RESPONSE INHIBITION AND CHILDHOOD TRAUMA IN SCHIZOPHRENIA

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Abstract

Childhood trauma (CHT) is consistently linked to increased risk for schizophrenia, but the mechanisms by which this risk is conferred are unclear. Recent research indicates there may be multiple developmental pathways linking CHT to schizophrenia, including affective and cognitive routes. The current study seeks to clarify the potential role of response inhibition in the cognitive pathway between CHT and symptoms of schizophrenia. I used archival data of 34 South African individuals with first-episode schizophrenia and 33 non-psychiatric controls. These participants completed the Stop-Signal Anticipation Task (SSAT; Zandbelt & Vink, 2010) as a measure of behavioral and brain imaging indices of response inhibition. I used the Childhood Trauma Questionnaire (CTQ) as a measure of CHT, and the Positive and Negative Syndrome Scale (PANSS) as a measure of schizophrenia symptoms. The present study did not replicate previous findings of increased CHT in people with schizophrenia, and it also did not replicate an association between severity of CHT and positive symptoms of schizophrenia. Results did yield significant group differences in behavioral and functional neuroimaging measures of proactive inhibition, and not reactive inhibition. Implications of these findings are discussed.

Response Inhibition and Childhood Trauma in Schizophrenia

Schizophrenia is a chronic mental illness associated with decline in social and occupational functioning (Frangou, 2008). This disorder affects approximately 1% of the population worldwide (Peralta et al., 2007), including the Western Cape of South Africa (Kleintjes et al., 2006) from which the present study sample was recruited. Schizophrenia may be particularly debilitating in regions of the world with fewer legal protections and treatment options for people with serious mental illness (Burns, 2009). Symptoms of schizophrenia are typically grouped into two clusters, positive and negative symptoms (Andreasen, 1985). The positive cluster includes symptoms, such as hallucinations (e.g., perceptions in the absence of external stimuli), delusions (e.g., fixed false beliefs not consistent with an individual's culture), and disorganized thoughts (e.g., thoughts that don't make sense). The negative cluster includes symptoms, such as emotional withdrawal (e.g., avoidance of emotional experiences), social withdrawal (avoiding social interaction), concrete thinking (e.g., difficulty comprehending abstract concepts), and blunted emotions (e.g., decreased experience of emotions; Kay, Fiszbein, & Opler, 1987). Schizophrenia is also characterized by prominent cognitive deficits, including impairments in working memory, executive function, and attention (Barch & Ceaser, 2012).

Schizophrenia as a Neurodevelopmental Disorder with Genetic and Environmental Risk Factors

Schizophrenia is commonly considered to be a neurodevelopmental disorder (Lewis & Levitt, 2002; Marenco & Weinberger, 2000; Weinberger, 1995), with abnormal brain development caused by a variety of both genetic and environmental factors (van Os et al., 2014). Over the years, an array of candidates for genetic and environmental risk factors have emerged,

suggesting there are likely multiple combinations of factors that interact to cause schizophrenia (Nagai, Ibi, & Yamada, 2011; Réthelyi, Benkovits, & Bitter, 2013). Teasing out the effects and interactions of environmental and genetic causes may lead to improvements in prevention and treatment of schizophrenia.

Typical estimates of schizophrenia heritability of range from 45-80% (Rapoport, Addington, Frangou, & Psych, 2005). Gene variants that have been implicated in schizophrenia code for a range of early brain development functions. These functions include neuronal migration, differentiation, and organization (Harrison & Weinberger, 2005; Notaras, Hill, & van den Buuse, 2015; Stefansson et al., 2003). However, identified schizophrenia risk genes explain only a small portion of the observed heritability of schizophrenia. This indicates that schizophrenia is likely caused by various combinations of many gene variants, each imparting a small degree of risk (Craddock, O'Donovan, & Owen, 2006; The International Schizophrenia Consortium, 2009). Environmental factors believed to increase the risk of schizophrenia are also multifarious, including maternal infection and nutritional deficits during pregnancy, advanced paternal age, obstetric complications, urban living, migrant status, childhood trauma, among others (Brown, 2011). Childhood trauma appears to be a particularly strong risk factor for schizophrenia (Morgan & Fisher, 2007), with an estimated 2.72-fold increased likelihood of individuals with schizophrenia having been exposed to CHT (Varese et al., 2012).

The precise means by which CHT increases the risk of schizophrenia are still poorly understood (Elton et al., 2014). However, several different pathways from CHT to schizophrenia have been proposed, including affective and cognitive pathways (Harrison & Weinberger, 2005; Isvoranu et al., 2016). Although numerous studies have examined the association between

affective symptoms and the link between CHT and schizophrenia (Elton et al., 2014), far fewer have addressed potential cognitive associations (Green et al., 2014). Inhibitory control, the ability to regulate a habitual or dominant response, has recently been identified as one possible component of the cognitive pathway from CHT to schizophrenia (Isvoranu et al., 2016). To date, only one study has directly examined any aspect of inhibitory control as a mediator between CHT and schizophrenia (Isvoranu et al., 2016). This study was limited, as it used only a single interview-based question as a general measure of inhibitory control.

General Aims and Justification

The current study used a subsection of data from a larger longitudinal study aiming to examine a range of cognitive, neurobiological, and psychosocial features of schizophrenia in a South African population. The current study used archival data from this larger dataset. In this study, I proposed five aims. First, I aimed to replicate findings of increased prevalence of CHT in people with schizophrenia using a South African sample. Although this is a well-established finding in Western samples, it has only been addressed in a South African sample in one study (Kilian et al., 2017). In the second aim, I intended to replicate findings of impaired response inhibition, a subfunction of inhibitory control, in South Africans with schizophrenia using a behavioral measure of response inhibition. The exact nature of response inhibition deficits in schizophrenia is still unclear. I hoped to clarify the role of response inhibition in schizophrenia by separately measuring two component processes, reactive and proactive inhibition. In the third aim, I intended to replicate findings of impaired response inhibition in South Africans with schizophrenia using neuroimaging measures, again dissociating reactive and proactive inhibitory processes. For both the second and third aim, the replication of these reactive inhibition findings

is important for two reasons. These aims are intended to better understand response inhibition in

schizophrenia. As well, the use of a South African sample is intended to help broaden the regions

of the world represented in the field of schizophrenia research. In the fourth aim, I had planned

to test the behavioral measures of response inhibition as possible mediator between CHT to

positive symptoms of schizophrenia. In the fifth aim, I had planned to test response inhibition as

possible mediator between CHT and positive symptoms of schizophrenia. In this aim, the

pathway was intended to be tested using neuroimaging measures.

Childhood Trauma

The definition of childhood trauma (CHT) varies throughout the literature. One

prominent definition divides CHT into abuse and neglect of persons below the age of 18

(Bernstein & Fink, 1998). Further, abuse includes three subcategories: 1) emotional abuse,

defined as highly embarrassing, demoralizing, or threatening verbal assaults, 2) physical abuse,

in which a minor endures physical attacks by an older person that results in, or could result in,

injury, and 3) sexual abuse, defined as any sexual interaction between a minor and an older

person, particularly when it involves coercion. Neglect is divided into two subcategories,

including 1) emotional neglect, in which a minor's basic emotional and psychological needs are

not met by adult caregivers, and 2) physical neglect, in which adult caregivers do not meet a

minor's basic physical needs, such as food, safety, and health care (Bernstein & Fink, 1998). The

current research used the Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998),

which is the gold standard measure of CHT and was developed within this framework based on

thorough reviews of the CHT literature. The CTQ is also the most commonly used and well-

validated scale to measure CHT in psychopathology research (Bernstein et al., 2003; Rossiter et

al., 2015).

CHT poses a serious public health concern worldwide (Anda, Tietjen, Schulman, Felitti, & Croft, 2010; MacMillan, 1998; Merrick & Brown, 1999; Mulvihill, 2005). Prevalence rates of CHT appear to vary widely among countries (Hughes et al., 2017; Pereda, Guilera, Forns, & Gómez-Benito, 2009). For females, reported international prevalence rates of CHT range from 0 to 53%, while rates ranged from 0 to 60% for males (Pereda et al., 2009). However, most studies report CHT rates of 10 to 20% in females and less than 10% in males (Pereda et al., 2009). In addition to actual regional variation in CHT incidence, differences in reported prevalence are likely affected by measurement discrepancies, including differing definitions of abuse and neglect, as well as cultural differences in the conceptualization and reporting of abuse and neglect (Pereda et al., 2009). Few studies have assessed CHT prevalence in South Africa, with only one study assessing multiple CHT subcategories (Jewkes, Dunkle, Nduna, Jama, & Puren, 2010). Jewkes et al. (2010) used a version of the CTQ culturally-adapted in a sample of rural Xhosa, a prominent ethnic group in South Africa. At a level of "often", females reported rates of CHT as: emotional abuse, 22.9%; physical abuse, 73.8%; sexual abuse, 15.2%; emotional neglect, 19.2%; physical neglect, 35.0%. At a level of "often", males reported rates of CHT as: emotional abuse, 22.0%; physical abuse, 84.9%; sexual abuse 3.9%; emotional neglect, 15.5%; physical neglect, 20.8%. These rates, while based on limited data with only one cultural group in South Africa, are notably higher than the worldwide average CHT rate (Pereda et al., 2009). The study mentions areas of vulnerability for children in sub-Saharan Africa, noting that physical and sexual abuse can often occur at school, and that physical discipline is prevalent in a home setting. Although more research is needed to replicate these findings, these elevated rates in subtypes of

CHT indicate that CHT may be of particular concern to South Africa.

Childhood trauma and schizophrenia. In samples throughout the United States and Europe, CHT is associated with increased likelihood of developing a mental illness (Green et al., 2010; Kessler et al., 2010; Kessler, Davis, & Kendler, 1997; Wittchen, Nelson, & Lachner, 1998), including schizophrenia (Gibson, Alloy, & Ellman, 2016). Notably, the great majority of research in the fields of CHT and schizophrenia has been conducted using samples from the United States, Canada, Europe, and Australia (Ramiro, Madrid, & Brown, 2010). Thus, the research on CHT and schizophrenia cited in this dissertation has used data from these countries, unless otherwise specified. A recent meta-analysis of 23 studies including 2017 people with schizophrenia (Bonoldi et al., 2013) found the prevalence rates of self-reported childhood sexual abuse, physical abuse, and emotional abuse in individuals with schizophrenia to be 26%, 39%, and 34%, respectively. The rates of CHT in individuals with psychosis are consistently above the general population (Bonoldi et al., 2013; Kessler et al., 2010), with meta-analysis indicating individuals with schizophrenia suffer CHT 2.72 times more often than the general population (Varese et al., 2012). As well, several studies have found evidence of a dose-response effect of CHT on schizophrenia, in which high level of exposure to CHT is associated with higher risk of developing schizophrenia (e.g. Janssen et al. 2004; Shevlin, Houston, Dorahy, & Adamson, 2007c; Spauwen, Krabbendam, Lieb, Wittchen, & van Os, 2006).

