regions supporting global cortical communication relies on efficient theta oscillations and their synchronization. Therefore, deficient theta activity may represent global dysconnectivity with abnormal neuronal participation and synaptic connectivity. Specifically, inferior frontal theta activity elicited during the framing tasks in SCZ patients may reflect deterioration of frontal integrity, consistent with neuroimaging reports of structural and functional impairments of frontal lobe and its connectivity in patients with SCZ. Given these results, theta may be considered a neurophysiological marker for frontal network function.

4.3 Insights into Impaired Stress Reactivity in Patients with Schizophrenia

SCZ patients exhibited a maladaptive stress response, suggestive of deficient autonomic flexibility and neural regulation of visceral state. In addition to an elevated baseline arousal state with increased heart rate and reduced heart period and RSA, patients demonstrated a unique progression in RSA from baseline to recovery and blunted stress reactivity to an acute psychosocial stressor. This was

the first study, to my knowledge, that examined RSA over a prolonged period in response to and recovery following a psychosocial stressor in SCZ patients. Results suggest that patients are unable to suppress RSA following stress exposure, which may underlie maladaptive behavioral consequences. Furthermore, the failure to suppress RSA has important implications for maladaptive behavioral responses, including social engagement, executive functioning, and symptom pathology (Porges, 2007). The maladaptive stress response in patients possibly contributes to heightened neural excitability, the exaggerated recruitment of limbic networks and impaired frontal engagement, further interfering with appropriate salience attribution and affective processing.

4.4 Disruption of Fronto-Limbic Oscillatory Indices of Salience and Affective Processing Following Stress Exposure

Stress modified electrophysiological correlates of affective processing and disrupted fronto-limbic oscillatory activity reflected in less efficient frontal theta activity and elevated beta excitability for all participants. Deficiencies in beta and theta oscillatory activity in patients with SCZ, were further exasperated following the stress manipulation. Results suggest that a maladaptive stress response may impair oscillatory activity, compromise neural integration, disrupt the excitatory and inhibitory balance, and promote network dysfunction in patients with schizophrenia. Accordingly, an aberrant baseline stress and arousal state in patients with SCZ, with maladaptive physiological measures of stress, was accompanied by opposing disruptions in frontal theta and beta excitability. This enhanced state of arousal, with enhanced beta excitability and physiological stress, may reflect exaggerated limbic recruitment, thus interfering with frontal allocation of attentional and cognitive resources to process information, especially emotionally salient stimuli. Additionally, aberrant beta activity was related to atypical stress responses and elevated symptom severity, reflecting the inability to regulate visceral state in patients with SCZ, which may interfere with frontal recruitment, and impede the successful employment of emotion regulation strategies. The heightened stress profile, elevated neural excitability and deterioration of frontal integrity observed in SCZ patients is not conducive for effective perceptual integration and cognitive regulation at baseline, let alone during stress exposure. Not surprisingly, stress appears to impact the efficiency of affective processing by disrupting frontal efficiency and arousal regulation. Furthermore, maladaptive stress responses were associated with impaired executive function,

enhanced negative symptom severity and psychosis. This is the first study to define the relationship between aberrant stress reactivity, clinical and neurocognitive measures, and dysregulated electrophysiological correlates of salience and affective processing in patients with schizophrenia and healthy controls. Results from these experiments have significant potential for identifying novel physiological biomarkers for the early detection and prediction of psychosis. Furthermore, results suggest that modifying fronto-limbic oscillatory activity by targeting the stress response may be effective for improving efficiency of fronto-limbic circuitry, critical for emotion regulation-dependent therapies.

4.5 Final Thoughts

Aberrant salience attribution, disturbances in perceptual integration and maladaptive brain state regulation are a result of insula dysfunction and are core deficits of schizophrenia, designating the insula as fundamental to the pathophysiology of schizophrenia. As a critical node in the salience network, the insula coordinates perceptual, internal emotional and physiological state information to appropriately motivate attention and promote adaptive behaviors (Uddin, 2015). Not only do patients with schizophrenia exhibit anatomical (Fornito et al., 2009; Glahn et al., 2008; Kasai et al., 2003; Shepherd et al., 2012) and functional (Li et al., 2010; van der Meer et al., 2014) abnormalities in the insula, they demonstrate neurophysiological correlates of insula dysfunction, including elevated beta activity. Adding to the significance of insula dysfunction in the etiology of schizophrenia is the fact that a unique type of evolutionary specific neurons with a characteristic spindle shape, referred to as Von Economo neurons, are specifically localized in the insula-dominated salience network and are critical for relaying information over long distances to govern network switching processes (Butti et al., 2013). Schizophrenia patients exhibit a reduced number of Von Economo neurons (Brüne et al., 2010), further highlighting the salience network as playing a critical role in the development, maintenance and treatment of neuropsychopathology. Results from Experiment 1 and 2 provide further evidence that the aberrant affective and stress regulation which is observed in schizophrenia patients may revolve around a central deficit in the insula-mediated salience network.

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