BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF), β-CATENIN, AND CORTISOL LEVELS CORRELATED WITH THE SEVERITY OF ADVERSE CHILDHOOD EXPERIENCES (ACES) SCORE IN PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS

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Abstract: Psychosis, as seen in Schizophrenia and Schizoaffective disorder, is the most debilitating of psychiatric dysfunctions, affecting more than 21 million people per year globally.

Adverse childhood experiences (ACE) and psychosis have significant correlation. We used the ACE Questionnaire (ACEQ) in this study to evaluate childhood trauma. There are, however, many instruments used to assess ACEs. Instruments vary and are used at the discretion of the study facilitator to meet the perceived needs of the study. We assessed the prevalence of the instruments used to assess childhood trauma in individuals with psychosis via a systematic review.

BDNF and β-catenin are critical in early and continued neuronal development and proliferation, particularly in the hippocampus (Hpc). Cortisol, well-known for being the major stress hormone, and is known to damage to Hpc neurons in chronic stress. In this study serum BDNF, β-catenin and cortisol will be measured in patients with a diagnosis of Schizophrenia (Sz) or Schizoaffective disorder (SzA) and evaluated for correlation with their respective ACEs scores.

We had a sample size of 11 patients (4 Female, 7 Male) with diagnosis of either Sz or SzA (Sz=2M, SzA=4F, 5M). All were administered a Structured Clinical Interview for DSM-5 - Clinician's Version (SCID-5-CV) to confirm diagnoses, the ACEQ, and a blood draw to evaluate serum for biomarkers.

We found a significant negative correlation ($p=0.027$) between cortisol levels and higher ACEQ scores in our sample population. β-catenin and BDNF demonstrated downward linear trends relative to higher ACEQ scores, which with increased power could show significant correlation.

170 studies met criteria for the systematic review, 24 instruments were isolated from those studies. Of those 100, (58.9%), of the studies isolated utilized the Childhood Trauma Questionnaire (CTQ) to assess adverse childhood experiences in patients with psychosis.

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CHAPTER I

INTRODUCTION

For millennia, severe mental illness has existed outside of the scope of science. Often it was associated with religious persecutions, demonic possessions, moral failures of the individual or one of their progenitors. As understanding progressed, dementia praecox, or dementia of the young, became the formal predecessor of the modern diagnoses of Schizophrenia Spectrum Disorders (SSD) (Jablensky, 2010).

Schizophrenia spectrum disorders (SSD) encompass psychotic disorders including both Schizophrenia and Schizoaffective Disorder. The criteria are defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM–5). SSD are diagnosed when psychotic symptoms persist for longer than six months. These diagnoses require two of five symptom criteria. There are four positive symptom categories. They are delusions, hallucinations, disorganized speech, disorganized or abnormal behavior. Delusions are fixed false beliefs and exist outside of the cultural norm for the individual. Hallucinations are experiences of the senses without corresponding external stimuli, most common are auditory and visual, with tactile and olfactory occurring less frequently. These must exist outside of individual cultural norms.

For example, an individual may live in a culture in which spiritual or religious visions are considered normal and these experiences would then not fall within the definition of a visual hallucination. Disorganized speech may be present in many forms, loose associations, tangentiality or circumferentiality. Tangential speech can present similarly to the word salad seen in Wernicke's aphasia, patients are responsive and fluent but seemingly nonsensical (Kuperberg 2010) or unrelated to the topic of the conversation. Disorganized or abnormal behavior may consist of unpredictable or inappropriate action or catatonia. Negative symptoms include inappropriate or absent affect, avolition, alogia, anhedonia, apathy, and aversion to regular social interaction. These negative symptoms are often the first symptoms to present (Correll & Schooler, 2020). Schizoaffective Disorder differs from Schizophrenia in that patients may have either a diagnosis of Major Depressive Disorder (MDD) or Bipolar Disorder (BD) I or II, in addition to psychotic symptoms that occur when they are not actively experiencing a depressive, manic, or hypomanic episode as defined by the DSM-5. Both positive and negative symptoms contribute to the significant hardship in the maintenance of social functioning for individuals afflicted with SSD, many of whom may have been thriving prior to onset, causing major personal and familial upheaval. Because of the major social toll of this disease, it is important that scientists continue to research its neuropathologies.

As information has become more available, our understanding of the etiology of these diseases has become more, rather than less, complicated. There have been many associated genetic variants identified, but so far none of these genes have been sufficient to define the disease (Vereczkey & Mirnics, 2011). Increasingly, the importance of various environmental components has been validated. Among the most important is the association of adverse childhood experiences (ACEs). In 1998 the clear and long-lasting impact of ACEs was validated in the sentinel study by Felitti et al. This study, and the development of its associated ACE Questionnaire (ACEQ), helped incorporate childhood trauma assessment as an aspect of standard medical care in the United States. The ACEQ is a ten-point self-reported diagnostic of early/childhood traumatic experiences. It has ten

either/or one-point questions to determine exposure to psychological, sexual, and physical abuse, parental mental illness or suicidality, neglect, and incarceration of a primary family member (Felitti et al., 1998). The study found that patients that reported an ACEs score of four or greater demonstrated a four-to-twelve-fold increased risk for negative health outcomes. Outcomes such as alcoholism, drug abuse, and suicidality. They also demonstrated a four-fold increase in risky sexual behaviors and obesity. The criteria defined by this study established a series of negative outcomes resulting from ACEs, increasing in severity from the bottom up. This was conceptualized as "The ACEs pyramid". The potential outcomes are defined from bottom to top as: social, emotional, and cognitive impairment, adoption of health-risk behaviors, disease, disability, and social problems, culminating in premature death.

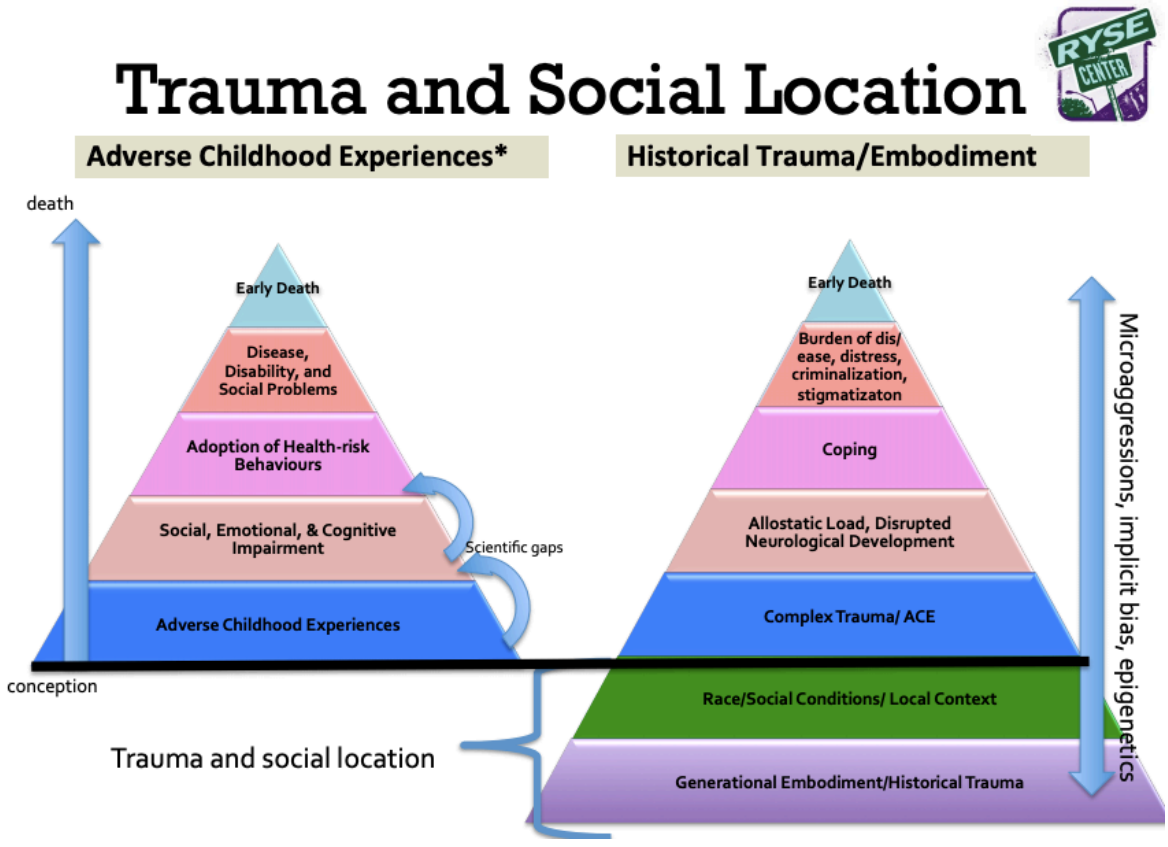

Figure 1. ACES Pyramid and Intergenerational and Social Location (RYSE 2015).

The study demonstrated significant correlation of ACEs and mental illness. Indicated by increased suicidality, hallucinations, and associated antipsychotic prescription with an ACE score of four or greater (Felitti et al., 1998). These insights spurred extensive research regarding the development and onset of Schizophrenia and its comorbidity with ACEs. There is now a significant body evidence to support the correlation of ACEs and the age of onset and development of Schizophrenia (Varese et al., 2012, Popovic et al., 2019). Correlation of ACEs and SSD has been demonstrated in diminished or modulated levels of cognitive function in first-episode psychosis patients and healthy controls both with a history significant for ACEs (Sideli et al., 2014). In a 2017 study by Vallejos et al., 63% of male patients diagnosed with Schizophrenia had an ACEs score of four or higher on the scale of zero to ten.

These formative traumatic experiences leave lasting changes in both gray matter volume (GMV) and neurochemical hormone production. Our study investigates Brain-derived neurotrophic factor (BDNF), β-catenin, and cortisol correlated with the severity of ACEs scores in patients with SSDs. BDNF, β-catenin, and cortisol have been chosen for this study because of their relevance to proper nervous system health and maintenance, as well as previously established relationships with SSDs and ACEs.

BDNF is a neurotrophin and key moderator in the function of actively firing neurons. It is believed to be critical in the dendritic spine remodeling associated with learning and memory via long-term potentiation (LTP) within the hippocampus (Hpc) (Borodinova & Salozhin 2017). This is the area of the brain strongly associated with learning and memory. BDNF functions to support many areas of the brain, including the prefrontal cortex (Pfc), the area in charge of executive function and decision-making (Chang et al., 2018). It is involved in axonal guidance and elongation, dendritic collateral branching, and synaptogenesis (Yoshii & Constantine 2010, Figurov et al., 1996). BDNF is also an important moderator of neuronal health via neurogenesis and plasticity. Because BDNF is associated with neurogenesis and dendritic remodeling, it has been a target of interest for stress and

trauma-related changes in neuronal function, physiology, and in psychological disorders (Theleritis et al., 2014). BDNF levels have been shown to be decreased in patients with Schizophrenia (Fernandes et al., 2015), making it an important potential biomarker for SSDs.

β-catenin is a highly conserved protein associated with the canonical Wnt/β-catenin signaling pathway during embryonic and fetal development (Medina et al., 2018). It serves two primary functions in adult physiology: cell adhesion and as a genetic transcription factor. Notably, in the brain, β-catenin has been shown to function in regulating neuronal development and differentiation of nerve cells (Teo et al., 2018). It functions in synaptic stabilization and neuroplasticity in the formation and maintenance of memory within the Hpc (Teo et al., 2018). β-catenin has also been shown to have important maintenance function in dendritic arborization by acting as a cytoskeletal element within the Hpc that supports synaptogenesis (Yu & Malenka 2003). Because of these important supportive functions in the brain, there has been some research on β-catenin in relationship to neurological disease. As early as 1998, Cotter et al. found a decrease in the concentration and distribution of β-catenin in Hpc of postmortem Schizophrenia patients compared to controls. It is however, more often studied in relation to its association with oncogenic processes in cancers, which makes it an exciting and more novel aspect to this study.

Cortisol is a glucocorticoid, or stress hormone, and is extremely important to species maintenance and survival during periods of external and internal stress stimuli. Cortisol can either induce or inhibit gene transcription and acts to modulate body functions to support endurance during stress (Teo et al., 2018). Prolonged cortisol exposure can be detrimental, causing changes in neuronal plasticity or loss of viability (Kim et al., 2002). Obtaining a cortisol level is of particular importance when looking at neurodegenerative disease or dysfunction because glucocorticoids modulate protein transcription, including BDNF and β-catenin, which are vital to neuronal health (Suri & Vaidya 2013). In studies with mice, chronic stress increased levels of glucocorticoid production resulting in decreased β-catenin expression in the Pfc and Hpc as well as the degeneration of Hpc neurons (Teo et

al., 2018). Studies measuring cortisol levels in patients with Schizophrenia indicated a statistically significant increase in fasting cortisol levels in patients with Schizophrenia versus controls (Ryan et al., 2003, Thakore et al., 2002). However, the 2014 meta-analysis by Ciufolini et al., showed that, in response to stressful stimuli, patients with Schizophrenia have lower levels than healthy controls. Another study looked at healthy controls versus non-psychotic subjects experiencing childhood trauma. The cortisol levels were found to be lower in the trauma group than the controls (Carpenter et al., 2007).

In the following study, subject serum samples were assessed for BDNF, β-catenin, and cortisol levels. As indicated above, BDNF levels have been found to be lower in both individuals with Schizophrenia (Chiou & Huang, 2019; Fernandes et al., 2014) and in ACEs populations. Therefore, a greater decrease in BDNF levels in patients with Schizophrenia as their ACEs scores increase is anticipated. Comparable results are expected with β-catenin levels as well, as it has been shown to be reduced in previous studies utilizing Schizophrenia patients (Cotter et al, 1998). The same results have been seen with cortisol levels. Studies have shown attenuated or diminished cortisol levels in Schizophrenia and childhood trauma (Ciufolini et al., 2014, Carpenter et al, 2007). In these previous studies, the biomarkers and ACEs scores within SSD populations have been demonstrated to consistently vary from control levels. Because of this, we will be looking at them specifically within only the SSD patient population. We believe we will see variation within the patient population itself with regard to biomarker level and ACEs severity.

CHAPTER II

REVIEW OF LITERATURE

The nature of SSDs is complicated. As discussed in the introduction, though genetic associations have been identified, they do not define these disease prodromes. With the long-lasting impact of ACEs on health, elucidated by the ACE studies in recent years, the intrinsic association of disease and environment has become clear. The impact of ACEs and important changes to neuronal networking (Boksa 2012), GMV, and neurochemical signaling molecules have begun to elucidate the development of SSDs.

SSD

Schizophrenia is a complex neurodevelopmental disorder. Disorder onset is usually seen in early adulthood (late 20's) and has been associated with dysfunctional synaptic pruning (Popovic et al., 2019). There is an established component of heritability, demonstrated by

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twin studies, wherein the rate of heritability is as high as 60–80% (Popovic et al., 2019). There is, however, an inextricable environmental component as well. In a study of children with genetic risk of Schizophrenia, those adopted into "harmonious" households showed rates of development similar to the general population. Those adopted into dysfunctional households had higher rates of Schizophrenia (van Winkel et al., 2008). The exposure to ACEs has been demonstrated to be a major factor in development of the disease.

Environmental risk exposure in association with some genetic predisposition is hypothesized to be a common process of severe mental illnesses, such as Schizophrenia, Bipolar disorder, and Major Depressive Disorder (Davis et al., 2016). The neural diathesis-stress (NDS) model, first posited in 1970 by Rosenthal, supposes that trauma mediates pre-existing vulnerabilities and triggers the symptoms of Schizophrenia (Walker and Diforio, 1997). Positing that cortisol dysregulation affects HPA-axis and leads to downstream dysfunctions in neural circuitry, including dysregulation of dopamine (DA) release (van Winkel et al., 2008). Cortisol dysregulation has also been an intuitive target for investigation as diseases of hypercortisolism or overuse of corticosteroids present with positive symptoms of psychosis.

Previously the most widely accepted etiology of SSDs was the "Dopamine Hypothesis" (DAH). The DAH posited that many of the symptoms presented in Schizophrenia can be attributed to the brain's dysregulation of the neurotransmitter DA (Seeman, 1987). DA is an excitatory neurotransmitter associated with the limbic system, the reward center of the brain. The limbic system has significant connections with the cortex and hippocampus, forming the neural bases for reward, decision, and learning associations, respectively. The limbic system is extremely influential in the formation of neural pathways. Reward is intrinsically tied to survival, such that eating, drinking, and mating, are considered pleasurable and therefore ensure species propagation.

In the DAH excessive DA signaling limbic system is believed to contribute to more strongly positive symptoms: hallucinations, delusions, and paranoia. In the cortex a diminished expression of DA is considered the probable cause of decreases in cognitive function and negative symptoms, such as anhedonia and social withdrawal. DA is the major extrapyramidal (substantia nigra, striatum, globus pallidus) neurotransmitter, and this is an important motor area related to intentioned motion. This center and its dysregulation have been associated with strange or unnatural motion or catatonia sometimes seen in Schizophrenia patients. Increased striatal DA release as well as decreasein prefrontal and temporal DA release as a result of receptor sensitization (van Winkel et al., 2008), neuronal receptor regulation in response to excess or limited neurochemical signaling. This allows cells to upregulate receptors when signals are limited and downregulate receptors when signals are too numerous. There is strong evidence in support of the complex dopaminergic activity in the instance of psychosis.

The DAH has prompted investigation of catechol-O-methyltransferase (COMT) as both an environmental and genetic instigator of SSDs. COMT is an enzyme that is critical to the degradation of DA, making it a natural target of investigation. These studies have come to focus on a functional COMT gene valine (Val) to methionine (Met) polymorphism (COMTVal158Met). The single nucleotide polymorphism (SNP) actively affects the enzyme's function. In the Met/Val polymorphism enzyme activity is 40% less than in the Val/Val genotype (van Winkel et al., 2008). It appears the polymorphism may be neuroprotective. Studies indicated correlation of the canonical Val/Val genotype and increased stress-induced paranoia response. In a study of 306, 19–24-year-old men, those with the Val allele showed the greatest increases in "paranoid ideation and psychoticism". The Val/Val genotype is also associated with hypodopaminergic activity in the Pfc, possibly facilitating stress-induced psychosis response (van Winkel et al., 2008). A meta-analysis by Bakker et al., 2008 found neuroprotective effects with

the Met variant genotypes against tardive dyskinesia in patients with Schizophrenia patients (Šagud et al., 2010).