Within people with schizophrenia, a history of CHT is associated with higher levels of negative outcomes, including poorer response to antipsychotic treatment (Misiak & Frydeck, 2016), greater social and functional impairment (Gil et al., 2009), lower educational attainment (Schenkel, Spaulding, DeLillo, & Silverstein, 2005), dysfunctional stress reactivity (Lange et al.,

2017), greater need for treatment resources (Janssen et al., 2004), higher levels of depression

(Bifulco, Brown, & Adler, 1991; Offen, Waller, & Thomas, 2003), aggression (Li et al., 2012),

and suicidality (Li et al., 2012; Schenkel et al., 2005). These increased difficulties of people with

both schizophrenia and a history of CHT indicates a need for a better understanding of these

related conditions.

Subcategories of CHT and symptoms of schizophrenia. Studies have suggested that

some subtypes of CHT may be more likely to increase overall risk of schizophrenia; however,

findings have been mixed (Gibson, Alloy, & Ellman, 2016). Several studies have found sexual

abuse to have the highest association with schizophrenia (Afifi et al., 2011; Bebbington et al.,

2011; Bechdolf et al., 2010), while others have found higher associations between schizophrenia

and emotional abuse (Duhig et al., 2015), physical abuse (Fisher et al., 2010; Shevlin et al.,

2007a), and physical and emotional neglect (Vogel et al., 2011). Methodological variations such

as the use of different measures to assess CHT, lack of comparison for multiple analyses, and

assessment of only some subcategories of CHT have made it difficult to draw conclusions from

the literature (Fisher et al., 2010; Varese et al., 2012). In addition, many studies have focused on

general associations between CHT and schizophrenia, with less focus on subcategories and

individual symptoms. As well, there is a tendency for different subcategories of CHT to co-occur

within an individual, making it difficult to tease apart associations among these subcategories

and symptoms of psychosis (Shevlin et al., 2011).

Positive and negative symptoms. Different subcategories of CHT have been also been

variably linked with different symptoms of schizophrenia. CHT is most consistently associated

with the positive symptom cluster in schizophrenia (Janssen et al., 2004; McCabe, Maloney,

Stain, Loughland, & Carr, 2012; Read, van Os, Morrison, & Ross, 2005; Whitfield, Dube, Felitti, & Anda, 2005). Different subtypes of CHT have been linked to individual positive symptoms of schizophrenia, though the findings are inconsistent.

Abuse is more strongly associated with positive symptoms as compared to neglect (Heins, Gray, & Tennant, 1990; Read, Agar, Argyle, & Aderhold, 2003). Several studies have found that childhood physical and sexual abuse are most strongly linked to increased hallucinations and delusions (Lysaker, Hunter, Strasburger, & Davis, 2005; Misiak & Frydecka, 2016), while others have found sexual abuse to be associated with only hallucinations, but not delusions (Bentall, Wickham, Shevlin, & Varese, 2012; Read & Argyle, 1999). Similarly, some studies have found childhood physical abuse to be associated with both hallucinations and delusions (Bentall et al., 2012), while others found only associations with hallucinations (Read & Argyle, 1999). One consistent finding is a dose-dependent association between severity of CHT and severity of hallucinations and delusions (Shevlin, Dorahy, & Adamson, 2007b; Varese et al., 2012). This finding indicates that individuals with schizophrenia who have higher levels of CHT are likely to have more frequent hallucinations and delusions. In addition, auditory hallucinations are more malevolent in individuals with schizophrenia with a history of CHT (Offen, Waller, & Thomas, 2003), with approximately half of schizophrenia individuals with CHT experiencing hallucinatory content related to their past trauma (Read & Argyle, 1999).

Within the general population of the United State, Europe, and Australia, approximately 5-8% of individuals have mild sub-clinical positive symptoms of schizophrenia, but do not meet criteria for schizophrenia or other psychotic disorders (Kaymaz et al., 2012). Prevalence of sub-clinical positive symptoms worldwide is not yet clear, as many regions of the world have not

been examined, including South Africa. Individuals with a history of CHT are more likely to have sub-clinical positive symptoms (Alemany et al., 2013; Lataster et al., 2006), and, in individuals at clinical high risk for developing schizophrenia, history of CHT is associated with higher rates of conversion to schizophrenia (Thompson et al., 2013). As well, in individuals identified as being at clinical high risk for developing schizophrenia, a history of CHT is associated with higher levels of positive symptoms. One study found that CHT in general was most highly associated with grandiosity (Thompson et al., 2013), while another found that abuse was associated with delusions, but not hallucinations (Salokangas et al., 2015).

As compared to positive symptoms, negative symptoms have been less consistently linked to CHT. A descriptive review of childhood abuse and schizophrenia found no studies indicating an association between CHT and negative symptoms (Read, van Os, Morrison, & Ross, 2005). However, limited assessment or analysis of negative symptoms in many studies examining CHT in schizophrenia may skew these findings (Bentall et al., 2014).

Overall, research suggests that there is some specificity of association between subcategories of CHT and symptoms of schizophrenia (Bentall et al., 2014). However, the nature of these associations is still unclear, due in part to methodological variation among studies and the difficulty of separating out association of subcategories of CHT that occur together.

Role of CHT in a Neurodevelopmental Model of Schizophrenia

CHT fits within the neurodevelopmental model of schizophrenia. As elaborated in detail below, the basic neurodevelopmental model of schizophrenia posits that early pathological processes in brain development create a brain vulnerable to the effects of environmental stressors (Fatemi & Folson, 2009; Howes & Murray, 2014; Owen, O'Donovan, Thapar, & Craddock,

2011). In this conceptual model, the onset of overt symptoms of schizophrenia is the result of a years-long or even life-long process of abnormal neural development (Rapoport, Giedd, & Gogtay, 2012). The developmental model of schizophrenia is supported by several observations. First, while schizophrenia typically emerges in late-adolescence to early-adulthood (van Os & Kapur, 2009), the disorder is almost invariably preceded by a period of up to several years of schizophrenia-like symptoms (e.g. hallucinations, delusions) at attenuated levels (Schultze-Lutter et al., 2015). This pre-disorder state is called the schizophrenia prodrome (Klosterkotter, Hellmich, Steinmeyer, & Schultze-Lutter, 2001). In addition to exhibiting overt behavioral signs of schizophrenia, such as attenuated hallucinations and delusions, individuals in the schizophrenia prodrome show a progressive worsening of functioning in cognitive domains that are typically affected in schizophrenia, including attention, memory, and executive functioning (Bentall & Fernyhough, 2008; Brewer et al., 2006). As well, neurobiological abnormalities associated with full-threshold schizophrenia are often observed in the prodromal phase, at lower levels of severity compared to full-threshold schizophrenia (Pantelis et al., 2009). These abnormalities include dopamine dysregulation (Howes, Fusar-Poli, Bloomfield, Sevarag, & McGuire, 2012) and abnormalities in the structure and function of prefrontal regions of the brain (Whalley, Harris, & Lawrie, 2007). In fact, some research shows that even before the prodromal phase, in the "premorbid" phase of schizophrenia, cognitive and neurobiological abnormalities can be retrospectively identified in individuals who will later develop schizophrenia (Rapoport, Addington, Frangou, & M.R.C. Psych, 2005). This is particularly striking, as the premorbid phase of schizophrenia is characterized by a lack of overt behavioral symptoms of psychosis, yet cognitive and neurobiological markers are often present (Seidman & Nordentoft, 2015).

Taken together, these observations indicate that pathological neurobiological processes likely start very early in life, well before any overt behavioral symptoms of schizophrenia (Rapoport et al., 2012). However, copious evidence indicates that the development of schizophrenia is not predetermined for individuals with genetic vulnerability (Pruessner, Cullen, Aas, & Walker 2017). The maturing brain, particularly a brain already vulnerable to later developing schizophrenia, can be affected by environmental stressors, such as CHT (Teicher, Andersen, Polcari, Anderson, & Navalta, 2002). Evidence suggest that the intense and prolonged stress of CHT, coupled with the vulnerability of the developing brain, creates abnormalities in brain function and structure (described in further detail below) that contribute to the risk for developing schizophrenia (Read, Perry, Moskowitz, & Connolly, 2001).

Despite suggested links between CHT and later development of psychosis, mechanisms for this link are not yet confirmed. Mounting evidence suggests two general pathways by which CHT increases the risk for schizophrenia, an affective pathway and a cognitive pathway (Isvoranu et al., 2016). The affective pathway is likely a frontolimbic system mediating affective disturbances, such as anxiety and depression, in CHT and schizophrenia ((Hart & Rubia, 2012). The cognitive pathway may be a frontostriatal system, mediating deficits in cognition, including attention, working memory, and inhibitory control (Hart & Rubia, 2012). Importantly, these pathways are likely not mutually exclusive, with evidence of connections between emotion and cognition being affected in both CHT (Wang et al., 2011) and schizophrenia (Silver & Schlomo, 2001).

Affective pathway from CHT to schizophrenia. The affective pathway is the most well-studied means by which CHT and schizophrenia are associated (Dannlowski et al., 2012). CHT

has a strong impact on the limbic system, which underlies many emotional functions. In turn, the limbic system plays a leading role in the pathogenesis of schizophrenia (Aleman & Kahn, 2005). Several studies have identified affective symptoms, such as anxiety and depression, as mediators of the association between CHT and schizophrenia (Bebbington et al. 2011; Kessler et al., 2010). These findings are consistent with general evidence of increased levels of anxiety, depression, and stress reactivity in individuals who suffered from CHT (Glaser, van Os, Portegijs, & Myin-Germeys, 2006; Roy, 2002). As well, these same symptoms are associated with development of psychosis (Lataster et al. 2006; Myin-Germeys & van Os, 2007; Phillips, Francey, Edwards, & McMurray, 2007).

   Cognitive pathway from CHT to schizophrenia. Little work has directly examined cognitive deficits as a pathway from CHT to schizophrenia. In a recent study, childhood history of abuse predicted the symptoms of grandiosity, excitement, and hostility in people with schizophrenia (Isvoranu et al., 2016). The study used a large sample of 552 people with psychotic disorders. The authors employed network analysis approach to examine the structure of associations among CHT, as assessed with the CTQ, and symptoms of schizophrenia, as assessed with the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987). The PANSS is a 30-item interviewer-rated measure designed to assess the severity of positive and negative symptoms of schizophrenia, based on a Likert-type scale ranging from 1 to 7. The PANSS also assesses for the severity of general psychopathology symptoms associated with schizophrenia, such as depression, anxiety, and inhibitory control. In the PANSS, a trained interviewer determines the severity of an individual's symptoms based on either an unstructured or semi-structured interview. In the network analysis, Isvoranu et al. (2016) included the five

subscales of the CTQ (Sexual Abuse, Physical Abuse, Emotional Abuse, Physical Neglect, Emotional Neglect) and the three subscales of the PANSS (Positive Symptoms, Negative Symptoms, and General Psychopathology). They also included all PANSS items scores. Results indicated that the association between abuse and schizophrenia symptoms was partially mediated by the score of the inhibitory control PANSS item, an item within the General Psychopathology subscale. This was the first study to specifically examine inhibitory control as a mediator between CHT and schizophrenia. However, one major limitation of the study was the use of interview to determine inhibitory control. On the PANSS, inhibitory control is assessed based on interviewee reports of difficulty controlling impulses during the past week. Thus, the PANSS is not a direct measure of inhibitory control, relying on the interviewee to a) be aware of their own difficulties with inhibitory control and b) openly and clearly express these difficulties to the interview. The primary goal of this dissertation was to expand on the findings of Isvoranu et al. (2016) by using more comprehensive indices of inhibitory control: behavioral and neuroimaging measures of response inhibition.