The DAH has found support with the relative effectiveness of both 1st and 2nd generation antipsychotic medicines. These medications all rely on dopamine 2 receptor (D2R) antagonism. In 1st generation, or typical antipsychotics, the affinity for D2R is high (Mauri et al., 2014). While these drugs can be effective, they cause concerning extrapyramidal side effects in patients, such as dystonia, uncontrollable muscle contraction, and tardive dyskinesia, repetitive involuntary jerking movements of body and face (Seeman, 1987). 2nd generation, or atypical antipsychotic, drugs have varying affinity for D2R but are lower than 1st generation Mauri et al., 2014). Some 2nd generation drugs, such as clozapine, amoxapine, risperidone, and olanzapine, act additionally via serotonin (5-HT) as an antagonist at the 5-HT2a receptor (5-HT2aR) (Schmid et al., 2014). Interestingly, clozapine not only acts as an antagonist at the 5-HT2aR, but also induces internalization of the 5-HT2aR and activates the Akt pathway, which is anti-apoptotic, contributing to the considerable efficacy of clozapine and its use in refractory treatment (Schmid et al., 2014). 2nd generation drugs have less extrapyramidal effects but have measurably increased effect on weight gain, increased risk for diabetes, and some neutropenia (Spertus et al., 2018, Ingimarsson et al., 2016). Clozapine can cause agranulocytosis and requires careful monitoring (Mijovic & MacCabe, 2020).

With the effectiveness of 2nd generation antipsychotics, it is reasonable to infer that a relationship with 5-HT exists in the disease process of Schizophrenia. Interestingly consideration of a 5-HT antagonist gained ground from research regarding the function of the psychedelic compound LSD on 5-HT2A receptors, notably it induces sustained receptor agonism (Preller et al., 2018). In the treatment of Schizoaffective or refractory Schizophrenia the addition of mood stabilizers such as lithium, shown to increase Hpc neurogenesis (Neto et al., 2011) and

anticonvulsants, which modulate both dopaminergic and serotonergic release (Romoli et al., 2019) indicate that regulation of DA alone is not sufficient (Chen et al., 2007).

There are GABA system mediated disturbances implicated in the development of Schizophrenia. GABA, or Gamma aminobutyric acid, is the brains major inhibitory neurotransmitter. In a meta-analysis of 20 genome-wide scans, chromosomal region 5q34 met criteria for significant genome wide association (GWA) with Schizophrenia. GABA-Aa6 is an isoform of the GABA-A receptor and is located in the same region (van Winkel et al., 2008). Glutamic acid decarboxylase (GAD67) is important for cortical interneuron GABA synthesis. Decreased expression in GABAergic chandelier interneurons is implicated in disruption of cortical activity synchronization and short-term memory in Schizophrenia (Brown, 2011). Increased DNA methyltransferase 1 (DNMT1) methylation resulted in decreased expression of GAD67 (Brown, 2011). Increased DNMT1methylation activity has also been found in post-mortem brains of Schizophrenia patients.

One hundred and forty-five genetic risk SNP loci were outlined in recent genome-wide association studies (GWASs) related to Schizophrenia (Popovic et al., 2019). Each of these however, demonstrated only weak effect. The studies showed GWAS-based polygenic risk scores associated with social and cognitive impairments during early childhood. These were interpreted as being possible early manifestations of genetic liability in Schizophrenia. Despite these associations, of a little over 8,300 SNPs associated with Schizophrenia, they have been estimated to contribute indefinitely to common risk of development (Popovic et al., 2019). This corroborates the position that environment has an important modulating aspect to the pathophysiology of the disease.

Explanations, therefore, that incorporate the brain as a system in relation to environment and development have begun to replace single agent hypotheses. In this context of brain

development and environment, ACEs play a major role. Increased hypothalamus-pituitary-adrenal (HPA) axis activation via stress from ACEs can cause neurobiological dysregulation and stress sensitization (Popovic et al., 2019). The effects of overproduction of cortisol and subsequent sensitization has been discussed in two pertinent meta-analyses. Patients with Schizophrenia have lower stress response cortisol levels than controls, both in anticipation of stress and after exposure (Ciufolini et al., in 2014, Zorn et al., 2016). This is indicative of blunted cortisol response as a result of sensitization. The systemic hyperstimulation of cortisol promotes overproduction of mesolimbic and striatal dopamine (Popovic et al., 2019), leading to overstimulation of D2 receptors. In one study, an infusion of 2-Deoxyglucose (2-DG), a non-metabolizable glucose analog which induces a well-characterized stress response, was administered to controls and patients with Schizophrenia. Both groups had appreciable increases in cortisol, with no significant difference between them. However, the Schizophrenia patient population showed a pronounced increase in DA and norepinephrine release versus controls (Ellman et al., 2004, Briere et al., 1993). This study implicates, again, the concomitant dysregulation of both HPA/DA systems in the development and symptomatic presentation of Schizophrenia and the upstream effect of ACEs.

ACEs

The idea that the environment affects outcomes is not a new one. However, the ACE study drastically modified the landscape of both physical health and mental health outcomes. Prior to the ACE study it was more commonly accepted that traumatic childhood experiences affected mental health, but whether they also held consequences for physical health was not well established. Physical health can be measured with tangible markers, such as HbA1Cs for diabetes.

The study confirmed long-term physical health could be measurably affected by experiences of childhood as well and lent a much-needed objectivity.

The ACEs Study was undertaken by Drs. Vincent Felitti and Robert Anda. The study was expansive and upon completion had surveyed over 17,000 people (about the seating capacity of Madison Square Garden). It was executed through Dr. Felitti and Kaiser Permanente's Department of Preventive Medicine in San Diego, CA in collaboration Dr. Anda at the CDC. Data from the departments' Health Appraisal Clinic was collected from volunteers over the age of 18 from 1992-1998. The study grew from a frustrating pattern observed by Felitti in his weight loss clinic. He had a substantial subset of patients that would drop out of the program, only after experiencing successful weight reduction. Motivated by this, he began to interview these patients. Through these interviews he discovered that a disconcerting number of them had experiences of childhood trauma. He eventually connected with Anda, an epidemiologist at the CDC. The collaboration that resulted in the execution of the massive study. The results changed the way scientific communities looked at the epidemiology of illness.

The ACEQ (see Appendix E) assesses eight categories. Those are divided into Subtypes of Abuse and Household Dysfunction. Abuse consists of: Psychological, Physical, and Sexual. Household Dysfunction: Substance Abuse, Mental Illness, Violence towards Mother, Divorce/Separation, and Household Incarceration. The number endorsed is totaled and the results assessed. If any single ACE had been endorsed the likelihood of endorsing another was 87%. The results found a staggering 16% of participants endorsed ≥4 ACEs, and 11% ≥5. Women were 50% more likely to endorse ≥5 ACEs (Felitti & Anda 2009).

The ACE study laid foundations in social health that would eventually be complemented with advances in epigenetic technology. The term epigenetic was coined in 1942 by C.H. Waddington, and defines the study of genetic assimilation, alterations made to an already existing

genetic code. The field gained traction with a 1969 review by Griffith & Mahler and their development of the idea that DNA methylation existed as a specific means of modifying the functionality of DNA in relation to neuronal adaptation. As research into epigenetics has grown, it has become an important facet in the study of both ACEs and mental illness. Life experiences are not intangible, they can leave a physical imprint via epigenetic changes on DNA. Additionally, these changes are not limited to the immediate health of those they affect. Epigenetic changes are potentially heritable and can affect the health of future generations. A 2019 study by Bruning et al., confirmed one of the major concerns of the ACE study is chronic stress. Chronic stress in high ACE households leads to a constant state of heightened sympathetic activation, this activity induces epigenetic changes. A large ongoing systematic review of epigenetics, ACEs, and mental disorders found methylation of the glucocorticoid receptor NR3C1 gene was robustly correlated with ACEs (Nöthling et al., 2020). The authors identified effects on "neuronal functioning and maintenance, immune and inflammatory processes, chromatin and histone modification, and transcription factor binding" (Nöthling et al., 2020). Another recent systematic review noted global DNA hypo-methylation in first episode psychosis patients with ACEs (Tomassi & Tosato, 2017) as well. Considering approximately one in four children will experience some form of trauma before the age of 18 (Klaric & Lovri, 2018), the potential for ACEs environmental impact on development and epigenetic change is pronounced.

Prior to the ACE study in 1998 there was little investigation regarding the scope of childhood trauma and its contribution to the health and well-being of an adult individual. There was limited scientific literature. This was particularly true in relation to ACEs and those afflicted by severe mental illness. Some studies began to surface in the late 1960's evaluating the effects of child abuse. In patients with Schizophrenia, one study found that 32% had experienced early childhood physical abuse (Green, 1968). Another study indicated that children in households with one parent suffering from Schizophrenia had a 15% probability of developing the illness

themselves. That probability increased to ≥32% when the illness was present in both parents (Tableman, 1981). In a 1987 study by Beck & van der Kolk, 46% of female patients suffering from severe intractable psychotic disorder were found to have been the victims of childhood incest. Another study in 1991 reported that approximately 43% of chronically psychotic patients reported childhood abuse. The abuse was associated with earlier onset of dysfunction, as well as a greater incidence of comorbid substance abuse (Goff et al., 1991).

The potential scope of ACEs in SSD is broad and inextricable. ACEs have a strong correlation with the presence of SSDs as well as earlier onset of disease prodrome. One study found that a diagnosis of Schizophrenia presented up to 4 years earlier in patients with the presence of ACEs (Alverez et al., 2011). In general, women have later onset of symptoms (Kocsis-Bogár et al., 2018) without the presence of any ACEs. However, this sex related difference is eliminated in the instance of physical abuse, with its presence indicating earlier onset in both women and men (Kocsis-Bogár et al., 2018). Another study demonstrated earlier age of onset in women alone with the presence of ACEs (Comacchio et al., 2019). Increased ACEs are not just associated with earlier onset in women but appear to be predictive for earlier onset in women as well (Kocsis-Bogár et al., 2018).

In a large meta-analysis of patient-control, prospective, and cross-sectional cohort studies, across all study types there was significant association of ACEs and psychosis (Varese et al., 2012). One study of 50 women with a diagnosis of Schizophrenia demonstrated that 90% of the participants had at least one ACE and over 50% had four or more ACEs (Prokopez et al., 2018). In that study a higher ACEs score also indicated a greater prevalence of persistent auditory hallucination (Prokopez et al., 2018). A similar result was found in the previously mentioned study by Vallejo et al., 2016. This was a study of 51 men with a diagnosis of Schizophrenia. Of them, 94% had at least one ACE, with over 60% scoring four or higher. The study found a greater association of the ACE of familial mental illness, as well as the association of increased ACEs

and the presences of auditory hallucination. In a study of 50 men and 50 women, all diagnosed with Schizophrenia, 92% of the participants endorsed at least one ACE and 45% endorsed five or more (Propokez et al., 2020). A recent meta-analysis indicated that the total number ACEs was strongly associated with the severity of positive symptoms (Bailey et al., 2018) in patients with SSDs. An extensive review of ACEs and psychosis (Stanton et al., 2019) demonstrated increased ACEs indicated "increased risk of developing psychosis, increased severity of psychotic symptoms, increased frequency of affective symptoms and substance use, and worse functional impairment" (Stanton et al., 2019).

There are noted changes in GMV in both ACE and SSD populations. A study on total GMV in psychotic patients indicated significant decrease of total GMV in the ACE group (Frissen et al., 2018) versus those without ACEs. Reduced Hpc GMV as well as amygdala hyperreactivity has been shown in association with ACEs. It predicted worse treatment outcomes for those at risk of mental illness (Popovic et al., 2020). Chronic stress, as is often associated with ACEs patients, was found to reduce hippocampal dendrites (Magarinos et al., 2011). A functional magnetic resonance imaging study showed that ACE exposure resulted in aberrant function of parietal areas involved in working memory and of visual cortical areas involved in attention. Exposure to any ACEs has been associated with increased activation of left inferior parietal lobule, affecting working memory (Quidé et al., 2017). Dorsolateral prefrontal cortex is important in working memory and has been shown to exhibit significant reduction in activity during stress induction (Qin et al., 2009). In SSDs, decreased GMV in the left dorsolateral prefrontal cortex has been associated with exposure to sexual abuse. Patients with Schizophrenia and exposure to emotional neglect demonstrated reduction of right dorsolateral prefrontal cortex (Quide et al., 2017). In another study in patients with Schizophrenia, sexual abuse and physical neglect were both negatively associated with functional connectivity of the amygdala and left precuneus during emotion processing tasks (Cancel et al. 2017). Results have indicated that with a greater incidence

of ACEs in SSDs there is increased activation of the posterior cingulate cortex/precuneus and dorsomedial prefrontal cortex, as well as reduced activation of the right temporoparietal junction (Quidé et al., 2017). The posterior cingulate cortex/precuneus are associated with self-related imagery and interpreting image information, dorsomedial prefrontal cortex social cognition, temporoparietal junction salience and social context. The functional variations within these areas are implicit in the observed social cognitive impairments of SSDs (Quidé et al., 2017).

Review of ACEs Instrument Prevalence

Adverse childhood experiences have been shown to have cumulative effects on the health and well-being of individuals well into adulthood (Felitti & Anda et al., 1998). The continued growth and expansion of this developmental research subsequently led to a number of instruments designed to measure adverse childhood experiences. Initially the number of studies of ACEs was limited as were the tools that scientists and physicians had to assess them. Prior to the ACEs study, the most frequently evaluated ACEs were sexual abuse, physical abuse/neglect, emotional abuse/neglect. Studies looked at all or one of these in any given population.

These newer ACEs instruments do not assess a consistent set of traumatic events (Saini et al., 2019), as some events are not even broadly designated as trauma, such as domestic chaos or parental discord (Roy & Perry 2004). Instruments continue to commonly measure physical, emotional, and sexual abuse; but some instruments now quantify additional events such as neglect, loss of a parent or parents, exposure to illicit activity by a parent, domestic violence, or parental mental illness (Felitti & Anda et al., 1998). Some instruments also attempt to measure severity of events and assess exposure time frames.

Because of these broad variations ACEs assessment instruments continue to have a lack standardization for use within patient populations. There are many studies that attempt to address

instrument metrics and validity, though there are still no clear guidelines for assessments (Briere, 1992, Bernstein et al., 2003). The use of many different instruments with widely different parameters presents a confounding element to the assessment of childhood trauma when correlated with disease incidence. Different parameters may present differences in disease association and skew the relationship between trauma and disease presentation. This could result in missing critical data in specific population groups. In these instances, an ACE/outcome association might exist and fail to be measured due to instrument variation. For example, in populations with incidence of a parent with severe mental illness, offspring had a risk that was more than double that of the control population (Rasic et al., 2014). Currently there are over 50 instruments available to assess ACEs with variations in content, criteria, and administration.

There are two systematic reviews, Williams et al., 2018 and Matheson et al., 2013, that look at the association of psychosis and childhood trauma, both assessing for association of childhood trauma and disease presentation. In the 2004 review by Roy & Perry endeavored to measure psychometric properties of various instruments and determined that despite the well-established association between childhood trauma and incidence of psychotic disease, consolidation of measurement used would facilitate translation of data across studies. And in 2018 Saini et al. published a systematic review looking at instrument criteria in general and determined that "refined instruments with a focus on capturing abuse events during development are warranted in addition to further evaluation of the psychometric properties of these instruments". Because of this variety and scope of instruments, it is important to assess the prevalence of instruments used. To our knowledge there are no studies that look at the prevalence of instrument use in the assessment of childhood trauma in individuals with psychosis.

BDNF

BDNF is a neurotrophin, a specialized peptide that acts similarly to a neurotransmitter in the brain. Neurotrophins require no mechanism to clear or recycle themselves, as is the case with neurotransmitters, and are not cytotoxic in excess. Collectively neurotrophins are important in neuronal growth, proliferation, and signaling. Of the seven known neurotrophins, four are found in humans: neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), nerve growth factor (NGF), and brain derived neurotrophic factor (BDNF).

Neurotrophin receptors, Tropomyosin-related kinase receptors or Trk, are part of the receptor tyrosine kinase superfamily. There are 3 Trk receptors: TrkA, B, and C. These receptors have a high binding affinity with neurotrophins. Each receptor has subset specificity for a particular neurotrophin. TrkA binds NGF and NT-3, TrkB binds NGF, NT-3 and NT-4, and TrkC binds NT-3. The Trk receptors have variations in the isoform of their extracellular domains. These variations in extracellular domain further regulate which neurotrophins can effectively bind the specific receptor. Because of isoform specificity, each receptor has an associated isoform specific neurotrophin. Trk A is isoform specific for NGF and TrkB is isoform specific for BDNF (Huang & Reichardt, 2003).

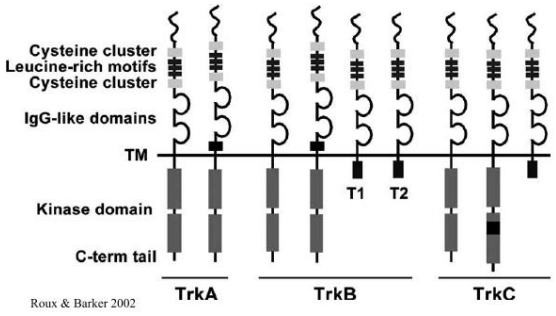

Figure 2. Trk domain and isoform specificity (Roux and Barker, 2002).

BDNF/TrkB receptor signaling is multifaceted and activates three important cellular cascades: phospholipase C (PLC) -γ1, phosphoinositol 3 kinase (PI-3K), and Ras via Son of Sevenless (SOS). Both the PLC-γ1 and Ras via SOS cell signaling cascades activate mitogen activating protein kinase / extracellular signal-related kinase (MAP/ERK) pathway. This pathway works via phosphorylation, which acts like an on/off switch for transcription factors (Orton et al., 2005). Here it upregulates the activity of transcription factor cAMP Response Element Binding protein (CREB) (Fang et al., 2003, Kaplan & Miller, 2000). CREB is an extremely prolific transcription factor and is activated by most neurotransmitters signaling cascades. It is responsible for the transcription of over 5000 genes including c-fos, BDNF, tyrosine hydroxylase, neuropeptides such as somatostatin, enkephalin, VEGF, and corticotropin-releasing hormone (operativeneurosurgery.com, Briand et al., 2015). CREB is critical in learning, memory, addiction, and mental health. The PI-3K cascade is anti-apoptotic, activating Akt which inhibits proapoptotic BCL2 associated agonist of cell death (BAD) and via up regulation of NF-κB transcription factor which promotes neuronal cell survival (Middleton et al., 2000) via Bcl-2, anti-apoptotic molecule.

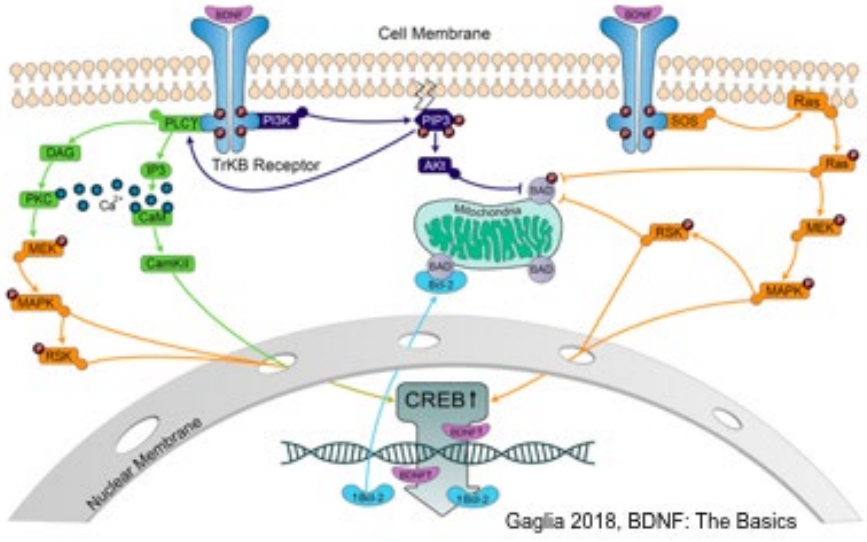

Figure 3. BDNF/TrkB activation and signal cascade, leading to CREB transcription factor activation and upregulation of BDNF and Bcl-2.

In addition to Trk receptors, neurotrophins may bind and activate receptor p75NTR. This receptor is a member of the tumor necrosis factor superfamily of receptors. It was discovered during early efforts to identify NGF receptors and because of this association was thought to be specific to NGF (Huang & Reichardt, 2001). However, it has since been determined to have an equally low binding affinity for all neurotrophins. p75NTR binding can induce apoptosis of some cells and support survival of others. In apoptosis, p75NTR activates p53 via the Jun kinase cascade. The Jun kinase cascade induces Fas ligand expression and receptor binding and up-regulates proapoptotic Bax gene. p75NTR promotes survival in only certain cell populations via activation NF-κB, promoting neuronal survival in both embryonic sensory and sympathetic neurons (Huang & Reichardt, 2001). If any of the Trk receptors and p75NTR are both activated, the Trk signaling suppresses the proapoptotic signaling of p75NTR. Interestingly Trk signaling does not suppress and appears to work synergistically with the NF-κB/p75NTR signaling pathway to support survival (Huang & Reichardt, 2001). The p75NTR signal suppression seems to be regulated by the Trk signaling Ras and PI-3K pathways.

BDNF is a peptide hormone. Transcription generates preproBDNF, which is translated to proBDNF and then cleaved to BDNF. Unlike many peptides, both proBDNF and mature BDNF are capable of signal activation. BDNF binds with great affinity and specificity to the TrKB receptor. ProBDNF, however, binds preferentially to the p75NTR receptor. In embryonal development P75NTR acts via the upregulation of the transcription factor NF-κB to support embryonal neurons (Huang & Reichardt, 2001). After birth p75NTR functions mainly to negatively regulate neurons via apoptosis and inhibition of dendritic arborizations. In the rapidly growing and changing brains of children and adolescents, p75NTR acts in tangent with the positive neuroplastic regulation of BDNF, supporting the dynamic plastic changes. Until adulthood the circulating levels of BDNF and proBDNF are relatively equal (Yang et al., 2014). In adulthood, BDNF levels rise and proBDNF decreases significantly. This change in

concentration is contributed to greater demand for plasticity and neuronal pathway remodeling because of rapid and constant growth and restructuring of pathways during development (Miranda et al.,). With age, the need for rapid changes in plasticity is moderated and thus the proBDNF declines. Increases in proBDNF are seen in pathologic issues of plasticity in diseases of advanced age such as Alzheimer's disease (Miranda et al., 2019).

BDNF transcription is activated by autocrine stimulation of BDNF binding TrkB receptors (Lu, 2003) or via paracrine stimulated activation of CREB transcription factor through the activity of excitatory neurotransmitters (Tao et al., 1998). BDNF transcription works on a positive feedback loop. The more circulating BDNF, the more activation of BDNF transcription and release. Levels of BDNF in serum have been shown to be consistent with levels in cerebrospinal fluid, making measurement in serum a reliable indicator of systemic BDNF (Pillai et al., 2010, Sahu et al., 2015). Enhancement of BDNF gene expression requires an increase in intracellular calcium concentrations necessary for PLC-γ1 signal cascade (Lu, 2003), a common signal cascade of most G-protein coupled neurotransmitters. The expression of BDNF mRNA is enhanced with glutamate receptor activity and suppressed with GABA-A receptor activation (Lu, 2003). Cholinergic afferent inputs to the cortex and Hpc also increase the levels of BDNF mRNA. D1 receptor activation leads to CREB up-regulation whereas D2 activation is inhibitory (Fang et al., 2003).

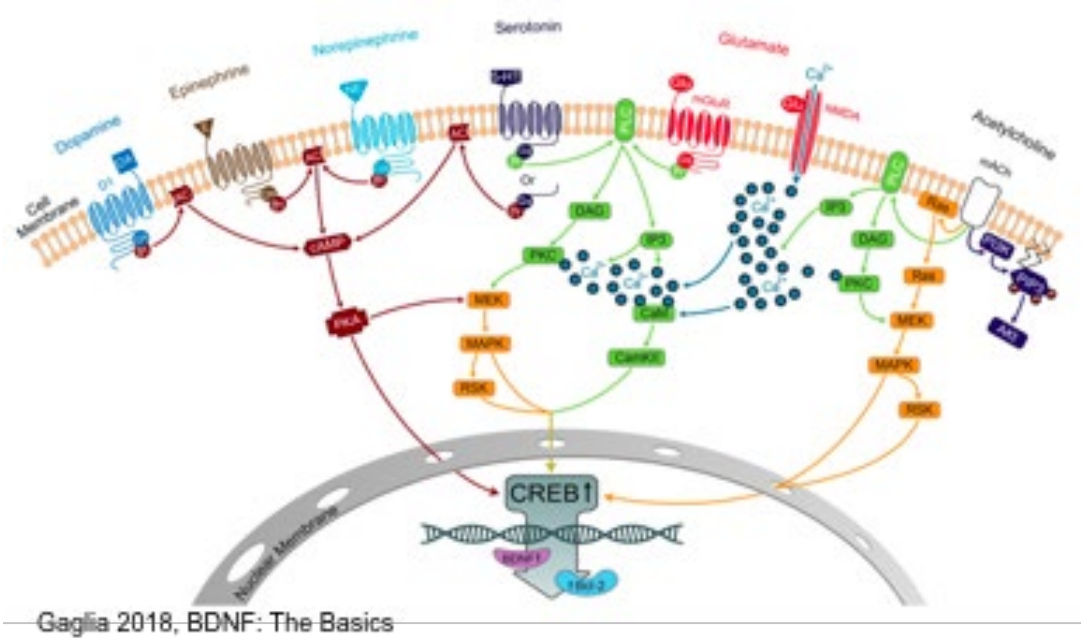

Figure 4. Neurotransmitter activation and signal cascade leading to upregulation of CREB transcription factor, BDNF, and Bcl-2.

BDNF functions to support various areas of the brain, including the Pfc, the area in charge of executive function and decision-making (Chang et al., 2018). It is important in axonal guidance and elongation, dendritic collateral branching, and synaptogenesis (Yoshii & Constantine 2010, Figurov et al., 1996). The shape and structure of dendritic spines change to aggregate and store incoming information over time. Axonal growth allows modification and adjustment of nervous system pathways to acclimate to changes in thoughts and behaviors. BDNF works on a positive feedback loop, dependent on those actively firing neurons. (Lu, 2003). Active neurons respond to excitatory synaptic activity from neurotransmitters or BDNF by rapidly inducing BDNF mRNA production as well as cell surface insertion of additional TrkB receptors (Lu et al. 2003). In the neocortex, BDNF is critical to dendritic arborization of pyramidal neurons and circuitry and signal modulation (Huang & Reichardt, 2001, Escobar et al. 2003). BDNF supports plasticity via LTP in the insular cortex (Escobar et al. 2003). In both the somatosensory and visual cortices activity induced expression of BDNF was decreased with signal deprivation.

In studies of Xenopus retinal ganglion, exogenous BDNF led to increased complexity of axonal branching and dendritic arborization (Lom & Cohen, 1999). BDNF is implicated in the formation of ocular dominance columns via sorting effects on thalamic afferents (Huang & Reichardt, 2001). Increased BDNF levels enhance maturation of interneurons. BDNF mediates the critical period of visual development via thalamic afferent sorting and excitation of pyramidal neurons from visual stimuli (Huang & Reichardt, 2001).

BDNF plays a key role in the Hpc. It maintains neuroplasticity and mediates neurogenesis throughout the brain in childhood and adolescence. Continued neurogenesis occurs only in the Hpc throughout adulthood as well (Stanton et al., 2020) and has continued support via BDNF activity. It functions to maintain neuroplasticity in the Hpc by acting as a signal protein for axonal guidance as well as assisting in conversion of early LTP to late LTP (Purves et al, 2001). Because BDNF has a slower rate of transcription than c-fos, another CREB protein associated with early LTP, it is considered critical for the transition of acute to late LTP which is critical for long-term memory formation in the Hpc (Lu, 2003). BDNF is expressed in pyramidal neurons of Hpc layers CA1 and CA3. TrkB is expressed more ubiquitously throughout the Hpc: CA1 and CA3 pyramidal cells, dentate granule cells, and inhibitory interneurons (Huang & Reichardt, 2001). Very few p75NTR receptors exist here, and therefore exhibit little influence on signaling. The BDNF/TrkB signaling in the Hpc is believed to support LTP via modulating the presynaptic nerve terminal effectiveness. BDNF generates repeated exocytotic signals to enhance the effectiveness of presynaptic signals reaching postsynaptic neurons. BDNF also enhances presynaptic vesicle release, promoting vesicle docking at presynaptic membrane (Huang & Reichardt, 2001).

Because BDNF is associated with neurogenesis and dendritic remodeling, it has been a target of interest for stress and trauma-related changes in neuronal function and physiology as well as psychological disorders (Theleritis et al., 2014) where levels have been shown to be

decreased. There is existing support for dose-response relationship in ACEs exposure and BDNF levels, with greater exposure demonstrating lower levels in patients with psychoses (Aas et al., 2013). Cortisol, the body's major stress hormone, reduces BDNF mRNA levels in the Hpc. Patients with low plasma BDNF levels who have a history of ACEs can indicate more progressive illness (Aas et al., 2019). Both acute and chronic stress demonstrate decreased BDNF levels in the Hpc in animal models (Neto et al., 2011). Exogenous glucocorticoids also reduce Hpc BDNF levels (Neto et al., 2011).

BDNF levels have been shown to be decreased in patients with Schizophrenia (Fernandes et al., 2015, Stanton et al., 2020). There is evidence that BDNF expression increases with the administration of antipsychotic medications, particularly atypical antipsychotics (Gonzales-Pinto et al., 2010). D1 receptor activation leads to CREB/BDNF up-regulation but D2 activation inhibits BDNF expression (Fang et al., 2003). Because both typical and atypical antipsychotics act predominantly as D2 receptors antagonists (Mauri et al., 2014), this may be why we see increases in BDNF levels in medicated vs drug-naïve patients with SSD. The plasma levels of BDNF in 18 first episode psychosis drug naive subjects were found to be decreased versus controls. Following antipsychotic treatment with olanzapine, the BDNF plasma concentration increased toward control levels (González-Pinto et al., 2010). The antagonism of 5-HT2A by ketanserin, a quinazoline derivative 5-HT antagonist sometimes used as an anti-hypertensive, partially blocks the effect of stress on BDNF expression (Neto et al., 2011). This 5-HT2AR antagonism again contributes to the effectiveness of atypical antipsychotics such as clozapine and olanzapine but may also be a relevant mechanism in the approximation towards normal BDNF levels in treated patients. However, meta-analyses indicate that, despite the measured increase in BDNF in patients with Schizophrenia on anti-psychotics, their levels remain statistically lower than controls (Green et al., 2011).

BDNF has an important polymorphism associated with both ACEs and SSD, it is BDNF Val66Met. It is a SNP replacement of a valine (Val) with a methionine (Met) at position 66. The Met variants, Met/Met and Val/Met, are strongly associated with decreased neuronal BDNF levels. They show greater incidence of stress-induced paranoia than Val/Val carriers (van Winkel et al., 2008). MRI's have shown Met carriers to have decreased hippocampal volumes with comorbid ACEs. ACEs have demonstrated an additive effect on volume loss in the hippocampal subregions CA4/dentate gyrus and CA2/3 with the presence of the Met allele in Schizophrenia (Popovic et al., 2019). The Met allele is also associated with significant executive function impairments of cognition, working memory, and attention (Stanton et al., 2019). In a study of 249 patients with SSD with increased ACEs, those with a Met variant displayed worse cognitive dysfunction than monozygotic Val carriers (Popovic et al., 2019).

BDNF has been considered a potential biomarker for Schizophrenia because of its consistently lower levels in SSDs (Stanton et al., 2020). BDNF is vital in mental health and decreases or variation in BDNF levels are seen not only SSDs but also in MDD, BP I and II, and neurocognitive disease such as Alzheimer's disease and Parkinson's. Because of this it has been difficult to establish it as a diagnostic biomarker for SSDs, despites its strong association (Cattaneo et al., 2016). There is, however, potential for it to be effectively used as a biomarker for treatment efficacy in patients with SSD as demonstrated Zhang et al. 2018. This study measured plasma BDNF in patients with Schizophrenia. They were started on olanzapine, administered Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and BDNF levels were assessed over a 12-week course. The study found a significant positive correlation between increase in plasma BDNF and improvement in the RBANS total scores. They found significant correlation of BDNF increase and RBANS attention sub-score improvement in (Zhang et al., 2018). In this context, BDNF levels could be utilized similarly to certain cancer markers to assess patient progress and monitor treatment.

β-catenin

β-catenin is a highly conserved protein most commonly associated with the canonical Wingless-type mammary tumor virus integration site (Wnt) signaling pathway during embryonic development (Medina et al., 2018). It serves two primary functions in adult physiology: cell adhesion and as a genetic transcription factor. It has since emerged as a critical neurotrophic factor (Zhang et al., 2018). β-catenin has been shown to function in regulating neuronal development and differentiation of nerve cells (Teo et al., 2018), and dendritic morphogenesis and axonal guidance (Zhang et al., 2018). It also functions in synaptic stabilization and neuroplasticity in the formation and maintenance of memory within the Hpc (Teo et al., 2018).

β-catenin is ubiquitously expressed throughout the body, including the brain. Animal studies have indicated expression is greatest in neurons during development, with an initial decline and plateaus throughout adulthood. In advanced age, β-catenin levels show increases (Teo et al., 2018). Levels during development are critical. Under expression may cause decrease in progenitor cells with premature differentiation of cells. Overexpression can cause the opposite, decreased differentiation and excessive neuronal outgrowth (Teo et al., 2018).

Wnt3a, a prototypic Wnt ligand, binds an NMDA receptor and activates the Wnt/β-catenin pathway, with stimulation of Wnt expression and rapid secretion. When the Wnt/β-catenin pathway is inactive, β-catenin is phosphorylated and marked for proteasome ubiquitination via glycogen synthase kinase 3 β (GSK3β). There are both canonical and non-canonical signaling pathways activated by the secreted Wnt. The canonical pathway is the Wnt/β-catenin pathway. Wnt ligand binds Frizzled (Fzd) and LRP5/6 co-receptors. This activates Dishevelled (Dvl). Dvl inactivates GSK3β, which inhibits the phosphorylation and ubiquination of β-catenin. This allows β-catenin to saturate the cytoplasm, which results in nuclear

translocation of β-catenin. In the nucleus, it acts as co-activator with TCF/LEF1, as a multifunctional transcription factor for target genes (Zhang et al., 2018, Teo et al., 2018).

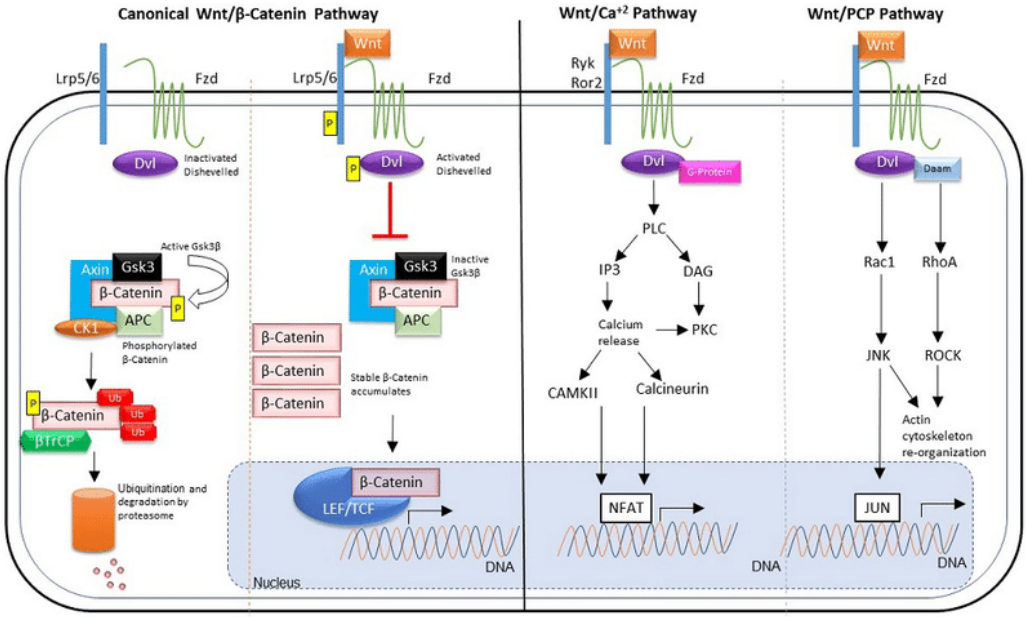

Figure 5. Overview of Wnt canonical and non-canonical signaling pathways.
(Garcia et al., 2018)

β-catenin supports synaptic stability by acting as an adhesion protein in cytoskeletal composition. It acts as an anchor for E-cadherin, which links to the actin cytoskeleton in Hpc, hypothalamus, and amygdala (Teo et al., 2018). β-catenin has also been shown to have important maintenance function in dendritic arborization as a cytoskeletal element within the Hpc supporting synaptogenesis (Yu & Malenka 2003). Cadherin-complexes are regulated during synapse formation and remodeling by redistribution of β-catenin to active spines (Chen et al., 2006).