Inhibitory Control and Response Inhibition

Executive functions are a set of higher-level processes that allow humans to adaptively modulate thought and behavior in response to changes in the environment or internal goals (Barch, Braver, Carter, Poldrack, & Robbins, 2009). Executive functions are vitally important to everyday functioning. Inhibitory control, the ability to control thoughts, behaviors, and emotions, particularly when overriding an external trigger or internal predisposition (Diamond, 2013), is one domain of executive functioning that has been linked to both CHT and schizophrenia (Aas et al., 2011). Recent evidence has implicated inhibitory control as a potential link between CHT

and schizophrenia symptoms (Isvoranu et al., 2016). Inhibitory control is often split into two subcategories, response inhibition and interference control (Thorell, Bohlin, & Rydell, 2004; Tiego, Testa, Bellgrove, Pantelis, & Whittle, 2018; Verbruggen, Liefooghe, & Vandierendonck, 2004). Response inhibition refers to the suppression of a planned response, typically suppressed because the response is no longer appropriate or needed (Logan & Cowan, 1984). Interference control refers to the ability to filter out irrelevant or unneeded information in order to best attend to a target task (Mullane, Corkum, Klien, & McLaughlin, 2009). The majority of research on inhibitory control, and subdomains within inhibitory control, has taken place in the United State, Canada, Europe, and Australia. Thus, the research cited in this dissertation relating to inhibitory control is from these regions of the world, unless otherwise specified.

      Response inhibition. In this study, I focused on response inhibition. Response inhibition is a major aspect of inhibitory control, allowing people to stop an action, such as talking or typing, when changes in the environment deem that action no longer appropriate (Verbruggen & Logan, 2009). Deficits in response inhibition have been shown in both individuals with CHT (Elton et al., 2014; Marshall et al., 2016; van Rooij, Geuze, Kennis, Rademaker, & Vink, 2015) and schizophrenia (Ethridge et al., 2014; Ettinger et al., 2017; Kaladjian, Jeanningros, Azorin, Anton, & Mazzola-Pomietto, 2011), as further elaborated in sections below. The prominence of response inhibition as a main component of inhibitory control makes it a candidate function for the cognitive pathway between CHT and schizophrenia (Isvoranu et al., 2016). Research on response inhibition in schizophrenia has been conducted almost entirely on samples in the United States, Canada, Europe, and Australia. Thus, all studies on response inhibition cited in this dissertation have been conducted in these aforementioned regions of the world, unless otherwise

specified.

   Proactive and reactive inhibition. Response inhibition is composed of two sub-functions,

proactive inhibition and reactive inhibition (Braver, 2012; Braver, Gray, & Burgess, 2007).

Reactive inhibition is the actual stopping of a planned response, triggered by a signal from the

external world, while proactive inhibition is the anticipatory slowing of a response (Vink,

Kaldewaji, Zandbelt, & du Plessis, 2015). Proactive inhibition facilitates reactive inhibition by

anticipatorily engaging a network of neural mechanisms associated with response stopping,

effectively slowing an activated response (Verbruggen & Logan, 2009).

   Measurement of response inhibition. Response inhibition is typically measured with one

of several tasks, including the Go/No-Go task, Stop-Signal Task (SST), Flanker task, and Stroop

task, (Lipszyc & Schachar, 2010). The most common of these tasks are the Go/No-Go task and

the SST (Congdon et al., 2012; Schall & Boucher, 2007). In the Go/No-Go task, participants

must respond to a certain set of stimuli while inhibiting the urge to respond to another set of

stimuli (Congdon et al., 2012). The SST is similar to the Go/No-Go tasks in that participants

must inhibit a response that they are already prepared to make (Logan & Cowan, 1984).

However, in the SST, the participant must inhibit a response that they have already started to

initiate (Logan, 2015). In both tasks, integrity of response inhibition is typically operationalized

as either the proportion of failed attempts to inhibit a response or the average length of time

taken to inhibit the response, with longer time indicating less robust response inhibition abilities

(Logan & Cowan, 1984). The Go/No-Go task and SST are similar but measure slightly different

functions (Criaud & Boulinguez, 2013) and recruit overlapping but not identical neural

mechanisms (Simmonds et al., 2008; Swick, Ashley, & Turken, 2011). While there is

disagreement on the precise neural mechanisms of each task (Chambers, Garavan, & Bellgrove, 2009), quantitative meta-analysis indicates that the only consistent overlaps in neural processes recruited by the Go/No-Go and SST are in the anterior insula, pre-supplementary motor cortex (Swick et al., 2011), and interior frontal gyrus (Swick et al., 2011). The SST, in contrast to the Go/No-Go task, appears to also recruit the basal ganglia, including the putamen (Swick et al., 2011), which is particularly associated with proactive inhibition processes (Zandbelt & Vink, 2010).

The SST has been identified by several experts as the preferred paradigm for the measurement of response inhibition (Barch et al., 2009). Despite the popularity of the Go/No-Go task, some suggest that it may not be ideal to measure response inhibition (Criaud & Boulinguez, 2013). In a meta-analysis and critical review of functional magnetic resonance imaging studies (fRMI) using the Go/No-Go task, Criaud & Boulinguez (2013) suggest that much of the neural activity observed in many versions of this task is may be related to high demand on attention and working memory. Go/No-Go task designs are often complex, with high numbers of stimulus-response associations that participants must remember, which increases working memory load (Simmonds, Pekar, & Mostofsky, 2008). As well, processes such as stimulus detection and identification can lead to high attentional load in the task (Simmonds et al., 2008). In addition, the SST is preferred for high construct validity in both humans and animal studies, good test-retest reliability, and minimal practice effects (Barch et al., 2009).

Since development of the SST over 30 years ago, researchers have refined the task to further parse out individual components of response inhibition. One such paradigm, the Stop-Signal Anticipation Task (SSAT; Figure 1; Zandbelt & Vink, 2010), is a modified version of the

SST that allows for distinct and separate measurement of proactive and reactive inhibition. While there are versions of the Go/No-Go tasks that selectively engage both reactive and proactive inhibition (Hikosaka & Isoda, 2010), the design of the SSAT allows for a cleaner dissociation between reactive and proactive processes (Criaud & Boulinguez, 2013).

The design of the SSAT builds upon the basic structure of the SST (Zandbelt & Vink, 2010). In a standard version of the SST, participants view a screen with three horizontal lines. During all trials, a bar moves vertically upwards from the bottom line. On the frequent GO trials, participants are asked to press a button to stop the moving bar when it reaches the middle. On the infrequent STOP trials, the bar stops moving slightly before it reaches the middle line, requiring participants to inhibit the prepotent response of pressing the button. The participant's ability to effectively inhibit the prepotent response of pressing the button is considered to reflect response inhibition processes. In the standard SST, primarily reactive inhibition is being measured (Aron, 2011). The SSAT adds an additional parameter that allows for relatively separate measurement of proactive and reactive inhibition (Zandbelt & Vink, 2010). In the SSAT, the color of the middle line on the display is varied based on the probability that a STOP trial will occur. Thus, the participant has information about the likelihood of a STOP trial and engages proactive inhibition processes commensurate with the likelihood of needing to inhibit the button press.

Figure 1. Stop-Signal Anticipation Task
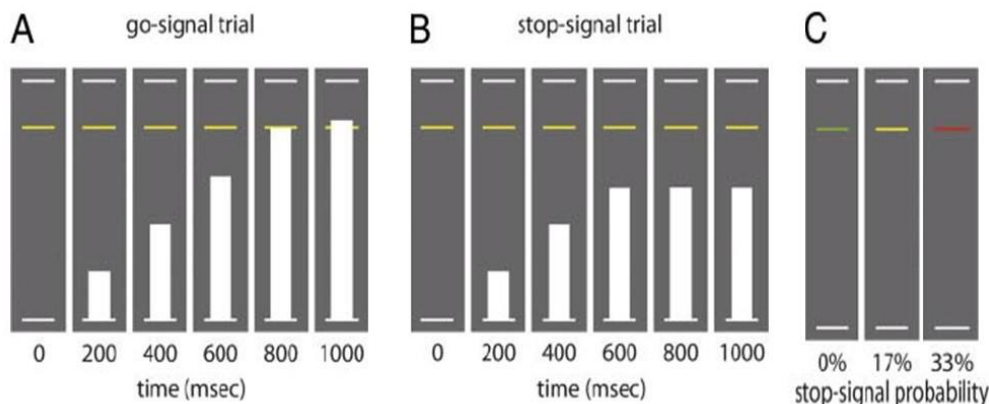
(Figure adapted from Zandbelt & Vink, 2010)

The distinction between proactive inhibition and reactive inhibition may be important in understanding connections between CHT and schizophrenia because these processes may not both be impaired in schizophrenia (Zandbelt, van Buuren, Kahn, & Vink, 2011). As well, proactive and reactive inhibition appear to develop at differing rates throughout the lifespan, indicating that proactive and reactive inhibition may be differentially affected by CHT depending on when the trauma occurs during development (Vink et al., 2014). In addition, different brain areas may be recruited in proactive and reactive inhibition. If CHT interrupts or slows development of brain areas differentially engaged in proactive or reactive inhibition, this may have varying impact on the likelihood of developing schizophrenia. Little research has been conducted on possible independent roles of proactive and reactive inhibition in the association between CHT and schizophrenia.