The Wnt/β-catenin pathway modulates BDNF expression. Activity-dependent Wnt secretion acts as paracrine stimulation of BDNF transcription in nearby cells, as well as activated neurons, contributing to the potentiation of neural circuits (Zhang et al., 2018). In a study of cortical cultures, Wnt3a induced both β-catenin and concomitant BDNF up-regulation (Zhang et

al., 2018). In vivo studies with intrathecal Wnt3a injection resulting in significantly increased BDNF expression following administration. β-catenin is likely to directly target BDNF expression because β-catenin's' promoter contains the binding motif for BDNF's co-activators, TCF/LEF1. Considering the common functions as both neurotrophic and cytoskeletal agents, their co-activation could be particularly important in diseases like schizophrenia, in which decreased or modulated expression of both proteins is indicated. Sutton et al., 2007 found that both haloperidol and clozapine up-regulated the expression of Wnt pathway molecules including β-catenin. This could be a modulating factor in the increase in BDNF expression seen in treated patients.

Studies on the expression or presence of β-catenin in relation to Schizophrenia have consisted of gene mapping and expression (Pedrosa et al, 2010), as well as protein expression in particular brain areas (Park et al, 2011). As early as 1998, Cotter et al. found a decrease in the concentration and distribution of β-catenin in Hpc of postmortem Schizophrenia patients. One study found significantly increased Wnt-1 expression in the CA3 area of the Hpc pyramidal cells in post-mortem patients with Schizophrenia (Miyaoka et al., 1999) vs controls.

In the dorsolateral prefrontal cortex of post-mortem schizophrenia patients, another study found reduced levels of the GSK3β (Kozlovsky et al., 2004). This is interesting given the effects of chronic stress and cortisol on GSK3β and β-catenin. Stress has been shown to modulate GSK3β activity and subsequent β-catenin expression (Garza et al., 2012). An animal study using dexamethasone to induce the physiologic state consistent with chronic stress found decreased phosphorylation of GSK3β and subsequent increased GSK3β activity and decreased levels of β-catenin (Garza et al., 2012) in the Hpc. A study of chronic stress induced by repeated forced swim tests resulted in a reduction of phosphorylated GSK3β, rendering it active with increased overall levels of GSK3β and decreased β-catenin in Pfc and dorsal Hpc (Teo et al., 2018). Another clinical study found a positive correlation of GSK3β and negative symptoms in psychosis

(Bouseman et al., 2013). Chronic stress upregulates activated GSK3β, and the subsequent increased negative symptoms, and decreases β-catenin. It is possible following a time with sensitization of cortisol, there is similar sensitization with GSK3β, seen in post-mortem Schizophrenia patients.

Wnt/β-catenin signaling is modulated by a family of secreted glycoproteins Dickkopf (Dkk) 1-4. These suppress Wnt signaling and are crucial for embryonic development (Ftouh et al., 2005). In adults they are involved in apoptosis and synaptic regulation (Ftouh et al., 2005). Dkk-1 promotes endocytosis of the LRP5/6 co-receptor, preventing β-catenin translocation, which results in neuronal apoptosis and dendritic atrophy (Teo et al., 2018). Elevated stress has been shown to induce elevated levels of Dkk-1 in mice. In patients with Schizophrenia significantly higher levels of Dkk-1 were found (Al-Dujaili et al., 2020). Dkk-3 is densely expressed in the superior temporal cortex. In patients with schizophrenia, Dkk-3 expression was significantly decreased (Ftouh et al., 2005). There is definite reason to continue to build understanding of the association of β-catenin and SSD.

Cortisol

Glucocorticoids are important hormones necessary to maintain homeostasis in times of biological insult. Cortisol is the active glucocorticoid in humans. It regulates metabolism, modulates inflammation and immune function, and mediates response to stress (Thau & Sharma, 2020). There are glucocorticoid receptors (GR) ubiquitously throughout the body. They affect most organ systems including metabolic, immune, and nervous. Cortisol will bind mineralocorticoid receptors (MR), but with lesser affinity. MR are not ubiquitous and therefore much more tissue specific.

Cortisol is a steroid hormone, synthesized from cholesterol. Cortisol release is regulated via a negative feedback mechanism at various levels of expression via GR in the PVN or in the adrenal gland. Expression of cortisol is elicited in response to stress stimuli. Excitatory signaling is sent via the nucleus of the solitary tract (NTS) of the sympathetic nervous system (SNS). The SNS signals the hypothalamus at the paraventricular nucleus (PVN) to release corticotropin releasing hormone (CRH) in response to a stress stimulus. CRH acts on the anterior pituitary which releases adrenocorticotropic hormone (ACTH). ACTH stimulates adrenal cortical cortical zona fasciculata cells and the release glucocorticoids, primarily cortisol. Only a small percent of cortisol circulates freely in the blood, approximately 4%. The rest is bound to corticosteroid-binding globulin (CBG) or albumin (Ramamoorthy & Cidlowsky, 2016). In the absence of stimuli, the HPA-axis is regulated by circadian rhythm, resulting in higher cortisol levels in the morning at waking and lower levels at night (Ramamoorthy & Cidlowski, 2016).

GR are intracellular and bound to chaperone proteins in the cytoplasm (Kadmiel & Cidlowski, 2013). When cortisol binds the GR, it undergoes a conformational change and translocates to the nucleus where it functions to suppress or enhance transcription. Cortisol functions this way to ensure availability of resources in the event of a challenge and suppressing unnecessary protein production. Transcriptional modulation of cortisol signaling is mediated via diverse receptor isoforms resulting from alternative splicing and alternative translation initiation. Transcriptional and translational isoforms of GRs are widespread allowing for refinement of GR signaling in a given cell or a tissue type (Kadmiel & Cidlowski, 2013). Cortisol transcriptional variation is also modifiable via the GRE unit upon translocation of the cortisol/GR unit (Kadmiel & Cidlowski, 2013). GREs are imperfect palindromic sequences of DNA containing two hexameric half sites separated by three base pairs (Kadmiel & Cidlowski, 2013). GREs provide additional signal modifications. These modifications allow increased selective regulation of both suppression and enhancement of gene expression.

In the immune system, cortisol is critical in mediating ant-inflammatory responses and acts on most cells of the immune system (Kadmiel & Cidlowski, 2013). It inhibits dendritic cell maturation, mediates migration and apoptosis. It has been shown to enhance phagocytosis of polymorphonuclear leukocytes (PMNs) by macrophages, thereby decreasing their inflammatory activity. It inhibits PMN migration by decreasing cell adhesion molecule expression (Kadmiel & Cidlowski, 2013) but also appears to inhibit PMN apoptosis. Cortisol induces apoptosis of inflammatory T cells, while enhancing survival of T regulatory cells. In B cells it can cause decreased mature cell numbers and increased number of progenitor cells. It decreases B cell levels of Bcl-2 anti-apoptotic protein, and subsequently increases B cell apoptosis. Cortisol is important in the management of metabolism and glucose availability, ensuring adequate availability for the brain. It acts on the liver, pancreas, adipose and muscle. Increased levels in the liver lead to decreased glycogen synthesis and increased gluconeogenesis. In the pancreas, cortisol increases glucagon expression and decreases the expression of insulin. (Thau & Sharma, 2020)

Cortisol activity in the nervous system is most important in response to stress via the HPA-axis. Cortisol is released in response to stress stimuli, which can be an actual threat or an anticipated threat or stress event. Cortisol enhances the expression of glucagon, epinephrine, and other catecholamines. GRs in the forebrain regulate HPA axis and behavior under stress. GRs in the amygdala play an important role in memory acquisition and fear conditioning (Kadmiel & Cidlowski, 2013). In a state of acute stress, the body will upregulate cortisol expression. The body does this with the intention of fueling catabolic processes to provide itself with energy via regulation of glucose in the liver and pancreas to support the fight or flight response to stress. In abbreviated instances of acute stress, this system functions well to mitigate the stress event. Levels will return to normal through feedback inhibition of the HPA-axis, Pfc, and Hpc (Lee et al., 2015).

In the Hpc, GR are most densely expressed in the dentate gyrus, though they are expressed throughout CA1-4 as well. As mentioned, the Hpc and Pfc are important areas in feedback regulation of cortisol. In the instance of chronic stress and the stress signaling is not abated, circulating cortisol remains elevated. This continued elevation eventually results in damage to both hippocampal and cortical neurons (Lee et al., 2015). This affects the brain's ability to regulate cortisol via the inhibitory feedback mechanism. GR density has been shown to be markedly decrease in the Hpc dentate gyrus, CA1, CA3, and CA4 of Schizophrenia patients versus controls (Webster et al., 2002). The same study also demonstrated decreases in GR in both Pfc and inferior temporal cortex (Webster et al., 2002). Receptor trafficking is a common method to manage signaling when an overabundance of a signal molecule is present to prevent excitotoxicity. These marked decreases in GR may be representative of actual cell loss as GMV loss is seen in SSD in these areas (Webster et al., 2002). In animal studies with induced chronic stress or repeated glucocorticoid administration, results show degeneration of Hpc neurons, with dendritic atrophy and decreased cell size (Popovic et al., 2020). This cortisol induced neurotoxicity can lead to impaired or decreased myelination. Cortisol induced neurotoxicity can also affect signaling related to calcium channels caused by pathologic increase in intracellular calcium concentrations (Damsted et al., 2011). Animal studies have shown that high doses of methylprednisolone or dexamethasone increase apoptosis in the PVN. The high dose GR activation in the PVN significantly inhibits Akt/CREB activation, which in turn reduced expression of anti-apoptotic Bcl-2 and BDNF, and increasing pro-apoptotic Bax gene expression and activating pro-apoptotic BAD signaling cascade leading to increased cell apoptosis (Zhang et al., 2020)

Higher cortisol activity levels seen in SSD have been associated with higher incidence of positive symptoms. This is suggestive of dysregulation of information coding, inhibiting patients with SSDs from discriminating between actual and irrelevant threats (Webster et al., 2002). As

mentioned previously, patients with Schizophrenia and/or ACEs have blunted cortisol levels in response to stress events versus controls (Ciufolini et al., in 2014, Zorn et al., 2016). A study of non-medicated first episode psychosis also indicated a blunted cortisol response (Popovic et al., 2020), indicating that antipsychotic medications are not mediating this response. This supports that cortisol expression itself is not mediated by antipsychotics. This differs from what has been seen with both BDNF and β-catenin levels and the use of antipsychotics, which appears to modulate levels.

CHAPTER III

METHODOLOGY

Institutional Review Board (IRB)

Human Subjects Protocols and Interventions IRB #2020021 Approved 6/29/2020.

IRB protocol was followed for all collection and handling of venous blood samples for this study.

See Appendices A, B, C, D, E, & F for all supplemental IRB materials.

Patient Selection

Participants were screened via onsite nursing staff to facilitate ease in assessing criteria for inclusion. Following positive recruitment assessment by nursing staff and willingness to participate, subjects were introduced to the research staff. All patients were required to be current on their medications to control for the potential of antipsychotics to modulate BDNF levels. Because the patients were recruited from an injection clinic, not only were they current but they

were all administered their injections on the day of recruitment, allowing for greater standardization of antipsychotic affect.

- Patient may qualify if they meet the following criteria:
    - Between the ages of 18-64
    - Current diagnosis and treatment of schizophrenia, schizophreniform disorder or schizoaffective disorder
    - Has completed at least 8 years of formal education
    - Speaks and reads English fluently
    - Does not have a proxy for medical decision-making, legal guardian, or been otherwise determined unable to give consent
    - Is current and compliant on antipsychotic medications
    - IQ >70 or no previous diagnosis of intellectual disability
    - No past diagnosis or suspected current diagnosis of a neurodevelopmental disorder (e.g., autism, learning disability) or neurocognitive disorder (e.g., dementia)
    - No history of major head trauma (defined as loss of consciousness for 30 minutes or longer) or brain surgery (Note: History of concussion, including brief loss of consciousness, is okay)
    - No history of psychosis secondary to a medical condition or diagnosis of psychosis secondary to substance abuse
    - No history of presence of endocrine conditions that would alter prolactin or cortisol levels, such as Prolactinoma or Cushings' respectively
    - If female, is not pregnant or lactating

Following assessment for inclusion criteria, all participants were administered informed consent forms, participant data sheet, ACEQ, and SCID-5-CV. Upon completion of all paperwork and assessments, participants were subject to collection of 8mL of blood in commercial red topped vacutainer tubes from Becton Dickinson (BD). Blood samples were collected on site at Family & Children's Services (FCS) by an FCS LPN/RN. Samples were spun down to separate clotted blood from serum on site by Primary Investigator (PI), Rebecca Gaglia.

See Appendix B.

ACEQ

The ACEQ is a self-reported instrument to assess Adverse Childhood Experiences designed by Filetti, et al 1998. One point is given for each affirmative answer to the assessment questions. The number endorsed per patient was totaled and the results assessed.

Adverse Childhood Experience (ACE) Questionnaire

Finding your ACE Score While you were growing up, during your first 18 years of life:

1. Did a parent or other adult in the household often …Swear at you, insult you, put you down, or humiliate you? Or Act in a way that made you afraid that you might be physically hurt?

2. Did a parent or other adult in the household often …Push, grab, slap, or throw something at you? Or Ever hit you so hard that you had marks or were injured?

3. Did an adult or person at least 5 years older than you ever…Touch or fondle you or have you touch their body in a sexual way? Or Try to or actually have oral, anal, or vaginal sex with you?

4. Did you often feel that …No one in your family loved you or thought you were important or special? Or Your family didn't look out for each other, feel close to each other, or support each other?

5. Did you often feel that …You didn't have enough to eat, had to wear dirty clothes, and had no one to protect you? Or Your parents were too drunk or high to take care of you or take you to the doctor if you needed it?

6. Were your parents ever separated or divorced?

7. Was your mother or stepmother: Often pushed, grabbed, slapped, or had something thrown at her? Or Sometimes or often kicked, bitten, hit with a fist, or hit with something hard? Or Ever repeatedly hit over at least a few minutes or threatened with a gun or knife?

8. Did you live with anyone who was a problem drinker or alcoholic or who used street drugs?

9. Was a household member depressed or mentally ill or did a household member attempt suicide?

10. Did a household member go to prison?

See also Appendix E.

Structured Clinical Interview for DSM-5 - Clinician's Version

The Structured Clinical Interview for DSM-5, Clinician Version (SCID-5-CV), is a structured interview for making DSM-5 diagnoses. Research PI, Rebecca Gaglia administered all SCID interviews for consistency. SCID results were reviewed with advisor following completion. The use of the SCID allows for consistency in diagnostic procedure as well as assessment of Use Disorder (UD), which has a strong association with SSDs. It takes care to attempt to confirm onset of disease prodrome in the context of illness, substance use, and changes or discontinuation of medication.

See Appendix F.

Blood Draw Procedure

Blood samples were obtained from participants. Following standard sanitary blood draw procedures, 8.0mL blood was drawn from an antecubital vein. Red topped Becton Dickinson (BD) Vacutainer tubes were used for all samples. Samples were transported by PI from FCS to OSU-CHS for processing and long-term refrigerated storage, according to the established protocols of the OSU-CHS Biohazard Biosafety committee.

Biological Sample Storage and Processing

Blood was allowed to clot, undisturbed, at room temperature for 15–30 minutes. Blood was then chilled 10-20 minutes. The sample was centrifuged at 1,600 x g for 10 minutes to separate serum supernatant from clot. Following centrifugation, the serum was chilled at 2–8°C until transfer to lab for storage. Blood samples were transported from FCS to the OSU-CHS (E-367) by PI,

Rebecca Gaglia, following the established protocols of the OSU-CHS Biohazard Biosafety committee. The samples were maintained at 2–8°C during handling. Serum not analyzed immediately was apportioned into 1 mL aliquots and stored at –20°C. Additional aliquots of 3 sets of 200 microliters were made and stored at –20°C. Repeated freeze-thaw cycles were avoided. All ELISAs were processed from secondary aliquots with no samples thawed more than three times.

BDNF ELISA

Thermo Scientific Pierce Human BDNF ELISA Kit (EH42RB) was used to measure serum sample BDNF levels. Standards were run in duplicate and patient serum samples run in septuplicate. All samples were read immediately at 450nm and 550nm. Values at 550nm were subtracted from those at 450nm to correct for optical imperfection. A standard curve was generated from the mean of standards, line of best fit determined by regression analysis using a four-parameter (IC50, x-intercept, y-intercept, and slope) logistic curve-fit. Sample concentration was determined with standard curve and then multiplying value times sample dilution factor, 1:200.

See Appendix G.

β-catenin ELISA

MyBiosource Human β-catenin (CTNNβ) ELISA Kit (MBS724736) was used to measure serum sample β-catenin levels. Standards were run in duplicate and patient serum samples were run in sextuplicate, except A2 which had limited serum and was run quintuplicate. All samples were read immediately at 450nm. Optical Density (OD) values are subtracted by the mean of the blank

control wells prior to result interpretation. A standard curve was generated from the mean of standard, line of best fit determined by regression analysis using a four-parameter logistic curve-fit. Sample concentration was determined by the standard curve.

See Appendix H.

Cortisol ELISA

Thermo Fisher Scientific Human Competitive ELISA Kit (EIAHCOR) was used to measure serum sample cortisol levels. Standards were run in duplicate and patient serum samples run in septuplicate. All samples were read immediately at 450nm. All Optical Density (OD) values are subtracted by the mean of the blank control wells prior to result interpretation. Standard curve was generated from the mean of standard, line of best fit determined by regression analysis using four parameter logistic curve-fit. Sample concentration was determined by the standard curve.

See Appendix I.

Methodology for Systematic Review

The study searched Embase and SCOPUS, using six sets of search terms: adverse child experience psychosis (ACE P), adverse child experience Schizophrenia (ACE S), adverse child experience Schizoaffective (ACE Sa), childhood trauma psychosis (CT P), childhood trauma Schizophrenia (CT S), childhood trauma Schizoaffective (CT Sa).

The articles were compiled separately in duplicate to account for bias and reproducibility. Studies were pulled into Paperpile, a web-based reference management software program. They were sorted via exclusion/inclusion criteria as follows. Exclusion criteria were: 1) Outside of the date

range of January 2000 to May 2019, 2) Study does not assess childhood trauma, and 3) Study that does not include psychosis, Schizophrenia or Schizoaffective disorder.

Exclusions included reviews, commentary, and meta-analysis, poster/conference abstracts, and studies that do not have a definitive trauma assessment instrument. Detailed criteria are outlined in the supplement. Two independent reviewers (RJG and AS) reviewed studies and evaluated the titles and abstracts of all articles identified by the search strategies. The full articles of those remaining were assessed for the instrument used. The instruments isolated from the search were evaluated to ascertain the categories of trauma included and the instruments' prevalence of use. The PRISMA-P (Shamseer et al., 2015) was followed for this systematic review. Upon completion of exclusion criteria, remaining studies were sorted into subcategories based on the instrument utilized in the study to assess childhood trauma. These instruments were then quantified by prevalence of use.

See Appendix J.

CHAPTER IV

RESULTS

This study looked specifically within an SSD patient population to assess variation of biomakers within the population with respect to severity of ACEs scores. The exclusion of controls was adopted given existing evidence that there are already demostrable differences in SSD populations and controls. Therefore, the investigation was focused on effect within the disease population. The data collected from them was assessed and including population demographic and Use Disorder associations as well as the variation of biomarker levels in relation to the ACEs score severity.

The systematic review of instrument prevalence found an unexpected predominance of one study, the CTQ, with more evenly distributed use among most other.

Patient Demographic Analysis

Subjects were recruited from FCS, an outpatient Community Mental Health Center. The patient sample consisted of 11 patients (4 Female, 7 Male) with diagnoses of either Schizophrenia (Sz) or Schizoaffective (SzA), (Sz=2M), (SzA=4F, 5M). All subjects were administered the SCID-5-CV to confirm diagnoses, the ACEQ, and a blood draw to evaluate serum for biomarkers. Demographic information is illustrated in Table 1. Five of eleven participants lived

with a non-spouse family member, two with a spouse, and the remaining four lived by themselves or with a non-relative roommate. All had achieved a GED/Diploma or higher. 63.6% including, all four of the female participants, were Caucasian. The seven men offered a more diverse sample with some overlap in ethnicity: 42.9% Caucasian, 42.9% African American, and 28.6% Native American. 36% endorsed earning $10,000-$35,000, putting them at or within 200% of the Federal Poverty Level (FPL) for households of 1-3. The remaining 64% endorsed $0-$10,000, putting them well below the FPL.

Table 1. Demographic information of study sample	(n=11)
Mean Age years, SD	33.36 (9.12)
% Female	36.4
Ethnicity % (May Overlap)	
African American	27.3
Native American	18.2
Caucasian	63.6
Native Hawaiian or Other Pacific Islander	0
Asian	0
Hispanic	0
Education %	
High School / GED	54.5
Some Undergraduate Education	27.3
Trade Degree / Certification	9.1
Associate degree	9.1
Bachelor's Degree	0
Some Graduate Education	0
Graduate / Professional Degree	0
Military %	0
Marital Status %	
Single	54.5
Married	18.2
Separated	0
Divorced	27.3
Widowed	0
Occupation Status %	
Unemployed / Disability	54.5
Employed PT	9.1
Employed FT	27.3
Student FT	9.1
Student PT	0
Annual Income %	
$0 - $10,000	63.6
$10,000 - $35,000	36.4
$35,000 - $60,000	0
$60,000 - $85,000	0
$85,000 - Above	0
Insurance %	
No Insurance	54.5
Medicaid	27.3
Medicare	9.1
Private Insurance	9.1

Table 1. Demographic Information of Study Sample (n=11)

SCID

SCID-5-CV for Mood Disorders, Schizophrenia, and Use Disorder was performed on each participant. The SCID is extremely valuable in research involving mental illness. Though most psychiatric intake assessments are based on the criteria of the DSM-5, the SCID is formatted directly from it and ensures consistency in diagnosis. Of the patients that opted to participate, seven were diagnosed as SzA BP (Schizoaffective Bipolar Disorder), two with SzA D (Schizoaffective Depressive Disorder), and two with Sz (Schizophrenia). All patients endorsed delusions, hallucinations, and negative symptoms in the form of avolition. Only four demonstrated disorganized speech. None of the participants demonstrated disorganized behavior. Three of those four with disorganized speech, however, did endorse a UD.

Patient SCID Dx	SCID Dx Use	Delusions	Hallucinations	Disorganized Speech	Disorganized / Catatonic Behavior	Negative Sx
SzA BP	Mi-A	✓	✓			✓
SzA D	X	✓	✓			✓
SzA BP	X	✓	✓	✓		✓
Sz	Sv-C	✓	✓			✓
SzA BP	Sv-A, Mo-C	✓	✓			✓
SzA BP	Mi-A	✓	✓	✓		✓
SzA D	X	✓	✓			✓
SzA BP	X	✓	✓			✓
Sz	Mo-A	✓	✓			✓
SzA BP	Mo-C	✓	✓	✓		✓
SzA BP	Mo-C, Sv-M	✓	✓	✓		✓

Table 2. SSD, UD Diagnoses and Positive and Negative Symptom Endorsement

Use Disorder (UD) was assessed in all participants. UD diagnosis is assessed based on use of a substance over a 12-month period of time. This includes use that has stopped at present but was active within the last 6 months. The SCID assesses for an exhaustive of list substances, except Nicotine, but in this population only these were endorsed: Alcohol (A), Cannabis (C), or Methamphetamine (M). It can be characterized as Mild (Mi), Moderate (Mo), or Severe (Sv).

Seven of the eleven, or 64% of participants, endorsed varying degrees of UD. The most common was cannabis, in four of the seven (57%) followed by alcohol with three (43%), and only one endorsing methamphetamine use (14%). Two of those seven had two concomitant UDs (29%), and none had more than two.

ACEQ

Table 2 summarizes the total number of ACEs endorsed per patient from the ACEQ. The mean number of ACEs was 4.18 (±2.23 SD). The most commonly endorsed ACE was parental separation or divorce, with nine of eleven, (82%) of patients endorsing. The second most common, endorsed by eight of eleven, (73%) of patients, was a problem drinker/alcoholic or use of street drugs in the home. Two of the four female patients endorsed the sexual abuse, none of the seven male patients did.

Patient / ACEQ#												Total / ACEQ
1.			1				1	1		1	1	4
2.							1			1	1	3
3.		1				1						2
4.			1		1		1	1				4
5.							1	1		1		3
6.		1	1	1	1	1	1	1	1	1		9
7.						1		1				2
8.		1	1	1		1	1	1	1	1		8
9.	1			1		1	1	1		1		6
10.					1	1	1		1			4
Total / Patient	1	3	4	3	3	6	8	7	3	6	2	

Table 3. ACEQ# and Patient endorsement. Patient mean 4.18 (±2.23SD)

ACEQ Item	% Endorsed
1. Verbal abuse/threat	45.45%
2. Physical abuse	27.27%
3. Sexual abuse	18.18%
4. Emotional neglect	36.36%
5. Physical neglect	27.27%
6. Parental separation	81.82%
7. Domestic/Maternal abuse	18.18%
8. Household alcohol/substance abuse	72.73%
9. Household mental health / suicide	54.55%
10. Household member in prison	36.36%

Table 4. ACEQ Item % Endorsed

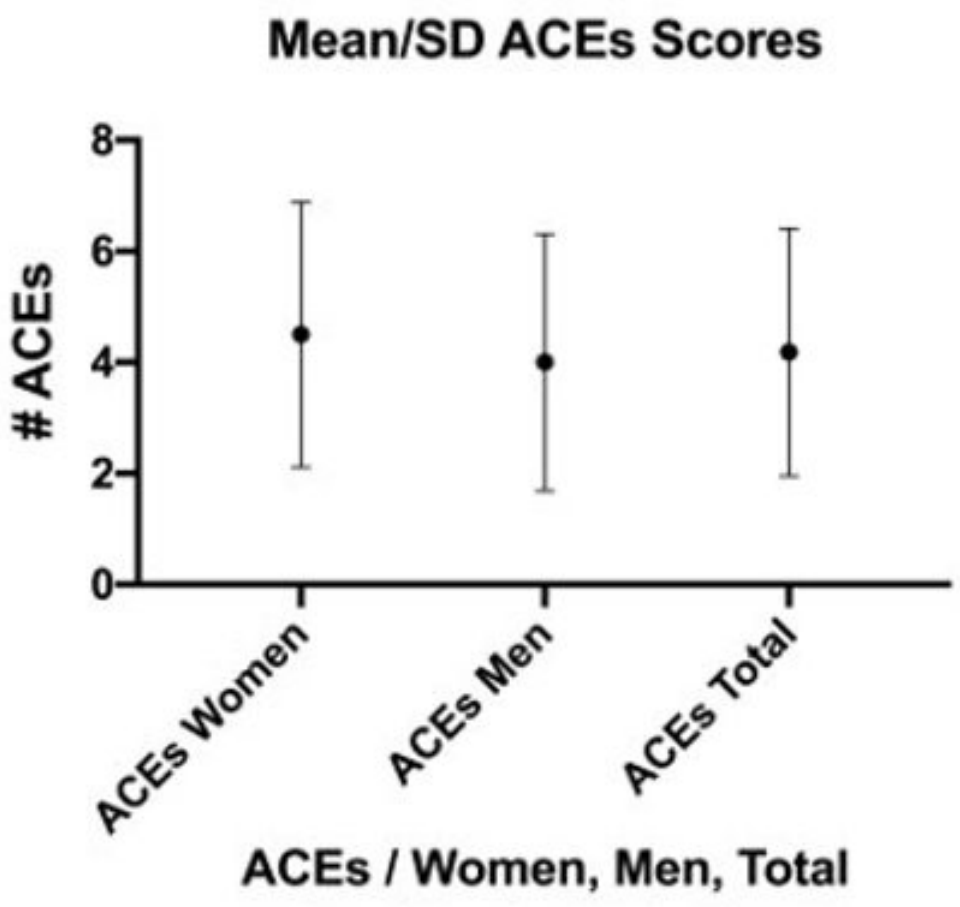

Figure 6. Mean & SD of ACEs Scores per population.

Every patient, (100%) endorsed at least 1 ACE. 90% endorsed ≥2 ACEs, 80% ≥3 ACEs, 45% ≥4 ACEs, and 36% ≥6 ACEs. Total ACEQ mean was 4.18 (±2.23 SD), Women had a slightly higher mean of 4.50 (±2.38 SD) than men 4.00 (±2.31 SD). In women 100% endorsed ≥2

ACEs, 75% ≥3 ACEs, and 50% ≥6 ACEs. In men 100% ≥1 ACE, 86% ≥3 ACEs, 43% ≥4 ACEs, and 28% ≥6 ACEs.

Evaluation of ACEs and BDNF, β-catenin, and Cortisol

ACEs score was assessed in relation to the expression of 3 hormones, BDNF, β-catenin, and cortisol. Pearson r correlation of ACEs, BDNF, β-catenin, and Cortisol. ACE and Cortisol demonstrate significant negative correlation (r=-0.66). BDNF and β-catenin demonstrated significant positive correlation (r=0.74).

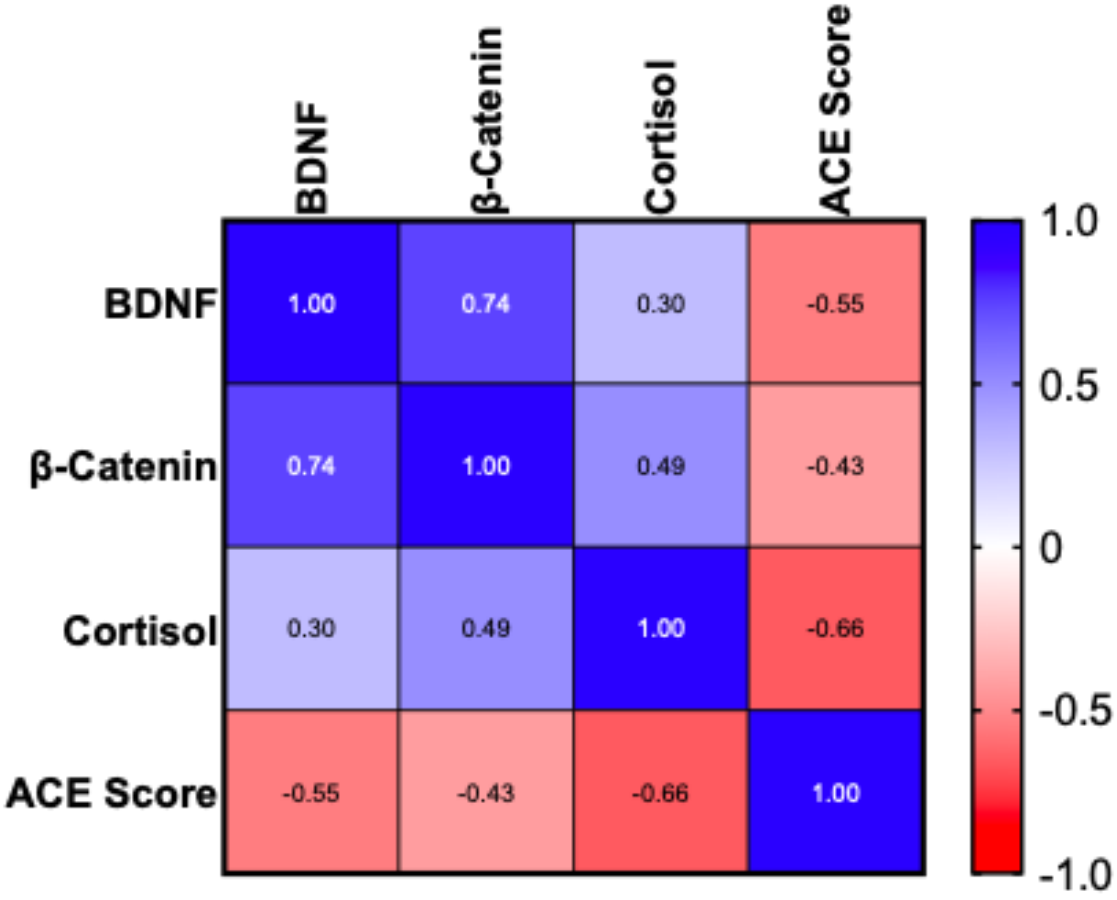

Figure 7. Pearson r correlation of ACEs, BDNF, β-catenin, & Cortisol.

Simple linear regressions were performed to analyze correlation and significance. BDNF and β-catenin both demonstrate downward trend but were not significant (p=0.08 & p=0.18

respectively). Cortisol demonstrated significant correlation (p=0.03). p≤0.05 for significance. The majority of patients were diagnosed as SzA BP. Because of the limited distribution of diagnoses in the limited sample size it wasn't possible to assess ACEs versus hormones across the different diagnoses.

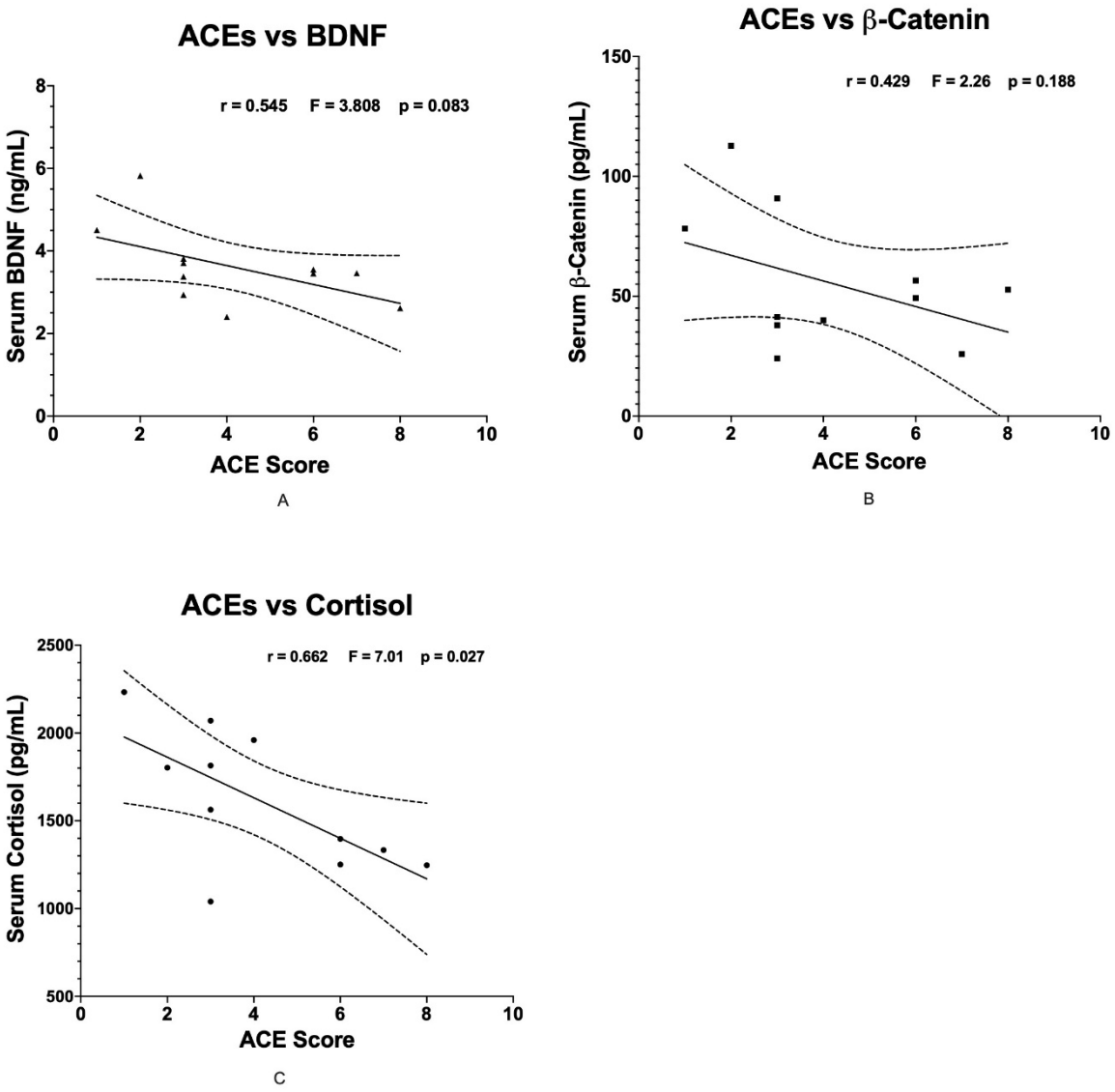

Figure 8. Simple linear regression of ACEs scores versus (A) BDNF, (B) β-catenin, (C) Cortisol

Populations were assessed comparing Female and Male ACE scores and hormone correlations. Simple linear regressions were performed to analyze correlation and significance. In Females BDNF and β-catenin both demonstrate downward trend but were not significant (p=0.45 & p=0.31 respectively). Cortisol demonstrated significant correlation (p=0.02). In Males all demonstrate downward trend, but none were significant (p=0.089, p=0.58, p=0.15, respectively).

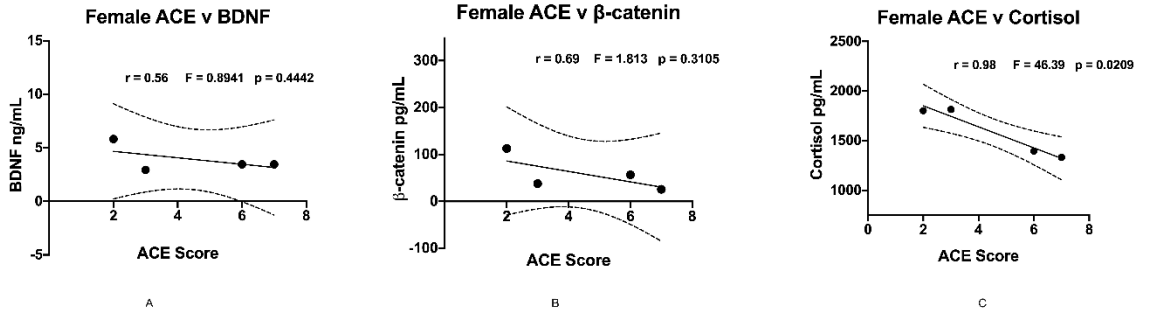

Figure 9. Simple linear regression of Female ACEs scores versus (A) BDNF, (B) β-catenin, & (C) Cortisol.