Inhibitory control in CHT. Abundant research indicates adverse effects of CHT on cognitive functioning, including intelligence quotient and academic functioning (Koenen et al., 2003; Pluck et al., 2011), and attention, memory, and executive functioning (Beers & DeBellis, 2002; Mezzacappa, Kindlon, & Earls, 2001). Few studies have examined response inhibition in

people with a history of CHT, though there is a broader range of literature exploring general

inhibitory control in people with CHT (Seghete, Kaier, DePrince, & Banich, 2017). In

individuals with CHT who experience cognitive impairment, these deficits may also interfere

with treatment (Pfeiffer, Sachser, de Haan, Tutus, & Goldbeck, 2017). A history of CHT has

been consistently linked to general deficits in inhibitory control in adulthood (Brodsky et al.,

2001; Mezzacappa et al., 2001; Narvaez et al., 2012). Psychological disorders associated with

impaired inhibitory control are more common in people with CHT, including ADHD (Sonuga-

Barke & Rubia, 2008) and intermittent explosive disorder (Nickerson, Aderka, Byrant, &

Hofmann, 2012). Several studies have also suggested inhibitory control as a link between CHT

and increased risk for suicidal behavior and self-harm (Braquehais, Oquendo, Baca-Garcia, &

Sher, 2010; Brodsky et al., 2001; Peh et al., 2017; Roy, 2005), aggressive behavior (Heide &

Solomon, 2006), and substance use (Clark, De Bellis, Lynch, Cornelius, & Martin, 2003).

      One model of CHT and deficits in inhibitory control suggests that reduced inhibitory

processes are part of a divergent neurodevelopmental pathway favoring cognitive processes that

support short-term survival benefits over processes that may be adaptive in the longer term

(Grassi-Oliveira, Ashy, & Stein, 2008; Perry, Pollard, Blakley, Baker, & Vigilante, 1995).

Inhibitory control, and the brain systems that underlie inhibitory control, develops throughout

childhood and adolescence (Cohen et al., 2010; Spear 2013). If a child or adolescent experiences

a high level of prolonged stress during a critical period of development in the brain, this level of

stress can affect neurotransmitters, hormones, and neurotrophic factors that play a large part in

the organization and development of brain structure and function (Andersen, 2003). In this

model, highly stressful events may actually accelerate the development of frontal regions of the

brain, causing premature development and negative impact on later functioning (Teicher et al., 2003). In this case, the immediate advantage of developing frontal regions more quickly throughout childhood later becomes a disadvantage when the hasty development of frontal regions results in less optimal adulthood functioning (Teicher et al., 2003).

Response inhibition in CHT. Research on response inhibition in individuals with a history of CHT is limited, with the majority of work focusing on emotional inhibitory control (Seghete et al., 2017). Several studies using a Go/No-Go task have found increased response time and decreased accuracy in adults with a history of CHT (Marshall et al., 2016; Navalta, Polcari, Webster, Boghossian, & Teicher, 2006; Stevens et al., 2016). Evidence suggests that general long-term stress, such as the stress associated with traumatic events during childhood, may impair response inhibition (Lyons, Lopez, Yang, & Schatzberg, 2000), while temporary stress may improve response inhibition (Schwabe, Hoffken, Tegenthoff, & Wolf, 2013).

Inhibitory control in schizophrenia. Deficits in a range of cognitive functions, including attention, working memory, and executive functions, are considered by many to be a core deficit in schizophrenia (Barch, 2005). Cognitive deficits are often observed before the onset of positive and negative symptoms (Reichenberg et al., 2006; Woodberry et al., 2008) and are associated with poor social functioning (Owen, Sawa, & Moertensen, 2016).

Impairments in the broader category of inhibitory control are consistently observed in people with schizophrenia (Barch & Ceaser, 2012). Some have suggested that poor inhibitory control is a central cognitive feature of schizophrenia (Clementz, 1998; Ouzir, 2013). Deficits in inhibitory control in schizophrenia are associated with a range of negative behavioral outcomes, including increased rates of substance abuse (Dawe, Gullo, & Loxton, 2004; Derveaux et al.,

2001), suicide (Gut-Fayand et al., 2001), and violence (Volavka & Citrome, 2008).

   Response inhibition in schizophrenia. Research on response inhibition in schizophrenia

has yielded mixed results, with some studies indicating impairment (Kaladjian, Jeanningros,

Azorin, Anton, & Mazzola-Pomietto, 2011; Raemaekers et al., 2002) and others finding no

impairment (Badcock, Michie, Johnson, & Crombrinck, 2002; Rubia et al., 2001). These

inconsistent findings may be due to the variety of tasks used, some of which measure other

cognitive functions in addition to response inhibition, or measure different aspects of response

inhibition (Zandbelt, van Buuren, Kahn, & Vink, 2011).

   Use of the SST and SSAT in schizophrenia. The majority of studies using the SST in a

schizophrenia sample have found impairment as compared to non-psychiatric controls (Bellgrove

et al., 2006; Davalos, Compagnon, Heinlein, & Ross, 2004; Enticott, Ogloff, & Bradshaw, 2008;

Hughes, Johnston, Fulham, Budd, & Michie, 2013; Nolan, D'Angelo, & Hoptman, 2011;

Thakkar, Schall, Boucher, Logan, & Park, 2011). At least one SST study did not find response

inhibition impairment in people with schizophrenia, though results did indicate significantly

increased variability in response inhibition performance as compared to controls (Badcock,

Michie, Johnson, & Crombrinck, 2002). Unaffected siblings of individuals with schizophrenia

appear marginally impaired on the SST, suggesting a genetic contribution to response inhibition

deficits in schizophrenia (Badcock et al., 2002). Only one study to date has used the SSAT in

schizophrenia. Zandbelt and colleagues (2011) found impaired proactive inhibition in individuals

with schizophrenia, as well as in their unaffected siblings, compared to non-psychiatric controls.

Schizophrenia participants performed as well as controls on reactive inhibition, but significantly

worse than controls on proactive inhibition, yielding preliminary evidence that proactive and

reactive inhibition may be differentially impaired in schizophrenia.

Shared Neurobiological Correlates of CHT, Schizophrenia, and Response Inhibition:

Prefrontal Cortex, Striatum, and Related Dopamine Transmission

Consistently, research does indicate that CHT affects brain areas and functions that are particularly susceptible to the effects of stress during development (McEwen, 2000). Shared biological mechanisms affected by both CHT and schizophrenia include the hypothalamic-pituitary axis (HPA), limbic system, prefrontal cortex (PFC), striatum, and transmission of dopamine (Bentall et al., 2014; Teicher et al., 2003; Wilson, Hansen, & Li, 2011). Several of these brain regions and functions are also implicated in response inhibition, particularly the PFC, striatum, and transmission of dopamine (Zandbelt et al., 2011).

The PFC is responsible for high-level cognitive functions, such as planning, problem-solving, working memory, regulation, and decision making (Strauss, Sherman, & Spreen, 2006). The striatum is a subcortical nucleus of the brain that includes the caudate, putamen, and the nucleus accumbens. The striatum is involved in motivation, reward, motor behavior, and inhibitory control (Yager, Garcia, Wunsch, & Ferguson, 2015), and has strong connections with both the limbic system and PFC (Marusak, Hatfield, Thomason, & Rabinak, 2016). Dopamine is one of the main neurotransmitters in the central nervous system, playing an integral role in inhibitory control, reward processing, motivated behavior, and motor control (Howes & Kapur, 2009). There are two major dopaminergic pathways in the brain: the mesocorticolimbic pathway, which includes the ventral tegmental area, limbic system, striatum, and prefrontal cortex, and the nigrostriatal pathway, which projects from the substantia nigra to the striatum (Marusak, Hatfield, Thomason, & Rabinak, 2016).

Prefrontal cortex, striatum, and related dopamine transmission in CHT. The PFC reaches maturity relatively late in life, with development extending well into the 20s and early 30s (Sowell et al., 2003). The protracted development of the PFC leaves this brain region vulnerable to environmental insults, such as CHT (Hart & Rubia, 2012).

Alterations of several areas of the PFC have been found in individuals with a history of CHT, although findings have been mixed on the precise PFC regions affected by CHT (Hart & Rubia, 2012). A meta-analysis concluded that one of the most robust alterations in adults with a history of CHT was reduced grey matter in the right dorsolateral PFC (Paquola, Bennett, & Lagopoulos, 2016), with gray matter reductions also observed in the right superior frontal gyrus (Lim, Radua, & Rubia, 2014), orbitofrontal cortex (Chugani et al., 2001; Saleh et al., 2017), medial PFC (Duncan et al., 2015), and inferior frontal cortex (Edminston et al., 2011).

Few studies have examined the structure and function of the striatum in CHT, as compared to other brain regions such as the limbic system (Hart & Rubia, 2012). Several studies have observed reduced caudate volumes in adults reporting abuse in childhood (Cohen et al., 2006; Dannlowski et al., 2011; Saleh et al., 2017), particularly in males (Edminston et al., 2011), though some studies examining whole-brain structural differences have reported no striatal alterations in CHT (Carrion et al., 2009; Treadway et al., 2009).

Frontostriatal connections may also be impaired in those with CHT (Cohen et al., 2006; Edminston et al., 2011; Monroy, Hernandez-Torres, & Flores, 2010). Childhood and adolescence are particularly sensitive periods for the formation and maturation of connective white matter tracts between the prefrontal lobe and the striatum (Deoni, Dean, O'Muircheartaigh, Dirks, & Jerskey, 2012; Rubia, Smith, Brammer, & Taylor, 2003). Development of white matter tracts is

important for information transfer and coordination between brain regions. Abnormal development of white matter tracts is associated with impairments in behaviors governed by the connected brain regions (Johnson & Munakata, 2005).

Dopaminergic systems appear particularly vulnerable to environmental threats. When a child's brain is exposed to high levels of stress, such as in CHT, dopamine-rich regions of the brain become sensitized to dopamine, creating increased baseline dopamine transmission (Howes & Murray, 2014). Dopamine sensitization allows for a quicker response to environmental threats but leaves the brain at greater risk for dopamine-related psychopathology, including substance use disorders and schizophrenia (Kasanova et al., 2016).

The effects of stress on dopaminergic systems may be selective, as long-term life stress appears to permanently affect the mesocorticolimbic, but not the nigrastrial dopaminergic, pathway (Cabib & Puglisi-Allegra, 1996; Haber & Fudge, 1997). Dopamine dysregulation in CHT is particularly pronounced in frontostriatal areas. People with a history of CHT exhibit general impairment in striatal dopamine functioning (Oswald et al., 2014; Pruessner, Champagne, Meaney, & Dagher, 2004), including higher levels of presynaptic dopamine in the striatum during stress (Egerton et al., 2013; Pruessner et al., 2004; Wand et al., 2007). Evidence from animal models additionally supports a role of early life stress in frontostriatal dopamine dysfunction. In rodents, high levels of stress during development leads to decreased transmission of dopamine in the PFC (Ventura et al., 2013; Watt et al., 2014), and increased transmission of dopamine in the striatum (Boksa & El-Kodor, 2003).

Prefrontal cortex, striatum, and related dopamine transmission in schizophrenia. Abnormal structure and function in the prefrontal lobes are well-replicated observations in

people with schizophrenia (Akbarian, 1995; Fahim et al., 2005; Weinberger, Berman, Suddath, & Torrey, 1992). Alterations in the prefrontal lobes in schizophrenia are associated with emotional and cognitive dysfunction (Lesh et al., 2013). Decreased connections between prefrontal and limbic areas are found in people with schizophrenia (Ursu et al., 2011). Similar to findings in CHT, abnormalities are observed in the structural and functional connections between the inferior frontal cortex and striatum (Meyer-Lindenberg et al., 2009; Waltz, Frank, Robinson, & Gold, 2007; Xiao, Barborica, & Ferrera, 2006), which have also been linked to impairments in inhibitory control (Knight, Staines, Swick, & Chao, 1999; Rubia, Russell, Bullmore, Soni, & Brammer, 2001).

The striatum has been implicated by many researchers as one of the main areas of dysfunction in schizophrenia, predominantly as part of the mesocorticolimbic dopaminergic system, considered by many to be at the core of schizophrenia pathogenesis (Antonova, Sharma, Morris, & Kumari, 2004; Barch & Dowd, 2010; O'Donnell & Grace, 1998). As well, the striatum receives inputs from almost every area of the brain implicated in schizophrenia (O'Donnell & Grace, 1998). In schizophrenia, abnormalities have been observed throughout the striatum, but are particularly pronounced in the rostral caudate (Weinstein et al., 2017), correlating with abnormally high levels of dopamine transmission (Abi-Dargham, 1998).

An array of neurotransmitter systems have been implicated in schizophrenia, including dopaminergic, glutamatergic, serotonergic, and cholinergic systems (Carlsson et al., 2001). However, of these systems, imbalance in the synthesis and release of dopamine has been most strongly and consistently linked to schizophrenia (Laruelle & Abi-Dargham, 1999). Patterns of dopamine dysregulation in schizophrenia are similar to those of CHT, with some researchers

suggesting the mesocorticolimbic system as the core link between CHT and schizophrenia (Howes & Murray, 2013). Schizophrenia is characterized by excess dopamine transmission in subcortical regions, including the limbic system and striatum, and decreased dopamine transmission in cortical regions, including the PFC (Frangou, 2008; Slifstein et al., 2015; Weinstein et al., 2017). Traditionally, excessive transmission of dopamine in subcortical regions is associated with the positive symptoms of schizophrenia, while decreased dopamine transmission in cortical regions is associated with negative and cognitive symptoms (Andreasen, 1985); however, the actual dynamics of these associations is likely more complex (Pogarell et al., 2012).

   Prefrontal cortex, striatum, and related dopamine transmission in response inhibition. Efforts to identify the core brain regions engaged in response inhibition have observed that response inhibition tasks appear to primarily engage a frontostriatal network (Verbruggen & Logan, 2009; Zandbelt & Vink, 2010), used for initiation and suppression of movement (Schall & Boucher, 2007). Within the frontal cortex, the inferior frontal cortex is most consistently implicated in response inhibition (e.g. Criaud & Boulinguez; Rubia et al., 2006; Rubia, Smith, Taylor, & Brammer, 2007).

   Other brain structures have been implicated in response inhibition, including the insula, medial prefrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, and inferior parietal cortex (Aron & Poldrack, 2006; Li et al., 2006; Rubia, Smith, Brammer, & Taylor, 2003). However, the degree to which these brain areas are directly involved in response inhibition is not clear, as many tasks used to measure response inhibition also recruit other cognitive functions such as working memory, attention, and response selection (Chambers,

Garvan, & Bellgrove, 2009; Simmonds, Pekar, & Mostofsky, 2008). For example, the anterior cingulate cortex likely does not represent the response inhibition, but rather error monitoring, anticipation of reward, and the delivery of reward (Rubia et al., 2007; Schall & Boucher, 2007). As well, the medial prefrontal cortex likely mediates error monitoring (Rubia et al., 2003), and the dorsolateral prefrontal cortex likely mediates working memory demands, rather than being central to response inhibition (Mars & Grol, 2007).

Dopamine transmission through frontostriatal pathways is heavily implicated in response inhibition (Courtney, Ghahremani, & Ray, 2013; Ghahremani et al., 2012). Poor dopamine function is related to impairments in response inhibition in healthy adults (Zhang et al., 2015).

Prefrontal cortex and striatum in proactive and reactive inhibition. Researchers have also identified candidate neural systems for the two subcomponents of response inhibition, proactive and reactive inhibition. These processes likely share some neural substrates but may also differ in recruitment of neural regions as well as the timing of processes (Barch et al., 2009; van Belle, Vink, Durston, & Zandbelt, 2014). Some studies also suggest that proactive inhibition may engage a pattern of neural activity that takes place over a longer period of time (Cunillera, Fuentemilla, Brignani, Cucurell, & Miniussi, 2014) while reactive control may take place in a short time frame (Egner & Hirsch, 2005; MacDonald, Cohen, Stenger, & Carter, 2000). Although the neural mechanisms of proactive and reactive inhibition are still not entirely clear, it does appear that there is at least involvement of the prefrontal and striatal regions in both aspects of response inhibition (Chikazoe et al., 2009; Swann et al., 2012; Verbruggen & Logan, 2009; Zandbelt & Vink, 2010).

Neural underpinnings of impaired response inhibition in CHT. To date, three studies

have examined the functional neural mechanisms underlying response inhibition deficits in people with CHT. To the best of my knowledge, proactive and reactive inhibition have never been separately measured in CHT. Using the CTQ and the SST, one study found impaired response inhibition in males with a history of CHT, but not in females (Elton et al., 2014). This study found that female adults with a history of CHT had greater activation of the left inferior frontal cortex. This finding was dose-related, meaning higher scores on the total CTQ were associated with both greater activation of the left inferior frontal cortex and more accurate performance on the SST. The opposite effect was found in males, with higher scores on the CTQ predicting less activation in the right interior frontal cortex and poorer performance on the SST. The results suggest CHT may have a different impact on response inhibition in females as compared to males. These gender differences may be due in part to differential effects of sex hormones on the developing brain (Lenroot et al., 2007), in which estrogen appears to have a neuroprotective effect on select regions, including the striatum (Dluzen, 2000).

Another study used a variation of the SST in a small sample of adolescents that had been neglected earlier in life (Mueller et al., 2010). Subjects with CHT were impaired on the response inhibition task as compared to controls, and impairment was associated with increased activation of inferior PFC, striatum, and insula. A similar study using a Go/No-Go task also found reduced response inhibition performance in adolescents with a history of CHT (Carrion, Garret, Meon, Weems, & Reiss, 2008). Poor performance on the response inhibition task was associated with decreased activation of the medial PFC, dorsolateral PFC, and insula in people with CHT.

The timing of CHT may affect the way in which response inhibition is impaired. Maturation of frontostriatal tracts occurs between the ages of 7-31, corresponding with improved

performance in response inhibition with age (Hwang, Velanova, & Luna, 2010; Liston et al.,

2006; Velanova, Wheeler, & Luna, 2009). Stressors earlier in development may lead to impaired

reactive inhibition, while stressors later in development may impair the later-developing

proactive inhibition (Vink et al., 2014).

　　　　Neural underpinnings of impaired response inhibition in schizophrenia. Few studies have

directly investigated the neural processes underlying response inhibition in schizophrenia, as

many studies have included measures that concurrently measure other cognitive processes

(Hughes, Johnston, Fulham, Budd, & Michie, 2012). Two studies have found slower stopping

time in people with schizophrenia as compared to non-psychiatric controls in the SST and

Go/No-Go task associated with decreased right inferior frontal gyrus activation (Hughes et al.,

2012; Zandbelt et al., 2011). However, at least one study did not support this finding (Rubia et al,

2001).

　　　　Only one study has examined the neural underpinnings of proactive and reactive

inhibition in schizophrenia. Using the SSAT, this study found that decreased activation of

proactive inhibition is associated with less activation of the right striatum and inferior frontal

gyrus but did not find these associations in reactive inhibition (Zandbelt et al., 2011). These

results indicate a possible impairment in neural mechanisms underlying proactive and reactive

inhibition in schizophrenia, underscoring the importance of measuring both aspects of response

inhibition in future work on schizophrenia. A better understanding of specific response inhibition

in schizophrenia could lead to a better understanding of the pathogenesis of schizophrenia and

may lead to more specific pharmacological and behavioral treatment targets.

Sub-Saharan African Sample

The current study was conducted in the Western Cape region of South Africa, located in sub-Saharan Africa. The location of the current work serves as partial fulfillment of Aims 1-3 of this dissertation, of diversifying research on CHT and schizophrenia. The overwhelming majority of research in psychopathology, including schizophrenia, takes place in Western countries, using samples of Western individuals (Cooper, 2013; Seedat & Mackenzie, 2008). The culturally diverse countries of sub-Saharan Africa, including South Africa, are sparsely represented in the global body of psychopathology research (Cooper & Nicholas, 2012; Painter & Blanche, 2004). Due to a relative lack of psychopathology research from the sub-Saharan region, knowledge gained primarily from Western countries is generalized to individuals in sub-Saharan Africa with little examination of whether these generalizations are true of sub-Saharan regions (Cooper, Nicholas, Seedat, & Statman, 1990).

The course and presentation of schizophrenia may look different in varying regions of the world. For example, the World Health Organization conducted the International Pilot Study of Schizophrenia (Leff, Sartorius, Jablensky, Korten, & Ernberg, 1992; Sartorius, Shapiro, & Jablensky, 1974) and the Determinants of Outcome of Severe Mental Disorder study (Sartorius et al., 1986) to better understand potential differences in schizophrenia and other serious mental disorders in developing regions of the world, including areas of sub-Saharan Africa. The general conclusion of both of these studies indicated more favorable outcomes for people with schizophrenia in developing regions of the world, including sub-Saharan Africa (e.g. Leffet al, 1992, Sartorius et al., 1986, Volavka et al., 1997). In the first of the two studies, less-developed countries appear to show lower levels of recent psychosis symptoms (e.g. hallucinations, delusions, negative symptoms) in people with schizophrenia at five-year follow-up (Leff et al.,

1992). The first study also indicated higher levels of social and occupational functioning for people experiencing schizophrenia in less-developed regions of the world, also at five-year follow-up (Leff et al., 1992). The second study found higher rates of complete psychosis symptom remission at two-year follow-up in people schizophrenia in less-developed countries (Sartorius et al., 1986).

However, in the years since the findings of the International Pilot Study and the Determinants of Outcome of Severe Mental Disorder study were reported, many have questioned the conclusions. Researchers have noted methodological limitations in these studies, including relatively few regions of the world being represented, limited outcome variables, and measures that were not culturally adapted for the region (Burns 2014; Edgerton & Cohen, 1994). For example, the hallmark symptoms of schizophrenia (e.g. hallucinations and delusions) can be interpreted differently across different cultures, possibly confounding the assessment of symptoms (Larøi et al., 2014). Some cultures maybe attribute hallucinations and delusions to spiritual phenomena, rather than a psychological disorder (Thomas et al., 2007). As well, conceptualizations of "good" social and occupational functioning can vary widely based on culture, making it difficult to use a single measure, not culturally validated, to accurately assesses these constructs across differing regions of the world (Edgerton & Cohen, 1994). Finally, the finding of increased occupational and social functioning in less-developed regions of the world is difficult to reconcile with studies indicating poor treatment of individuals in many developing countries (Saraceno et al., 2007; Semrau et al., 2015). Studies of some regions of sub-Saharan Africa have recorded cruel treatment, such as chaining and beating of people with schizophrenia (Read, Adiibokah, & Nyame, 2009, Read, Doku, & De-Graft, 2015). The

conversation regarding the course and presentation of schizophrenia in sub-Saharan Africa is impeded by a lack of research in the area.