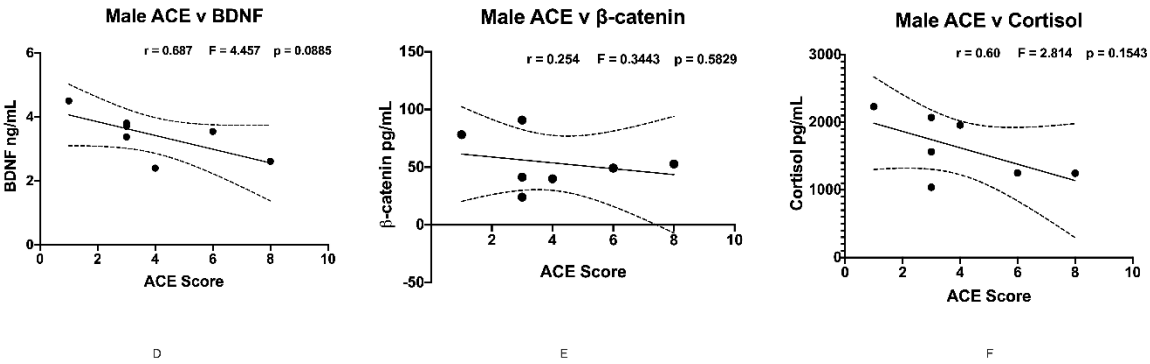

Figure 10. Simple linear regression of Male ACEs scores versus (A) BDNF, (B) β-catenin, & (C) Cortisol.

Patients with UD were extracted, and ACEs and hormone correlation were assessed. Simple linear regression of ACE scores in only patients that indicated UD versus hormone levels.

All demonstrated downward trends, but none were significant (p=0.16, p=0.35, p=0.12 respectively).

Linear regression of hormone levels versus number of UDs were performed. BDNF was significant for positive correlation with number of UDs (p=0.014). β-catenin demonstrated upward trending but was not significant (p=0.10). Cortisol indicated no correlation (p=0.77).

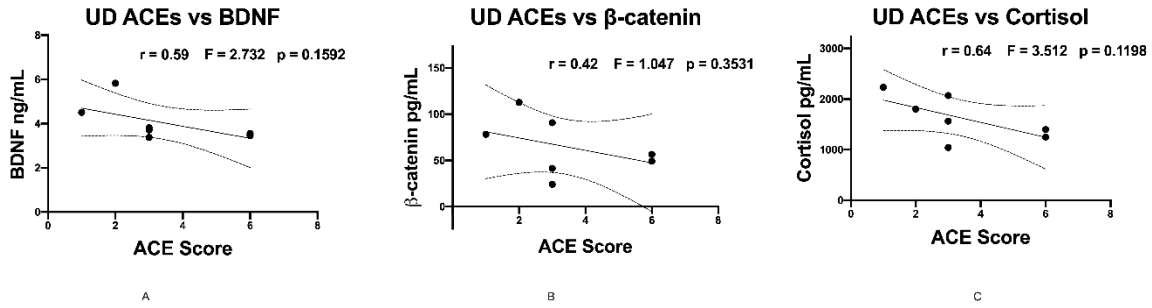

Figure 11. Simple linear regression of ACEs scores in only patients that endorsed UD versus (A) BDNF, (B) β-catenin, & (C) Cortisol

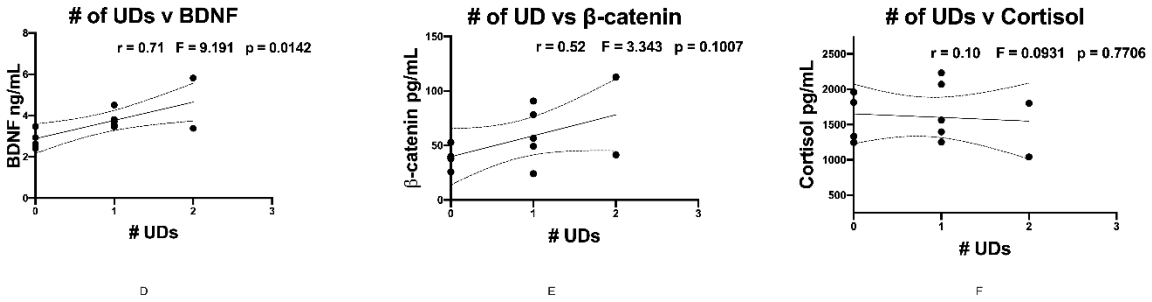

Figure 12. Simple linear regression of number of UDs endorsed per patient versus (D) BDNF, (E) β-catenin, & (F) Cortisol.

Systematic Review

Initial search generated 6,957 results, these were reviewed and included with confirmation of eligibility. Of these there were 170 studies that met criteria. Within these there were 24 instruments used alone or in combination with each other to assess childhood trauma in patients with psychosis.

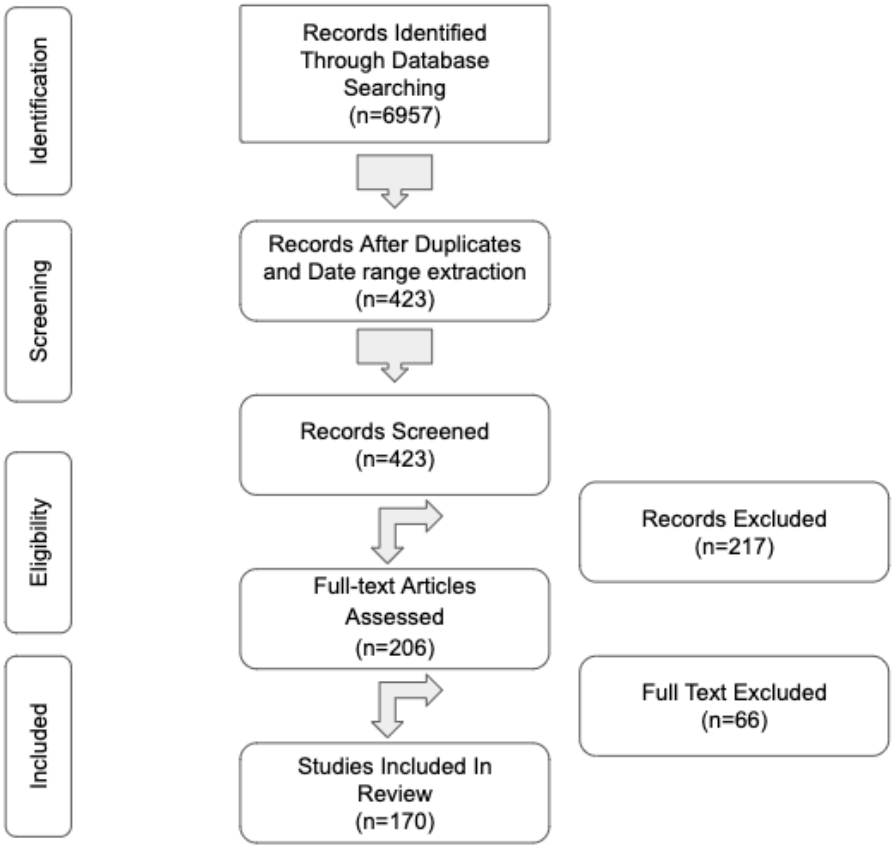

Fig. 13 Study Selection PRISMA Flow Chart

The instruments were isolated from each study and tallied by instrument. If a study used two separate instruments both were included to calculate prevalence. The Childhood Trauma Questionnaire (CTQ) accounted for 58.8% of studies. The Childhood Experience of Care and

Abuse Questionnaire and Childhood Experience of Care and Abuse Interview accounted for approximately 18.5% of studies, at 16.7% and 1.8% respectively. The Early Trauma Inventory accounted for 4.7% of studies. The remaining 20 studies account for the remaining 20%.

Instrument	# Studies	Prevalence
Childhood Trauma Questionnaire (CTQ)	100	58.82%
Childhood Experience of Care Abuse Questionnaire (CECA.Q/I)	31	18.24%
Early Trauma Inventory (ETI)	8	4.71%
Childhood Adversity Questionnaire (CAQ)	5	2.94%
Maltreatment and Abuse Chronology of Exposure (MACE)	4	2.35%
Childhood Abuse Questionnaire (CAQ)	4	2.35%
Adverse Childhood Experiences Questionnaire (ACEQ)	3	1.76%
Risky Families Questionnaire (RFQ)	3	1.76%
Traumatic Experiences Checklist (TEC)	3	1.76%
Child Abuse and Trauma Scale (CATS)	2	1.18%
Brief Betrayal Trauma Survey (BBTS)	1	0.59%
Childhood Experiences Questionnaire (CEQ)	1	0.59%
Childhood Sexual Trauma Questionnaire	1	0.59%
Child Psychological Maltreatment Scale	1	0.59%
Childhood Traumatic Events Scale (CTES)	1	0.59%
Scale of stressful events during childhood-adolescence	1	0.59%
Stressful life events screening questionnaire-Revised	1	0.59%
Structured Trauma Interview (STI)	1	0.59%
Trauma Antecedents Questionnaire (TAQ)	1	0.59%
Trauma History Questionnaire (THQ)	1	0.59%

Table 5. Prevalence of Instrument from Study Population

Instrument	Year Publication	# Studies
Childhood Traumatic Events Scale (CTES)	1988	1
Structured Trauma Interview (STI)	1989	1
Childhood Experience of Care Abuse Questionnaire/Interview (CECA.Q/I)	1994	31
Child Abuse and Trauma Scale (CATS)	1995	2
Childhood Trauma Questionnaire (CTQ)	1997	100
Adverse Childhood Experiences Questionnaire (ACEQ)	1998	3
Childhood Sexual Trauma Questionnaire	1998	1
Childhood Abuse Questionnaire (CAQ)	1999	4
Early Trauma Inventory (ETI)	2000	8
Traumatic Experiences Checklist (TEC)	2002	3
Childhood Adversity Questionnaire (CAQ)	2004	5
Risky Families Questionnaire (RFQ)	2004	3
Brief Betrayal Trauma Survey (BBTS)	2006	1
Scale of stressful events during childhood-adolescence	2007	1
Child Psychological Maltreatment Scale	2010	1
Trauma History Questionnaire (THQ)	2011	1
Maltreatment and Abuse Chronology of Exposure (MACE)	2015	4
Stressful life events screening questionnaire-Revised	2016	1
Childhood Experiences Questionnaire (CEQ)	2018	1
Trauma Antecedents Questionnaire (TAQ)	2019	1

Table 6. Year of Instrument of Publication

CHAPTER V

DISCUSSION

In this study population demographic was consistent with epidemiological associations with SSDs. The population was predominantly male with a younger mean age for men, consistent with earlier onset in in men (Kahn et al., 2015). Employment is statistically low for patients with SSDs, with rates ranging from 10-20% (Mueser & McGurk, 2004). In this study 36.4% endorsed employment either full or part time. Despite employment status, they were still at or within 200% of the FPL, as noted in results, with the remaining 63.6% below the FPL. Socioeconomic hardship is strongly associated with both the incidence of ACEs and development of an SSD (Mueser & McGurk, 2004).

SSD, UD, and ACEs

It is interesting to consider the predominance of the SzA diagnosis and whether that is indicative of the population sample, if willingness to participate is possibly more diagnosis dependent, or if mood disorder and psychosis are strongly comorbid. The presence of UD and early substance use are also associated with SSDs (Khokhar et al., 2018). Early use of cannabis, nicotine, and alcohol have all been studied in relation to age of onset and severity in SSDs (Khokhar et al., 2018). Additionally, in a study of 29 patients diagnosed with UD, 100% reported having at least one ACE (Chandler et al., 2018). Unfortunately, the SCID does not specifically screen for nicotine use or dependence. In 2018 it was estimated that 746,000 Oklahomans 18 or older had either Illicit Drug, Substance, Alcohol, or Painkiller Use Disorders (NSDUH, 2018). The population of Oklahoma is a little over 3.9 million, with just over 3 million age 18 or over. That means a staggering 25% of that population in Oklahoma would have a UD. According to the Oklahoma Department of Mental Health and Substance Abuse Services (ODMHSAS) in 2012, Oklahoma ranked 3rd (22.4%) in the nation for rates of Any Mental Illness and 2nd in the nation at 11.9% for Any Substance Abuse Disorders. They estimated that currently 700,000-950,000 adult Oklahomans need services, and most are not receiving them (www.odmhsas.org). They estimated that in Tulsa county alone, almost 94,000 people over the age of 18 need mental health treatment and 81% of them are not receiving any. This means that of those in need of service, 10% of them are in Tulsa county.

Along with the high incidence of severe mental illness and substance abuse, Oklahoma has one of the higher incidence rates for ACEs. In previous years, Oklahoma has regularly held the number on spot in number of ACEs per state. According to the National Survey of Children's Health, U.S. Department of Health and Human Services, Health Resources and Services Administration (HRSA), Maternal and Child Health Bureau (MCHB), 2018-2019, Oklahoma in is

in the top 12% for ACEs in children 0-17 years old. Meaning almost 20% of all children in Oklahoma under 18 have experienced two or more ACEs. The national average is 15%.

In previous studies of ACEs and SSD, patients endorsed at least one ACE at rates of 90 – 94% (Prokopez et al., 2018, Vallejo et al., 2016, Propokez et al., 2020). In our sample, 100% of the participants endorsed having at least one ACE, with 90% endorsing two, and 80% three or more. The mean for our study was 4.18 (±2.23 SD). In the original ACEs study, an exposure to 4 or more ACEs was found to consistently increase odd ratios of disease presentation (Felitti et al., 1998). ACEs exposures can be intergenerational, and a large percent of the adult population in general experience ACEs (Dube, 2018). We could anecdotally see ACEs reflected intergenerationally in our study if we look at the ACEs endorsed and their associated demographic and mental health indicators. For example, 64% of participants endorsed UD, and 73% endorsed household alcohol or substance abuse. A systematic review and meta-analysis of the effect of multiple ACEs on health found that the outcomes of mental illness and substance abuse had the strongest relationships with multiple ACEs (Hughes et al, 2017). Only two of the study participants were married, the rest, 82%, were divorced, or single, and parental separation/divorce was endorsed by 82% of participants. Also 55% of participants, all of which had a SSD, endorsed parental mental illness/suicide. The importance of parental mental illness in a cohort of patients with SSD is reflected in the 1981 study by Tableman. The study indicated a 15% likelihood of developing Schizophrenia when one parent was affected and 32% if both parents were affected. A meta-analysis assessed mental health outcomes of the offspring of parents with a severe mental illness versus controls. It indicated in incidence of severe parental mental illness, offspring had a 32% probability of developing a severe mental illness as adults, a risk that was more than double that of the control population (Rasic et al., 2014). These outcomes support the perpetuation of intergenerational ACEs by increasing likely exposure to ACEs in the form of parental domestic violence, mental illness, and substance use (Hughes et al, 2017).

ACEs and BDNF, β-catenin, and Cortisol

In ACEs regressions with BDNF, β-catenin, and cortisol, all saw downward trends with cortisol demonstrating significance. The decreased hormone levels with increase in ACEs score was hypothesized. In power analysis, increased downward trend to significance is projected in both BDNF and β-catenin with an increase in n.

Significant cortisol levels in our pilot data suggest that cortisol is not affected by antipsychotic medication or substance use as appears to be the case with BDNF and β-catenin. Both BDNF and β-catenin levels have been noted to increase with antipsychotic medications (Green et al., 2011, Sutton et al., 2007). BDNF levels have also been shown to be modulated by substance use. In the instance of methamphetamine use, there has been shown to be significant increase in BDNF expression while cannabis use showed no significant difference in BDNF expression (Ornell et al., 2018) when compared to controls in an extensive meta-analysis. It demonstrated significant decrease in BDNF in alcohol abuse versus controls across multiple studies from the same meta-analysis (Ornell et al., 2018). Within our study there is a significant positive correlation with the number of UDs endorsed and BDNF levels. β-catenin levels showed an upward trend in relation to the number of UDs. Finally, cortisol showed no modulation associated with substance use. Interestingly, cortisol showed no trend to correlation at all with the number of UDs, supporting speculation that UD may be a confounding factor in the levels of DNF and β-catenin expressed.

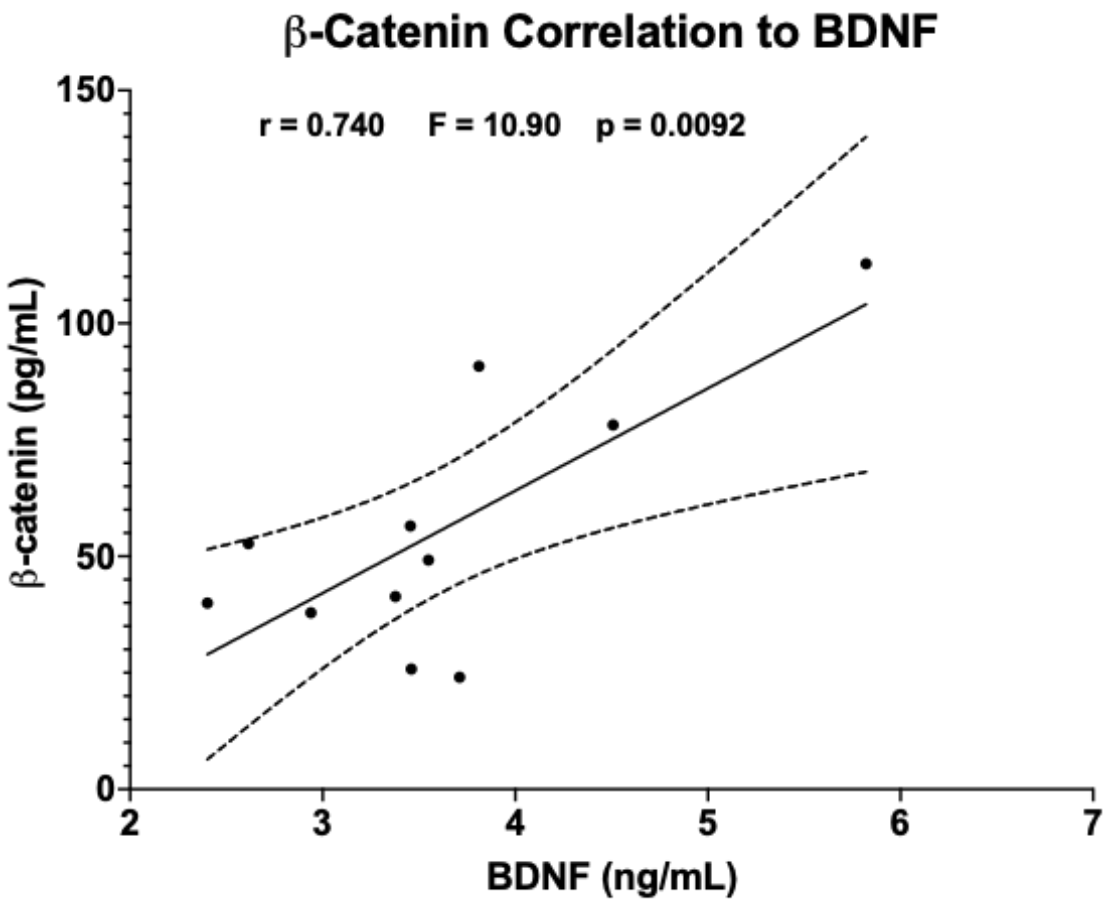

Figure 14. β-catenin correlation to BDNF.