Conducting studies of schizophrenia and other psychological phenomena in sub-Saharan Africa is one incremental step in understanding whether the Western models of psychological phenomena hold up in non-Western settings. Increasing the representation of sub-Saharan populations in psychopathology research would help make psychology research more representative of the diversity of human psychology (Cooper, 2014; Pillay, 2013).

Aims and Hypotheses

The current proposal had five aims.

Aim 1: Test between-groups differences in CHT. The first aim was to replicate previous findings of increased prevalence of CHT individuals with schizophrenia in a South African sample.

Hypothesis 1: The schizophrenia group would have a significantly higher rate of CHT as compared to non-psychiatric controls, as measured by total score on the CTQ.

Aim 2: Test between-groups difference in response inhibition using behavioral measures. The second aim was to replicate previous findings of poor proactive inhibition and intact reactive inhibition in a South African sample of people with schizophrenia.

Hypothesis 2a: The schizophrenia group would have intact reactive inhibition, as found in previous work (Zandbelt et al., 2011).

Hypothesis 2b: The schizophrenia group would have poorer proactive inhibition than controls, as found in previous work (Zandbelt et al., 2011).

Aim 3: Test between-groups difference in response inhibition using neuroimaging measures. The third aim of this study was to replicate previous findings of poor response inhibition in a South African sample of individuals with schizophrenia using neuroimaging indices.

Hypothesis 3a: The schizophrenia group would have no statistically significant differences in blood-oxygen-level-dependent (BOLD) activation as compared to controls in a combination of regions of interest (ROIs) previously identified as being associated with reactive inhibition (Figure 3; Zandbelt et al., 2011). This will reflect intact reactive inhibition neural processes in schizophrenia.

Hypothesis 3b: The schizophrenia group would have significantly reduced BOLD activation compared to controls in a combination of ROIs previously identified as being associated with proactive inhibition (Figure 4; Zandbelt et al., 2011). This will reflect impaired neural processes underlying proactive inhibition in the schizophrenia group.

Aim 4: Test behavioral indices of response inhibition as a mediator between degree of CHT and positive symptoms. The fourth aim was to examine a behavioral measure of proactive inhibition as a potential mediator between childhood trauma and psychotic symptoms in the schizophrenia group.

Hypothesis 4: Proactive inhibition performance on the SSAT would partially mediate a significant correlation between scores on the CTQ and scores on the positive symptom subscale on the PANSS.

Aim 5: Test neuroimaging indices of proactive inhibition as a mediator between degree of CHT and positive symptoms. The fourth aim was to examine a neuroimaging

measure of proactive inhibition as a potential mediator between childhood trauma and psychotic symptoms in the schizophrenia group.

Hypothesis 5: Combined proactive inhibition BOLD activation would partially mediate a significant correlation between scores on the CTQ and scores on the positive symptom subscale on the PANSS.

Methods

Participants

Participants included 34 individuals with schizophrenia spectrum disorders and 33 non-psychiatric control participants. All participants were fluent in either Afrikaans or English and were permitted to complete assessments in either language. Schizophrenia and control participants did not differ on mean age (see Table 1; $t(65) = 1.158$, $p = .251$) or ethnicity, X^2 (3, $N = 66) = 4.267$, $p = .234$. The schizophrenia participant group did include significantly fewer females, X^2 (1, $N = 67) = 5.486$, $p = .019$, and had mean lower educational attainment. Lower educational attainment is typical in schizophrenia samples (Swanson et al., 1998) as lower socio-economic status may be both a causal factor in schizophrenia and a consequence of predisposition to the disorder (Meehl, 1971)

Schizophrenia participants were recruited as part of a larger research protocol within the Department of Psychiatry at the University of Stellenbosch in Stellenbosch, South Africa. The larger protocol was led by Dr. Robin Emsley, DMed, DSc, head of the Schizophrenia Research Unit at the University of Stellenbosch. The study was a 2-4-year longitudinal study; the current data were collected at baseline. The larger protocol included over 135 people with schizophrenia. The larger protocol had several main aims including assessing functional, clinical, and biological

outcomes of schizophrenia, examining the acute effects of antipsychotic medication on the brain, and comparing relative efficacy of two long-acting antipsychotic medications. Recruitment sites included outpatient and inpatient mental health facilities at Stikland and Tygerberg Hospitals and nearby mental health clinics within and around Cape Town, South Africa. Inclusion criteria for the schizophrenia participants were: schizophrenia spectrum disorder (including schizophrenia, schizophreniform, and schizoaffective disorder) as assessed by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, text revision (DSM-IV-TR; American Psychiatric Association, 2000), age of 16-45, and right handedness. Exclusion criteria were substance abuse in the past 6 months (as determined by report from the participant, report from any available caretaker or relative of the participant, and urine screen), serious or uncontrolled general medical condition, and IQ lower than 70. Non-psychiatric control participants were recruited from non-medical hospital staff, their relatives and acquaintances, and independent sources within the community. Control participants were recruited through flyers and word of mouth. Exclusion criteria for control participants were: current or previous mental illness as determined by the DSM-IV-TR, current or previous usage of psychotropic medication, and substance abuse (as determined by participant report and urine screen).

All participants were reimbursed for transportation costs but received no additional compensation. Written informed consent was obtained from all participants. The larger research protocol was approved by the Health Research Ethics Committee of Stellenbosch University and the Human Research Ethics Committee of the University of Cape Town, Cape Town, South Africa.

Table 1. Participant Demographic Characteristics

	Schizophrenia Mean (SD)	Control Mean (SD)	N (SZ, control)	t/X^2	df	p
Age	31.18 (7.38)	29.21 (6.46)	34/33	1.158	65	.251
Gender (F/M)	9/25	18/15	34/33	5.486	1	.019
Ethnicity	-	-	33/33	4.267	3	.234
Mixed (%)	82.4%	97.0%	-	-	-	-
African	2.9%	3.0%	-	-	-	-
European	8.8%	0%	-	-	-	-
Asian	2.9%	0%	-	-	-	-
Years of Education	10.4 (1.8)	12.2 (3.1)	33/33	-2.994	64	.004
PANSS Total	70.9 (25.9)	-	33	-	-	-
PANSS Disorganized	9.5 (3.6)	-	33	-	-	-
PANSS Positive	12.3 (6.3)	-	33	-	-	-
PANSS Negative	17.1 (6.3)	-	33	-	-	-
PANSS Emotional Distress	7.1 (3.6)	-	33	-	-	-
PANSS Excitement	5.7 (3.1)	-	33	-	-	-

Materials

Diagnostic measures. Diagnosis of schizophrenia was determined by trained mental health practitioners using the Structured Clinical Interview for DSM-IV (SCID) – Patient Edition (First, Spitzer, Gibbon, & Williams, 2002), a structured interview designed for diagnosis of major mental illness. The SCID was administered in either English or Afrikaans, depending on preference of the participant. The SCID Non-Patient Edition was used to rule out mental disorder in control participants. Inter-rater reliability was periodically assessed in the current study, with raters achieving intraclass correlation of .70 or higher. In previous research, the SCID has been

found to have validity kappa values between .76 - .78 for comparisons between SCID diagnosis and diagnosis made with other standard interview methods (Lobbestael, Leurgans, & Arntz, 2011). The current study used the DSM-IV version of the SCID because the DSM-5 version had not been released at the time of data collection. The diagnostic criteria for schizophrenia and schizoaffective disorder are nearly identical in the DSM-IV and 5, and the few differences that exist can be ascertained from queries on the DSM-IV version.

Psychological symptoms rating. Psychological symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987), included in Appendix B. The PANSS is a 30-item, 7-point Likert-type scale used to rate common symptoms of schizophrenia. The PANSS was administered in either English or Afrikaans, depending on the preference of the participant. The Structured Clinical Interview for the PANSS (SCI-PANSS; Opler, Kay, Linden Mayer, & Fiszbein, 1999) was used as a semi-structured interview. Subscales of Disorganization, Positive Symptoms, Negative Symptoms, Excitement, and Emotional Distress were calculated according to a commonly-used five-factor model (van der Gaag et al., 2006). The PANSS has adequate construct validity and external validity (Kay et al., 1987). In the current study, inter-rater reliability was periodically assessed, with raters achieving intraclass correlation of .70 or higher.

Trauma assessment. Childhood trauma history was assessed using the short form of the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003), included in Appendix C. Participants took the CTQ in either English or Afrikaans, depending on their preference. The short form of the CTQ is a 28-item self-report measure that uses a five-point Likert-type scale to assess abuse and neglect before the age of 18. Verbal labels of the five-point scales included

"Never True", "Rarely True", "Sometimes True", "Often True", and "Always True". The CTQ may be used with individuals 12 years of age and older. The CTQ items are grouped into five maltreatment subscales, each containing five items. The CTQ also contains a Minimization/Denial scale, containing three items designed to detect potential underreporting of abuse or neglect. Within the five maltreatment subscales, Abuse is assessed with Emotional, Physical, and Sexual subscales, while Neglect is assessed with Emotional and Physical subscales. Example items include: "I thought that my parents wished I had never been born" (Emotional Abuse), "I got hit so hard by someone in my family that I had to see a doctor or go to the hospital" (Physical Abuse), "Someone tried to make me do sexual things or watch sexual things" (Sexual Abuse), "I felt loved" (Emotional Neglect; reverse-scored), and "I didn't have enough to eat" (Physical Neglect).

Subscale scores are determined by adding each item within the scale, for a subscale score range of 5-25. In previous research, test-retest reliability over an average of 3.6-month periods was .80 (Bernstein & Fink, 1998). In the current study, and internal consistency coefficients for the five subscales were all above .70. Evidence for construct validity of the CTQ is satisfactory, with correlations between the CTQ and semi-structured interviews assessing CHT ranging from .50 to .75 and confirmatory factor analysis indicating structural invariance across three different samples (Bernstein & Fink, 1998).

Stop-Signal Anticipation Task (SSAT). While undergoing functional magnetic resonance imaging (fMRI), participants completed the Stop-Signal Anticipation Task (SSAT; Zandbelt & Vink, 2010) using Presentation software (Version 14). Response time was recorded using the California Computerized Assessment Package (CALCAP; Miller, 2011; Miller, Satz, &

Visscher, 1991). Prior to imaging, participants were trained on the task in English or Afrikaans, depending on their preference. Participants were told that GO and STOP trials were equally important, to encourage equal effort on all conditions.