The regulation and expression of both BNDF and β-catenin appears to be affected concomitantly, given the upregulating effect β-catenin has on BDNF their coupled expression is not improbable. This is true especially in relation to the tight correlation demonstrated in this study between the two, p=0.0092. There was no obvious relationship between either BNDF or β-catenin and cortisol. A negative correlation was expected given cortisols' regulatory association with both.

Systematic Review

There are many instruments available to assess childhood trauma. In this review, there are two studies that have significantly greater use of the CTQ and the CECAQ/I. We believe this may be explained by the availability of the instrument proximal to the release of the major ACEs study by Filetti et al. in 1998. The instruments existed and had been used prior to the study's release, CTQ 1997 and CECA 1994, lending them an existing credibility in the fast-growing field. In review, there are only three other instruments that were identified in use prior to 1998, two of those being close to a decade older used in one study and the other, the CATS in 1995, was identified in two studies.

The attempt to further develop a tool to assess childhood trauma explains the number of instruments developed following the ACEs study's release and the somewhat disparate use throughout assessments. Clearly, the importance of assessment is demonstrated as well as the necessity to better define what is most beneficial and important to assess.

CHAPTER VI

CONCLUSION

We expected to see downward trend in all biomarkers as the severity of the ACEs score increased. This study indicated that the expectation, though not wholly met, could be seen with an expanded study and the data are encouraging.

The systematic review highlighted the large number of instruments available However, it clearly illuminated that the CTQ may be a potential standard worth modifying or with an adjunct in future studies to affirm psychometric viability as well as inclusiveness of assessment criteria.

SSDs, ACEs, BDNF, β-catenin, and Cortisol

In general, the data we collected is consistent with existing data. In SSDs there is a greater than 90% probability of having one or more ACE. A mean of 4 ACEs in this population is consistent with SSD and UD, as well as socioeconomic status.

While only cortisol was significant, this study is strongly supportive that all three hormones are related to ACEs distribution. With an increase in sample size, significance is likely to be found in BDNF and β-catenin, as well as cortisol. Our sample is small, n=11, and while

effective as a pilot, larger power studies are needed to demonstrate results with greater clarity. Looking into the study on a larger scale is an important future direction.

It is very exciting to contribute to the developing interest in the association of β-catenin and SSD as a more novel aspect of this study. Especially considering the strong relationship that BDNF and β-catenin have to each other, and the ability of β-catenin to upregulate BDNF. It continues to be of interest to examine the possible downregulation of both via cortisol. It would be of interest to examine cortisol, BDNF, and β-catenin levels over time in individuals, as well as in monitoring treatment progress.

Systematic Review

The CTQ is the most widely utilized measure of childhood trauma. It encompasses physical, emotional, sexual abuse/neglect, and socioeconomic hardship. It allows the taker to quantify the degree to which the experience affected them. The psychometric properties of the CTQ have been extensively analyzed in multiple reviews (Roy & Perry, 2004, Saini et al., 2019, Matheson et al., 2013, and Hulme, 2009).

There are many aspects of the childhood trauma instrument that can be followed up on from this study. There is potential to do analysis of instrument criteria assessed, the relevance of childhood trauma type reported in relation to psychosis, schizophrenia, or schizoaffective disorder per instrument, how strong/consistent is the correlation indicated per instrument.

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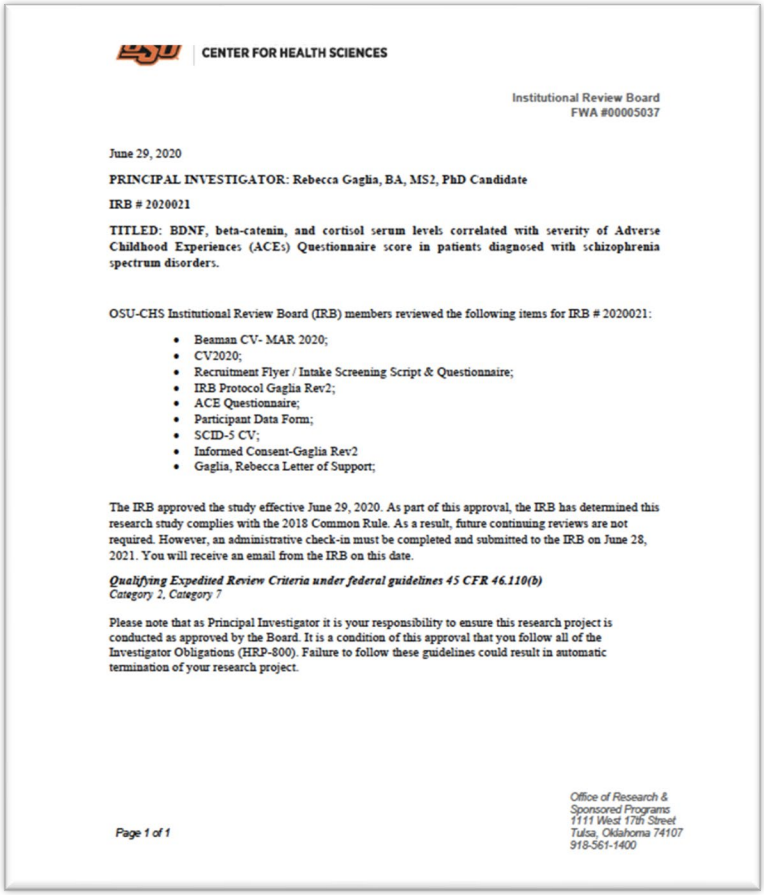
APPENDICES

APPENDIX A: IRB #2020021 Approval Letter



CENTER FOR HEALTH SCIENCES

Institutional Review Board
FWA #00005037

June 29, 2020

PRINCIPAL INVESTIGATOR: Rebecca Gaglia, BA, MS2, PhD Candidate

IRB # 2020021

TITLED: BDNF, beta-catenin, and cortisol serum levels correlated with severity of Adverse Childhood Experiences (ACEs) Questionnaire score in patients diagnosed with schizophrenia spectrum disorders.

OSU-CHS Institutional Review Board (IRB) members reviewed the following items for IRB # 2020021:

- Beaman CV- MAR 2020;
- CV2020;
- Recruitment Flyer / Intake Screening Script & Questionnaire;
- IRB Protocol Gaglia Rev2;
- ACE Questionnaire;
- Participant Data Form;
- SCID-5 CV;
- Informed Consent-Gaglia Rev2
- Gaglia, Rebecca Letter of Support;

The IRB approved the study effective June 29, 2020. As part of this approval, the IRB has determined this research study complies with the 2018 Common Rule. As a result, future continuing reviews are not required. However, an administrative check-in must be completed and submitted to the IRB on June 28, 2021. You will receive an email from the IRB on this date.

Qualifying Expedited Review Criteria under federal guidelines 45 CFR 46.110(b)
Category 2, Category 7

Please note that as Principal Investigator it is your responsibility to ensure this research project is conducted as approved by the Board. It is a condition of this approval that you follow all of the Investigator Obligations (HRP-800). Failure to follow these guidelines could result in automatic termination of your research project.

Page 1 of 1

Office of Research & Sponsored Programs
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APPENDIX B: IRB #2020021 Recruitment Script

Participants were screened via onsite nursing staff to facilitate ease in assessing criteria for inclusion. Following positive recruitment assessment from nursing staff and willingness to participate, research staff were introduced to patient and informed consent was explained and acquired.

During intake assessment:

- Patient may qualify if they meet the following criteria:
    - Between the ages of 18-64
    - Current diagnosis and treatment of schizophrenia, schizophreniform disorder or schizoaffective disorder
    - Has completed at least 8 years of formal education
    - Speaks and reads English fluently
    - Does not have a proxy for medical decision-making, legal guardian, or been otherwise determined unable to give consent
    - Is current and compliant on antipsychotic medications
    - IQ >70 or no previous diagnosis of intellectual disability
    - No past diagnosis or suspected current diagnosis of a neurodevelopmental disorder (e.g., autism, learning disability) or neurocognitive disorder (e.g., dementia)
    - No history of major head trauma (defined as loss of consciousness for 30 minutes or longer) or brain surgery (Note: History of concussion, including brief loss of consciousness, is okay)
    - No history of psychosis secondary to a medical condition or diagnosis of psychosis secondary to substance abuse
    - No history of presence of endocrine conditions that would alter prolactin or cortisol levels, such as Prolactinoma or Cushings' respectively
    - If female, is not pregnant or lactating
- If they meet the above criteria, give them a flier and tell them:

<u>Recruitment Scripts</u>

"Some OSU researchers are doing a study to see how people's life experiences may change the amount your brain manufactures certain brain chemicals. You may qualify to participate. Here is a flier with some more information. Someone from the research team can give you some more information about it. if you are interested"

Research Staff, initial patient contact:

- "Hi, I'm _____, a researcher from OSU. Your doctor might have given you a flier about the research project that we are doing here at FCS and I would like to tell you a little bit more about it if you are interested in hearing more.
- "We're interested in seeing how different aspects of people's brain functioning might change when they have been diagnosed with schizophrenia and exposed to certain

- childhood life experiences. To do this, people are given mental health diagnostic test, and fill out a short self-answered survey about those childhood experiences. We're also interested in chemical changes that might be happening in the brain at the same time, so we take some small blood samples to test as well."
- Answer any questions the person has at this point.
- "If you think you might be interested, I just need to ask you a few questions to make sure that you would qualify. Then I can go over the rest of the details and you can decide if you would like to participate."
- Check that the person meets all of the inclusion criteria:
    - Between the ages of 18-64
        - **Date of birth __/__/_____**
    - Current diagnosis of schizophrenia, schizophreniform disorder or schizoaffective disorder
        - **Do you have a current diagnosis of one of schizophrenia, schizophreniform disorder or schizoaffective disorder?**
            - **Y or N**
    - Has completed at least 8 years of formal education
        - **What is the highest grade level you have completed? _____**
    - Speaks and reads English fluently
        - **Is English your first language or do you consider yourself fluent in English?**
            - **Y or N**
    - Does not have a proxy for medical decision-making, legal guardian, or been otherwise determined unable to give consent
        - **Is there someone other than yourself that is responsible for making your medical decisions?**
    - Is current and compliant on antipsychotic medications.
        - **Are you current and compliant with your antipsychotic medications?**
            - **Y or N**
    - IQ >70 or no previous diagnosis of intellectual disability
        - **Have you ever been previously diagnosed with an intellectual disability?**
            - **Y or N**
    - No past diagnosis or suspected current diagnosis of a neurodevelopmental disorder (e.g., autism, learning disability) or neurocognitive disorder (e.g., dementia)
        - **Do you have past or present diagnosis of a neurodevelopmental disorder (e.g., autism, learning disability) or neurocognitive disorder (e.g., dementia)?**
            - **Y or N**
    - No history of major head trauma (defined as loss of consciousness for 30 minutes or longer) or brain surgery. (Note: History of concussion, including brief loss of consciousness, is okay
        - **Do you have a history of major head trauma (defined as loss of consciousness for 30 minutes or longer) or brain surgery?**
            - **Y or N**
            - History of concussion, including brief loss of consciousness, is okay

- No history of psychosis secondary to a medical condition or diagnosis of psychosis secondary to substance abuse.
    - **Do you have a history of psychosis secondary to a physical medical condition or diagnosis of psychosis secondary to substance abuse?**
        - **Y or N**
- No history of presence of endocrine conditions that would alter prolactin or cortisol levels, such as Prolactinoma or Cushings' respectively
    - **Do you have a history of any endocrine conditions such as a Prolactinoma or Cushing's?**
        - **Y or N**
- If female, is not pregnant or lactating
    - **Are you currently pregnant or lactating?**
        - **Y or N**

- If criteria are met, verbally summarize each section of the consent form, allow the person time to read each page and initial when done. Answer all questions as they arise. Complete signature block.

APPENDIX C: IRB #2020021 Informed Consent

OKLAHOMA STATE UNIVERSITY

Center for Health Sciences

PARTICIPANT INFORMATION AND CONSENT FORM

Title of Project**: BDNF, beta-catenin, and cortisol serum levels correlated with severity of Adverse Childhood Experiences (ACEs) Questionnaire score in patients diagnosed with schizophrenia spectrum disorder.**

Investigators: **Rebecca Gaglia, BA, MS2, Biomed PhD Candidate**

Jason Beaman, DO., MS., MPH., FAPA

Department of Psychiatry & Behavioral Sciences

Department of Biomedical Sciences

Oklahoma State University-Center for Health Sciences

gaglia@okstate.edu, jason.beaman@okstate.edu

"You" refers to the participant.

"We" refers to the research team at Oklahoma State University-Center for Health Sciences.

You are being offered the opportunity to take part in this research study because you are receiving psychiatric treatment at Family and Children Services (FCS). This research is being done to study the association of childhood trauma and selected biomarkers in patients diagnosed with schizophrenia spectrum disorder.

What you should know about participating in a research study:

Participation in research is a voluntary choice, and this consent form will provide you with information about the risks, benefits or alternatives to participation in the study.

- Someone will explain this research study to you.
- You may volunteer to be in the research study.
- Whether or not you take part is up to you.
- You can choose not to take part in the research study.
- You can agree to take part now and later change your mind.
- Whatever you decide it will not be held against you.
- Feel free to ask all the questions you want before you decide.

Who can you talk to?

Although this consent form provides detailed information about this study, a research team member is available to answer any questions you may have about this study and/or participation in it. If you have questions, concerns, or complaints, or think the research has hurt you, talk to the researcher or identified members of the research team at (phone number).

This research has been reviewed and approved by the Oklahoma State University Center for Health Sciences Institutional Review Board (IRB). You may contact the chairperson of this committee at 918-561-1400 or chsirb@okstate.edu for any of the following:

- Your questions, concerns, or complaints are not being answered by the researcher or research team.
- You cannot reach the researcher or a member of the research team.
- You want to talk to someone other than the researcher or the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research or your experience in this research study. ***Why are we doing this research?***

The purpose of the research is to study the association of childhood trauma and selected biomarkers.

How long will the research last?

We expect that you will be in this research study for 1 day. You will have 1 study appointment that will last about 1 hour.

How many people will be studied?

We expect about 10-20 people to be enrolled into this study.

What happens if you say yes, you want to be in this research?

You will be asked to complete 2 different types of activities. These will all take place at FCS:

1. Structured Clinical Interview DSM-5-CV: you will be administered a clinical interview to confirm psychiatric diagnosis for inclusion in the study. This will take 30-45 minutes to complete.
2. Adverse Childhood Experience Questionnaire: you will be asked to complete one self-report surveys that asks about experiences in childhood. This will take about 7-10 minutes to complete.
3. Blood Sample: you will be asked to give 8mL of blood to study some of the chemical markers that are related to childhood trauma and schizophrenia.

What happens if you say no, you do not want to be in this research?

You may decide not to take part in the research, and it will not be held against you. A refusal to participate in this research study will involve no penalty or loss of benefits to which you are otherwise entitled.

What happens if you say yes, but you change your mind later?

You can agree to take part in the research now and stop at any time. It will not be held against you. If you want to stop your participation in the study, you may tell one of the investigators or another OSU research team member at FCS, verbally or in writing that you no longer want to participate. Stopping participation will not result in penalty or loss of benefits to which you are otherwise entitled. However, you will not be paid the full amount of the study compensation if you do not complete all of the activities.

If you stop participating in the research study, data already collected may not be removed from the study database.

Is there a risk to being in this study?

Participation in this study may involve risks or discomforts. These include the following:

- It is possible that you may become frustrated, bored, or tired during the Structured Clinical Interview. You may take a break and/or stop at any time.
- It is possible that the questions being asked about your childhood may make you feel uncomfortable. You may skip questions that make you feel uncomfortable.
- You may experience slight pain when the needle is inserted for the blood draw. There is a small risk of bruising and/or infection at the site. It is possible that a participant may feel lightheaded, nauseated, or faint.
- There is possible risk for loss of confidentiality. We have several measures in place to keep your study information private, including using code numbers instead of names on study documents whenever possible, password-protecting all electronic data files, and storing other materials in locked cabinets, but it may still be possible for some of the information collected to become known outside of this research setting. Some of this information, could negatively affect your personal reputation, your ability to get a job, or have other unknown outcomes.
- In addition to these risks, this research may harm you in ways that are unknown and unforeseeable. If we learn of new risks that we think might affect your desire to stay in the research, we will tell you. If major risks are discovered after the study is finished, it is possible that the sponsor may attempt to contact you.

What benefits can be reasonably expected?

There is no expected direct benefit to you for participating in this study. The researchers, however, may learn more about childhood trauma, biomarkers and development of schizophrenia. Such understanding may assist in the creation of better diagnosis, treatment procedures, and early interventions for patients with or at risk for the development of schizophrenia spectrum disorders.

Will it cost you anything to be in this study?

There is no cost to you for taking part in this research study.

Will you be compensated for participating in this study?

If you agree to take part in the research study, FCS will provide you with $10 QT prepaid gift card following completion of all study activities.

What are your responsibilities?

Tell the researcher or research study staff about any changes in recent medication or medication compliance.

What happens to the information we collect?

Efforts will be made to limit sharing of your personal information, including study data and medical records, to people who have a need to review this information. We cannot promise complete confidentiality. Organizations that may inspect and copy your information for quality assurance and data analysis include:

- The Researcher and his/her research staff
- Oklahoma State University staff or its agents
- The IRB and staff

We may publish the results of this research. However, we will keep your name and other identifying information confidential and anonymous in any presentations or publications.

We do not intend to share any individual results with you, should you wish to receive a summary of your study results you may contact the PI and a summary will be sent once the information is available.

Use of your blood samples

The blood samples that are collected for this study may be stored for years in what is called a "biobank" that may be used by scientists in the future to study other questions that arise due to new scientific or technological advances.

- The samples will be stored with only a unique code and will not have your name or other identifying information.
- It is possible that your blood sample may be used in the future for commercial profit. You will not share in this commercial profit.
- Research using your blood will not include whole genome sequencing.

Federal law provides additional protections of your personal information. These are described in a later section (HIPAA Authorization for Release of Health Information for Research Purposes).

Can you be removed from the research without your permission?

The investigators can remove you from the research study without your approval. Possible reasons for removal include:

- If you have recent changes in medication or medication compliance
- If you do not keep appointments
- If the researcher or FCS treatment team considers it in your best interest
- The investigator (or sponsor) can also end the research study early

HIPAA Authorization for Release of Health Information for Research Purposes & Authorization for Release of Confidential Substance Use Disorder Patient Records

The Health Insurance Portability and Accountability Act (HIPAA) allows a hospital or doctor's office to use or release protected health information (PHI) for the purposes of treatment, payment or health care operations. Health care operations activities include such things as audits, quality assurance initiatives, audits from insurance companies, treating physicians, legal advisors, insurers and data storage companies.

This HIPAA authorization gives permission from you to use or release your PHI for research purposes. A HIPAA authorization is in addition to your consent to participate in this research study.

What will be done with your protected health information?

Your protected health information (PHI) will be collected through on-site access and review of your FCS treatment records and entered in a database along with the information from other people taking part in this study.

Why are you being asked to release it?

Your protected health information (PHI) will be used for study eligibility, for contact purposes, and to help us understand the association of childhood experience and selected biomarkers in patients diagnosed with schizophrenia spectrum disorders.

What will be released?

To complete this research study, we will need to collect and release (disclose) information about you. This information includes:

- Your contact information and insurance status for treatment payment
- Your medical and psychiatric diagnoses

The information authorized for release may include records which may indicate the presence of a communicable or venereal disease which may include, but are not limited to, diseases such as hepatitis, syphilis, gonorrhea and the human immunodeficiency virus also known as Acquired Deficiency Syndrome (AIDS). [63 O.S. § 1-1502 (B)]

Who will use it or share it?

- The researcher and her research study staff
- Oklahoma State University staff or its agents
- The IRB and staff
- The Sponsor(s) of the research or its agents (monitors, auditors)

Once your protected health information (PHI) has been disclosed it is possible that anyone who receives that information may re-disclose it. Because some of these individuals who receive your PHI may not be required by law to keep your information confidential, we cannot guarantee that your information will not be released or made available to another party once it leaves Oklahoma State University. Therefore, we share your information only if necessary and we use all reasonable efforts to request that those individuals who receive your information take steps to protect your privacy.

How long will this authorization last?

This authorization has no expiration date.

Can you stop your protected information (PHI) from being used?

You can tell us to stop collecting health information that can be traced to you at any time unless action has already been taken based upon this consent. We will stop, except in very limited cases

if needed to comply with law, protect your safety, or make sure the research was done properly. If you have any questions about this, please ask.

If you want us to stop using PHI, you must tell us in writing. Write or email Rebecca Gaglia at gaglia@okstate.edu or 1111 W. 17th Street, Tulsa, OK 74107.

What happens if you do not want us to collect your personal health information (PHI)?

If you decide not to authorize release of your protected health information (PHI) to be used as part of this study, your decision will in no way affect your medical care or cause you to lose any benefits to which you are entitled. You cannot participate in this research study if you do not authorize the use or release of your PHI.

When will it be destroyed?

We do not know when your information will no longer be used therefore the information will be kept for an indefinite length of time. The minimum amount of time it will be retained is 3 years after the completion of the final study report. The Primary Investigator, Rebecca Gaglia, will be responsible for destroying the data.

Do not sign this consent form until you have had a chance to ask questions and have received satisfactory answers to all of your questions.

Signature Block for Capable Adult: Long Form

Your signature below documents your consent to take part in this research and to the use and disclosure of your protected health information, as specified in this consent form. Signing this authorization will not affect your eligibility for benefits, treatment, enrollment, or payment of claims. I understand that upon my request I will be provided with a list of agencies that my information has been disclosed to. I understand that treatment services are not contingent upon or influenced by my free and voluntary decision concerning authorization of the release of information. I understand that the information disclosed as a result of this consent may be subject to redisclosure by the recipient and may no longer be protected by federal regulations. You will receive a signed copy of this complete form.	
Signature of participant	Date
Printed name of participant	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	

APPENDIX D: IRB #2020021 Participant Data Sheet

Demographic Information

Date of Birth ____/____/_____

Sex

- Female
- Male

Ethnicity (Optional) Select all that apply

- American Indian or **Alaska** Native
- Asian
- Black or African American
- Hispanic or Latino
- Native Hawaiian or Other Pacific Islander
- White
- Other _____

Education Highest Level Completed (Optional)

- High School / GED
- Some Undergraduate Education
- Trade Degree / Certification
- Associate's Degree
- Bachelor's Degree
- Some Graduate Education
- Graduate / Professional Degree

Military Service (Optional)

- Yes
- No

Marital Status (Optional)

- Single
- Married
- Separated
- Divorced
- Widowed

Occupation Status (Optional)

- Unemployed
- Employed PT
- Employed FT
- Student FT
- Student PT

Annual Income (Optional)

- $0 - $10,000
- $10,000 - $35,000
- $35,000 - $60,000
- $60,000 - $85,000
- $85,000 - Above

APPENDIX E: IRB #2020021 ACEQ

http://www.odmhsas.org/picis/ACE.pdf

Adverse Childhood Experience (ACE) Questionnaire

Finding your ACE Score While you were growing up, during your first 18 years of life:

1. Did a parent or other adult in the household often …Swear at you, insult you, put you down, or humiliate you? Or Act in a way that made you afraid that you might be physically hurt?

Yes No If yes enter 1 _____

2. Did a parent or other adult in the household often …Push, grab, slap, or throw something at you? Or Ever hit you so hard that you had marks or were injured?

Yes No If yes enter 1 _____

3. Did an adult or person at least 5 years older than you ever…Touch or fondle you or have you touch their body in a sexual way? Or Try to or actually have oral, anal, or vaginal sex with you?

Yes No If yes enter 1 _____

4. Did you often feel that …No one in your family loved you or thought you were important or special? Or Your family didn't look out for each other, feel close to each other, or support each other?

Yes No If yes enter 1 _____

5. Did you often feel that …You didn't have enough to eat, had to wear dirty clothes, and had no one to protect you? Or Your parents were too drunk or high to take care of you or take you to the doctor if you needed it?

Yes No If yes enter 1 _____

6. Were your parents ever separated or divorced?

Yes No If yes enter 1 _____

7. Was your mother or stepmother: Often pushed, grabbed, slapped, or had something thrown at her? Or Sometimes or often kicked, bitten, hit with a fist, or hit with something hard? Or Ever repeatedly hit over at least a few minutes or threatened with a gun or knife?

Yes No If yes enter 1 _____

8. Did you live with anyone who was a problem drinker or alcoholic or who used street drugs?

Yes No If yes enter 1 _____

9. Was a household member depressed or mentally ill or did a household member attempt suicide?

Yes No If yes enter 1 _____

10. Did a household member go to prison?

Yes No If yes enter 1 _____

Now add up your "Yes" answers: _____ This is your ACE Score.

APPENDIX F: IRB #2020021 SCID

The *Structured Clinical Interview for DSM-5, Clinician Version (SCID-5-CV),* is a semistructured interview for making the DSM-5 diagnoses. It is administered by a clinician or trained mental health professional who is familiar with the DSM-5 classification and diagnostic criteria. This was used to establish a diagnosis of schizophrenia or schizoaffective disorder with uniform diagnostic criteria, in an effort to eliminate subjective diagnostic bias. Research PI, Rebecca Gaglia, administered all SCID interviews for consistency. SCID results were reviewed with advisor following completion.

APPENDIX G: BDNF ELISA Protocol

Standard curve in duplicate.

All Serum Samples in septuplicate.

All materials and prepared reagents brought room temperature prior to use.

1. Prepare 1X Wash Buffer.
    a. 20mL Wash Buffer Conc
    b. 380mL Distilled (DI) water
    c. Agitate solution.
2. Prepare 1X Assay Diluent B
    a. 15mL Assay Diluent B Conc
    b. 75mL DI water
3. Prepare Standard Dilutions - Using Assay Diluent A for Serum Samples
    a. Label tubes for Standard dilutions
        i. Std1: 16ng/mL
        ii. Std2: 6.4ng/mL
        iii. Std3: 2.56ng/mL
        iv. Std 4: 1.02ng/mL
        v. Std 5: 0.41ng/mL
        vi. Std 6: 0.16ng/mL
        vii. Std 7: 0.066ng/mL
        viii. Std8/Blank: 0ng/mL
    b. Spin vial BDNF Standard
    c. Pipette 720μL Assay Diluent A into standard vial, gently vortex 10sec
    d. Pipette 960μL Assay Diluent A into Std1 tube
    e. Pipette 300μL into Std2 - 8 tubes
    f. Pipette 40μL in Std1 vial
    g. From Std1 make serial dilutions of 200μL through Std7
4. Prepare Serum Sample Dilutions 1:200 - Using Assay Diluent A for Serum Samples
    a. Pipette 4μL per Serum Sample to corresponding labeled vial.
    b. Pipette 800μL Assay Diluent A per sample
    c. Vortex each sample gently for 7 seconds
5. Plate Binding Incubation
    a. Pipette 100μL of each standard and sample into designated wells
    b. Cover and incubate 2.5 hours at room temp with shaking.

6. Prepare 1X Biotinylated anti-Human BDNF Detector Antibody for Step 8
    a. Vortex both Biotinylated anti-Human BDNF Detector Antibody vials 10 seconds
    b. Biotinylated anti-Human BDNF Detector Antibody Conc
        i. Pipette 100μL 1X Assay Diluent B into each vial
        ii. Vortex each vial 10 seconds
    c. 1X Biotinylated anti-Human BDNF Detector Antibody
        i. Pipette 100μL from each vial (200μL total)
        ii. Add to 16mL 1X Assay Diluent B
        iii. Gently agitate.
7. Wash
    a. Discard the solution and wash 4 times with 1X Wash Solution. Wash by filling each well with 1X Wash Solution (min 300μL) using disposable graduated pipette. Removal of liquid at each step by decanting. After the last wash decant, invert the plate and blot against clean paper towels.
8. 1X Biotinylated anti-Human BDNF Detector Antibody Incubation
    a. Add 100μL of 1X Biotinylated anti-Human BDNF Detector Ab to each well.
    b. Incubate 1 hour at room temperature with shaking.
9. Prepare 1X HRP-Streptavidin solution for Step 11.
    a. Vortex HRP-Streptavidin Conc vial 10 seconds
    b. Pipette 50μL HRP-Streptavidin Conc
    c. Add to 10mL 1X Assay Diluent B
    d. Vortex 20 sec
10. Wash
    a. Discard the solution and wash 4 times with 1X Wash Solution. Wash by filling each well with 1X Wash Solution (min 300μL) using disposable graduated pipette. Removal of liquid at each step by decanting. After the last wash decant, invert the plate and blot against clean paper towels.
11. 1X HRP-Streptavidin solution Incubation
    a. Add 100μL of prepared 1X HRP-Streptavidin solution to each well.
    b. Incubate 45 minutes at room temperature with shaking.
12. Wash
    a. Discard the solution and wash 4 times with 1X Wash Solution. Wash by filling each well with 1X Wash Solution (min 300μL) using disposable graduated pipette. Removal of liquid at each step by decanting. After the last wash decant, invert the plate and blot against clean paper towels.
13. TMB Incubation
    a. Add 100μL of TMB One-Step Substrate Reagent to each well.
    b. Incubate for 30 minutes at room temperature in the dark with gentle shaking.
14. Stop Solution
    a. Add 50μL of Stop Solution to each well.
    b. Read at 450nm and 550nm immediately within 30 minutes of Stop Solution.
15. Read the plate and generate the standard curve.
    a. Read at 450nm and 550nm.

b. Subtract 550nm values from 450nm values to correct for optical imperfections.
c. Calculate the mean value of the duplicate readings for each standard and samples in septuplet.
d. To generate a standard curve, plot the graph using the standard concentrations on the x-axis and the corresponding mean 450 nm absorbance (OD) on the y-axis. The best-fit line was determined by regression analysis using four parameter logistic curve-fit.
e. Determine the unknown sample concentration from the Standard Curve and multiply the value by the dilution factor.

APPENDIX H: Beta-Catenin ELISA Protocol

Standard curve in duplicate.

All Serum Samples in non-diluted sextuplicate - except A2 serum quantity limited to quintuplicate.

All Standard Dilutions provided in kit.

All materials and prepared reagents brought room temperature prior to use.

1. Prepare 1X Wash Solution.
    a. 10mL Wash Solution Conc
    b. 990mL Distilled (DI) water
    c. Agitate solution.
2. Plate Binding Incubation
    a. Pipette 50μL of each standard and sample into designated wells
    b. Add 50μL of PBS to Blank Control wells
    c. Pipette 100μL of Enzyme Conjugate to each well, excluding blank control wells.
    d. Cover and incubate 1 hours at room temp with shaking.
3. Wash
    a. Discard the solution and wash 5 times with 1X Wash Solution. Wash by filling each well with 1X Wash Solution (min 300μL) using disposable graduated pipette. Removal of liquid at each step by decanting. After the last wash decant, invert the plate and blot against clean paper towels.
4. Substrate A and B Incubation
    a. Add 50μL of Substrate A to each well.
    b. Add 50μL of Substrate B to each well.
    c. Cover and incubate for 15 to no more than 30 minutes at room temperature.
5. Stop Solution
    a. Add 50μL of Stop Solution to each well.
    b. Read at 450nm immediately.
6. Read the plate and generate the standard curve.
    a. Read at 450nm.
    b. All Opitcal Density (OD) values are subtracted by the mean of the blank control wells prior to result interpretation.
    c. Calculate the mean value of the duplicate readings for each standard and sample replicates.
    d. To generate a standard curve, plot the graph using the standard concentrations on the x-axis and the corresponding mean 450 nm absorbance (OD) on the y-axis.

e. The best-fit line was determined by regression analysis using four parameter logistic curve-fit.
f. Determine the unknown sample concentration from the Standard Curve.

APPENDIX I. Cortisol ELISA Protocol

Standard curve in duplicate.

All Serum Samples in septuplicate.

All materials and prepared reagents brought room temperature prior to use.

1. Prepare 1X Wash Buffer.
    a. 15mL Wash Solution Conc
    b. 285mL Distilled (DI) water
    c. Agitate solution.
2. Prepare 1X Assay Buffer.
    a. 14mL Assay Buffer Conc
    b. 56mL DI water
    c. Agitate solution.
3. Prepare Standard Dilutions - Using 1X Assay Buffer.
    a. Label tubes for Standard dilutions:
        i. Std1: 3,200pg/mL
        ii. Std2: 1,600pg/mL
        iii. Std3: 800pg/mL
        iv. Std 4: 400pg/mL
        v. Std 5: 200pg/mL
        vi. Std 6: 100pg/mL
        vii. Std 7: 50pg/mL
        viii. Std8/Blank: 0pg/mL
    b. Pipette 450μL 1X Assay Buffer into Std1 tube
    c. Pipette 250μL 1X Assay Buffer into Std2 - 8 tubes
    d. Pipette 50μL in Std1 tube
    e. From Std1 make serial dilutions of 250μL through Std7
4. Prepare Serum Sample Dilutions 1:100 - Using 1X Assay Buffer.
    a. Pipette 5μL Dissociation Reagent into tube
    b. Pipette 5μL per Serum Sample to corresponding labeled tube.
    c. Pipette 490μL 1X Assay Buffer per sample
    d. Vortex each sample gently for 7 seconds
5. Conjugate & Antibody Incubation
    a. Add 50 µL of standards or samples to the appropriate wells.
    b. Add 75 µL 1X Assay Buffer into wells for detecting non-specific binding (NSB).
    c. Add 25 µL of Cortisol Conjugate to each well.
    d. Add 25 µL of Cortisol Antibody to each well except NSB wells.

e. Tap the side of the plate to mix.
f. Cover and incubate 1 hour at room temperature with shaking.

6. Wash
    a. Discard the solution and wash 4 times with 1X Wash Solution. Wash by filling each well with 1X Wash Solution (min 300μL) using disposable graduated pipette. Removal of liquid at each step by decanting. After the last wash decant, invert the plate and blot against clean paper towels.
7. Chromogen Incubation
    a. Add 100 µL TMB Substrate to each well.
    b. Incubate for 30 minutes at room temperature.
8. Stop Solution
    a. Add 50 µL Stop Solution to each well.
    b. Tap side of the plate gently to mix.
    c. Read at 450nm within 10 minutes of Stop solution.
9. Read the plate and generate the standard curve.
    a. Read the absorbance at 450 nm.
    b. Use curve-fitting software to generate the standard curve. A four-parameter algorithm provides the best standard curve fit.
    c. The background absorbance is subtracted from all data points, including standards, unknowns and controls, prior to plotting.
    d. Read the concentrations for unknown samples and controls from the standard curve. Multiply value(s) obtained for sample(s) by the appropriate factor to correct for the sample dilution.

VITA

Rebecca Jean Gaglia

Candidate for the Degree of

Doctor of Philosophy

Dissertation: BRAIN DERIVED NEUROTROPHIC FACTOR (BDNF), β-CATENIN, AND CORTISOL LEVELS CORRELATED WITH THE SEVERITY OF ADVERSE CHILDHOOD EXPERIENCES (ACES) SCORE IN PATIENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS

Major Field: Biomedical Sciences

Biographical:

Education:
Completed the requirements for the Doctor of Philosophy in Biomedical Sciences at Oklahoma State University, Stillwater, Oklahoma in May, 2021.

Completed the requirements for the Bachelor of Arts in Philosophy at University of Tulsa, Tulsa, Oklahoma in 2006.

Experience:
MS2 Psychiatry Lecture 2020 - Neurobiology of Mental Illness
OSU-COM Dept of Psychiatry and Behavioral Sciences

3MT Presentation 2020 – ACEs High: Oklahoma's Childhood Trauma Epidemic
OSU-CHS Dept of Psychiatry and Behavioral Sciences

Psychiatry Grand Rounds August 2018 - BDNF: The Basics
OSU-CHS Dept of Psychiatry and Behavioral Sciences

Presentation OSU-CHS Research Week February 2017 - Getting out of the net: Morphine use in adolescents and the effects on Perineuronal Nets.
Oklahoma State University Center for Health Sciences (OSU-CHS)

Professional Memberships:
BSGSA (Biomedical Sciences Graduate Student Association) 2016 - 2020
SNMA (Student National Medical Association) 2019 – Present
OMSA (Oklahoma State Medical Association) 2018 – Present