During the SSAT (Figure 1), participants viewed a screen with three parallel horizontal lines. The middle line was colored and placed at 80% of the distance between the white top and bottom lines. During GO trials, a bar moved vertically, starting at the bottom line, and passing through the middle line at 800 ms. Participants were to stop the moving bar as close to the middle line as possible by pressing a button with their right index finger, with a perfect response time being 800 ms. If the participant was too slow, or failed to respond, the ascending bar would reach the top line in 1000 ms, resulting in a failed GO trial. On STOP trials, there were again three lines and an ascending bar. However, in STOP trials, the bar would halt before hitting the colored line, indicating to the participant that they were not to press the response button.

All participants started with a stop-signal delay (SSD) of 550 ms, meaning the bar stopped moving on STOP trials after 550 ms. For each trial, the SSD was adjusted based on the success or failure of the previous trial, to increase or decrease the difficulty of the task, respectively. If a previous STOP trial was successful, the SSD was increased by 25 ms, while unsuccessful STOP trials resulted in an SSD decrease of 25 ms. This staircase method created an approximately equal amount of successful and unsuccessful STOP trials between participants. The number of trials and length of experiment was equal amongst all participants, with only the SSD varying between participants.

To assess for proactive inhibition, the probability of the stop-signal was varied. Probability of the stop-signal was indicated to the participant based on the color of the middle

horizontal line. Probability level of the stop-signal included 0% (green), 17% (yellow), and 33% (red). Probability levels were presented in a pseudorandom order.

Trials were separated into baseline and experimental blocks, each block containing 12-15 trials. Baseline blocks included only GO trials with 0% stop-signal probability. Experimental blocks included all STOP trials and GO trials with a stop signal probability greater than 0%. Within experimental blocks, STOP trials were positioned among GO trial in a pseudorandom order. As well, GO trial probabilities were varied in a pseudorandom order within experimental blocks. Inter-trial interval was 1000 ms for all conditions. Each participant completed 414 GO trials (0%, $n = 234$; 17%, $n = 30$; 20%, $n = 48$, 25%, $n = 54$, 33%, $n = 48$) and 60 STOP trials (17%, $n = 6$; 20%, $n = 12$, 25%, $n = 18$, 33%, $n = 24$). Response time and accuracy were calculated separately for each trial condition.

The SSAT is a relatively new task and has yet to be explicitly examined for construct validity. However, the SST shows high test-retest reliability (Barch et al., 2009). As well, evidence for construct validity of the SST is derived from correlations with other behavioral measures of response inhibition and self-reported measures of inhibitory control (Logan, Schacher, & Tannock, 1997).

Imaging methods.

Image acquisition. Functional and anatomical magnetic resonance imaging (MRI) scans were acquired using a 3 Tesla Siemens Skyra MRI scanner. Acquisition parameters included: MPRAGE sequence, 2080 ms repetition time, 4.88 ms echo time, 230 mm field of view, 176 slices, 0.9 mm x 0.9 mm x 1 mm voxel size. The brain scans were inspected by a radiologist to ensure absence of intracranial pathology. Scans were also visually inspected for motion artifacts.

Preprocessing. I completed preprocessing according to methods previously used by the creators of the SSAT (Zandbelt & Vink, 2010) and my collaborators at Stellenbosch University (Du Plessis et al., 2015). These analyses were completed using Statistical Parameter Mapping (SPM8) software running in Matlab 9. Fourier interpolation was used to correct for differences in slice timing by resampling all slices relative in time to the middle slice. To correct for head motion, images were re-aligned to the mean image using fourth-degree B-spline interpolation. Motion parameters were analyzed to ensure motion did not exceed a cutoff threshold of 3mm scan-to-scan (van Dijk, Sabuncu, & Buckner, 2012). To remove low-frequency drifts, a 128 Hz high-pass filter was applied to functional data. Using the Montreal Neurological Institute brain template, the images underwent spatial smoothing with a 6 mm full-width at half-maximum Gaussian kernel in order to account for individual differences in brain anatomy.

Data Analysis

Demographic comparisons. I tested for differences between groups in gender and ethnicity using chi-square tests of independence. I tested for differences between group in age using independent samples *t*-tests.

Aim 1. Testing between-groups differences in CHT. I tested for differences between the schizophrenia group and the control group on history of CHT, as assessed by the CTQ. I used separate independent *t*-tests to compare CTQ total and subscale scores between the schizophrenia and control groups. Based on previous findings that increased CHT is only associated with schizophrenia if more than one subtype of trauma has been experienced, I also compared number of types of trauma experienced between groups.

Aim 2: Test between-groups difference in response inhibition using behavioral
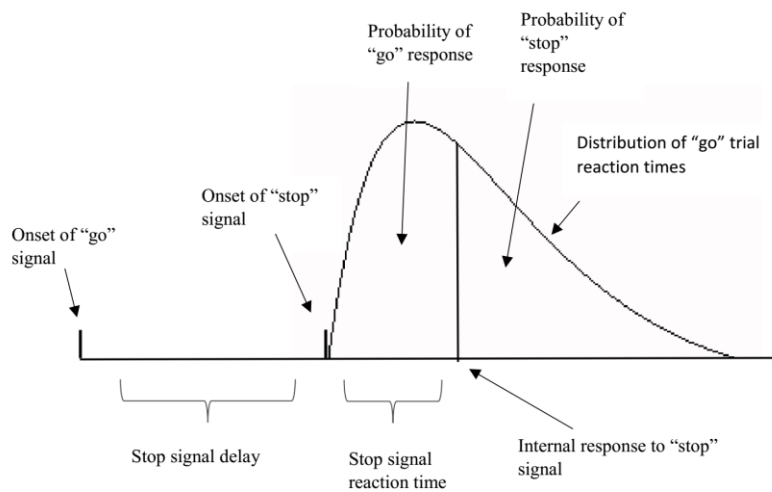
measures

I analyzed behavioral SSAT data were using custom software written for Matlab 7. Under the supervision of Dr. du Plessis, I made changes to the pre-existing SSAT script to accommodate idiosyncrasies of the current dataset, such as adjusting for the number of conditions and trials in the current SSAT task. General inhibition functions were calculated for each participant, representing the proportion of successful STOP trials for each stop signal delay (SSD), the latency between the "go" signal and the "stop" signal. Inhibition functions were combined across all probability conditions.

Motor execution. Motor execution was assessed using the reaction times of the GO trials with 0% probability of a stop-signal.

Reactive Inhibition. The stop-signal reaction time (SSRT) was used as the behavioral measure of reactive inhibition. The SSRT is an indication of how difficult the stop process is for a participant, with shorter SSRTs interpreted as representing more difficult stopping conditions. SSRT was calculated according to standard methods (Logan & Cowan, 1984; Verbruggen, Logan, & Stevens, 2008). These methods are based on the horse race model of response inhibition, in which a STOP signal engages a "stop" process that races against the prepotent "go" process to determine whether a response will be inhibited or completed (Figure 2; Logan & Cowan, 1984). In this model, the "go" process is triggered by an external indicator. In the case of the SSAT, this external indicator is the "go" signal, the bar starting from the bottom line on the screen and rising upwards. When this "go" signal starts, the "go" process is initiated, and the participant will perform the "go" task of pressing a response key when the rising bar reaches the middle line on the screen. In the case of "go" trials, there is no horse race; the participant

completes the baseline task uninterrupted. However, in "stop" trials, the bar stops moving before

hitting the middle line, thus engaging the "stop" process. When the "stop" process is engaged, it

is theorized that a race occurs between the "stop" and "go" processes. If the "go" process wins,

the participant presses the response key, resulting in a failed "stop" trial. If the "stop" process

wins, the participant successfully abstains from pressing the response key, resulting in a

successful "stop" trial. The later the "stop" signal occurs, the less time the "stop" process has to

engage, and the more difficult it is for the "stop" process to win the race. Thus, the shorter the

SSRTs (the time between the appearance of a "stop" signal and the winning of the race by the

"stop" process) on a successful "stop" trial, the greater the integrity of an individual's reactive

inhibition mechanisms. With increased SSD, the "stop" process starts later, and finishes later as

compared to the "go" process, which always starts at the same time across trials (i.e. when the

trial starts). With increased SSD, the probability that the "go" process will finish before the

"stop" process also increases. When the "go" process finishes before the "stop" process ("go"

reaction time < SSRT + SSD), the response action is not successfully inhibited, resulting in an

unsuccessful "stop" trial. When the "stop" process finishes before the "go" process ("go"

reaction time > SSRT + SSD), the response action is successfully inhibited and the "stop" trial is

successful.

Figure 2. Calculation of SSRT

Probability of
"go" response

Probability of
"stop"
response

Distribution of "go" trial
reaction times

Onset of "stop"
signal

Onset of "go"
signal

Stop signal delay

Stop signal
reaction time

Internal response to "stop"
signal

Unlike the reaction time of the "go" process, the reaction time of the "stop" process (SSRT) is difficult to measure directly. There is no overt behavioral measure on successful "stop" trials; the "stop" process could theoretically be finishing (i.e. winning the race against the "go" process) from just after the "stop" signal occurs to the time that there is a lack of a response when the bar hits the middle line. Due to the covert nature of the stopping process, the SSRT must be estimated using other task parameters.

Logan and Cowan (1984) developed one common means of calculating the SSRT using the SSD and "go" trial reaction time distribution. In this method, the SSRT is assumed to be a constant based on the observation that this assumption does not significantly affect results of the calculation (Band, van der Molen, & Logan, 2003). The probability of responding is assumed to be proportional to the amount of GO trial reaction times that are too fast to be inhibited as compared to STOP trial reaction times that are correctly inhibited (Hughes et al., 2012). The SSRT is calculated by subtracting the stop signal delay (SSD; the latency between the "go" signal and the "stop" signal) from the estimated "stop" process finish time. The finishing time of

the stop process is estimated by calculating the distribution of an individual's reaction times on all GO trials and identifying the point at which the integral of STOP trials is equal to the probability of responding for a given delay. Data were combined for all GO trials.

Proactive Inhibition. Proactive inhibition was determined by comparing the effect of STOP signal probability on GO signal reaction time, based on previous methods (Zandbelt & Vink, 2010). Higher effect of STOP signal probability on GO signal reaction time, indicating anticipation of the STOP signal, is considered more robust functioning of proactive inhibition processes (du Plessis et al., 2015).

To test for between-group differences on reactive inhibition, SSRTs were compared using an independent *t*-test. Differences between groups on proactive inhibition were calculated using a repeated-measures analysis of variance (ANOVA) on mean GO signal reaction time, with STOP signal probability and group as factors.

Aim 3: Test between-groups differences in response inhibition using neuroimaging measures.

SSAT fMRI data analysis. Imaging data analysis was completed according to methods previously used by the creators of the SSAT (Zandbelt & Vink, 2010) and my collaborators at Stellenbosch University (du Plessis et al., 2015). These analyses were completed with Statistical Parameter Mapping (SPM8) software running in Matlab 9. Data were modeled voxel-wise using general linear models (GLM). In the first step of analysis, events included as regressors included: GO trials with 0% probability of STOP trials, successful STOP trials, failed STOP signals, rest, and outlier trials, for each participant. I also included parametric regressors modelling variations in response time and STOP signal probability.

Regions of interest (ROIs) were chosen based on the results of a previous study using the SSAT in non-psychiatric healthy participants (Figures 3 and 4; Zandbelt & Vink, 2010), as well as additional literature on brain areas implicated in response inhibition (Verbruggen & Logan, 2008). The ROI for motor execution is comprised in the primary motor cortex. ROIs for reactive inhibition included: 1) left putamen; 2) right putamen; 3) left middle occipital gyrus; 4) right middle occipital gyrus; 5) left pre/postcentral gyrus; 6) right precuneus; and 7) right supramarginal gyrus. ROIs for proactive inhibition included; 1) right striatum; 2) right inferior frontal cortex, extending into the precentral gyrus; 3) left middle frontal gyrus; 4) left temporoparietal junction; 5) left superior parietal gyrus, extending into the angular gyrus; 6) right superior parietal gyrus, extending into the angular gyrus; 7) right temporoparietal junction; 8) left precuneus; 9) anterior cingulate gyrus, extending into the superior frontal gyrus; 10) right superior frontal gyrus; 11) left superior frontal gyrus; 12) left inferior frontal gyrus; and 13) right anterior insula. The ROIs were defined using a cluster-level threshold, with cluster-defining threshold alpha <.001, cluster probability of alpha <.05, and family-wise error correction for multiple comparisons.

Figure 3. Regions of Interest for Proactive Inhibition Processes

Figure adapted from Zandbelt, van Buuren, Kanh, & Vink, 2011. ROIs for proactive inhibition included 1) right striatum; 2) right inferior frontal cortex, extending into the precentral gyrus; 3) left middle frontal gyrus; 4) left temporoparietal junction; 5) left superior parietal gyrus, extending into the angular gyrus; 6) right superior parietal gyrus, extending into the angular gyrus; 7) right temporoparietal junction; 8) left precuneus; 9) anterior cingulate gyrus, extending into the superior frontal gyrus; 10) right superior frontal gyrus; 11) left superior frontal gyrus; 12) left inferior frontal gyrus; and 13) right anterior insula.
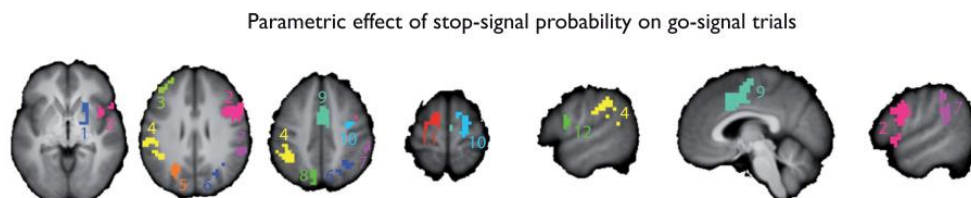
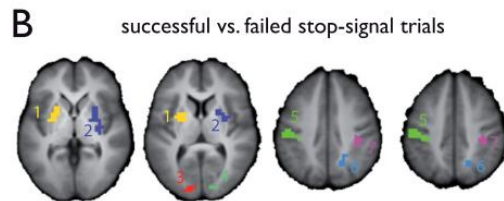Figure 4. Regions of Interest for Reactive Inhibition Processes

Figure adapted from Zandbelt, van Buuren, Kanh, & Vink, 2011. ROIs for reactive inhibition included 1) left putamen, 2) right putamen, 3) left middle occipital gyrus, 4) right middle occipital gyrus, 5) left pre/postcentral gyrus, 6) right precuneus, and 7) right supramarginal gyrus.

For reactive and proactive inhibition, the ROIs were combined into a total BOLD score representing the areas of the brain that are believed to be recruited during the SSAT task (Zandbelt & Vink, 2010). The ROIs were also analyzed separately using independent samples t-tests. Combining ROIs in this manner makes it more likely to detect difference in activation in the network of neural regions associated with reactive and proactive inhibition. This technique has been used as an approximate measure for brain networks in previous fMRI studies (Downing, Wiggett, & Peelen, 2007; Fesl et al., 2010; Hou & Lui, 2012). The fMRI techniques used in the current study do not allow for enough temporal resolution to determine whether brain areas are being recruited for reactive or proactive inhibitory processes at a given time point. In the current design, brain images were acquired every 2080 ms, while the response inhibition task lasted 800 ms or less. As well, portions of reactive and proactive inhibition processes may happen simultaneously (Zandbelt & Vink, 2010). ROIs were combined in this manner because there is likely overlap in the areas of the brain recruited during reactive inhibition and proactive inhibition, though maybe at slightly different times, but it is not possible to detect these small timing differences with the current methods.

Three BOLD contrast images were created for each participant, representing average

neuronal activity during motor execution, reactive inhibition, and proactive inhibition. The contrasts included: 1) activation during baseline GO trials compared to rest (activation during motor response initiation); 2) activation during successful STOP trials compared against unsuccessful STOP trials (activation during reactive inhibition); 3) effect of STOP probability on GO signal activation compared to rest (activation during proactive inhibition).

Aim 4: Behavioral indices of response inhibition as a mediator between degree of CHT and positive symptoms. With the current study design, it was not possible to test for a causal role of response inhibition in the development of schizophrenia. However, it was possible to rule out a role of response inhibition in the association between CHT and schizophrenia. I planned to test proactive inhibition score as a mediator between total CTQ score and PANSS positive symptom subscale score in the schizophrenia group. I proposed to use three steps to test this mediation model (Baron & Kenny, 1986):

1) (Bivariate regression analysis) I regressed PANSS positive symptom subscale score on CTQ total score to ensure that severity of CHT is a significant predictor of schizophrenia symptoms.

2) (Bivariate regression analysis) If the first step was significant, I had planned to regress the behavioral proactive inhibition score on the CTQ total score to ensure that CHT was a significant predictor of response inhibition performance.

3) (Multiple regression analysis) If the first step was significant, I had planned to regress PANSS positive symptom subscale score on the proactive inhibition score and CTQ total score, to ensure that proactive inhibition was a significant predictor of schizophrenia symptoms, while removing shared variance with CHT severity. If there

was a full mediation of proactive inhibition on the relationship between CHT severity

and schizophrenia symptoms, I would have found that the significant relationship

between CTQ score and PANSS positive symptom subscale score was eliminated

when I covaried for proactive inhibition. If proactive inhibition partially mediated

CHT severity and schizophrenia symptoms, I would have found the significant

relationship between CTQ score and PANSS positive symptom subscale score was

reduced, but not eliminated, when I covaried for proactive inhibition.

If all steps of the mediation model were successful, I would have concluded that

proactive inhibition mediates the association between CHT and schizophrenia symptoms. If any

step of the process was not successful, I would not be able to conclude a mediating relationship.

Aim 5: Neuroimaging measure of proactive inhibition as a mediator between degree

of CHT and positive symptoms. I planned to complete one addition mediation model to test for

mediation of the association between CHT and positive symptoms by response inhibition neural

activity. For each mediation model, I had planned to use the same mediation test procedure as

outlined with the proactive inhibition behavioral data, using the combined ROI score for

proactive inhibition.

Power analysis. Power analysis was not completed prior to analysis of data as

calculation of statistical power in fMRI studies is complex, mainly due to the intricate modelling

of fMRI analysis (Desmond & Glover, 2002). Calculation of power previous to an fMRI study is

not as common as it is less complex study designs (Mumford, 2012) with power analyses in

fMRI considered too complex for a non-statistician until this past decade (Mumford & Nichols,

2008). Due to recent software advances, analysis of fMRI study power can now be carried out

through the use of semi-automated toolboxes; however, all currently available toolboxes require pilot data (Mumford, 2012), which was not available at the time of designing study analyses.

<div align="center">

Results

</div>

Data for 68 total participants were preprocessed. I excluded one control participant listwise due to a mean stop signal reaction time more than three standard deviations above the group mean. One schizophrenia participant did not complete the CTQ.

Aim 1: Between-Groups Comparison of Childhood Trauma

In order to test for differences between the schizophrenia group and the control group on history of CHT, separate independent t-tests were used to compare CTQ total and subscale scores between groups. Scores on the CTQ total and all subscales did not differ significantly between schizophrenia participants and controls (Table 2).

To better understand this overall lack of group difference, additional independent t-tests were used to compare CTQ scores in females with schizophrenia against female control subjects and males with schizophrenia against male controls. Females differed significantly between groups on one subscale, Physical Abuse, with female controls experiencing higher levels of physical abuse (Table 3). Males with schizophrenia scored significantly higher on the Emotional Neglect subscale and showed higher scores on the Physical Neglect subscale at a trend level of significance (Table 4). Males with schizophrenia also scored significantly higher on overall Neglect total.

Differences in CTQ scores were also compared between genders within the two groups. There were no significant gender differences in the schizophrenia group (Table 5). In the control group, females scored significantly higher on CTQ total, Neglect total, and the Emotional

Neglect subscale (Table 6). Females had trend-level higher scores on Abuse total and the Sexual Abuse subscale.

Separate independent *t*-tests were used to compare groups on the number of types of traumas experienced in childhood. Number of types of trauma did not differ significantly between groups (schizophrenia participants $M = 1.697$, $SD = .951$, control participants $M = 1.636$, $SD = 1.194$; $t(64) = .228$, $p = .820$).

Table 2. Childhood Trauma Questionnaire Scores in Schizophrenia and Control Participants

	Schizophrenia Mean (SD)	Control Mean (SD)	N (SZ, control)	*t*	*df*	*p*
CTQ Total	44.33 (12.14)	44.06 (14.27)	33/33	0.084	64	.934
CTQ Abuse Total	25.97 (7.80)	27.42 (10.18)	33/33	-0.651	64	.517
CTQ Neglect Total	18.36 (6.28)	16.64 (5.65)	33/33	1.175	64	.244
CTQ Emotional Abuse	12.00 (3.61)	12.15(3.50)	33/33	-0.173	64	.863
CTQ Physical Abuse	7.61 (4.47)	8.42 (4.27)	33/33	-.0760	64	.450
CTQ Sexual Abuse	6.36 (3.44)	6.85 (4.96)	33/33	-0.461	64	.646
CTQ Emotional Neglect	9.33 (4.75)	8.42 (4.35)	33/33	-0.810	64	.421
CTQ Physical Neglect	9.03 (2.39)	8.21 (2.46)	33/33	1.370	64	.175

Table 3. Group differences in Childhood Trauma in Females

	Schizophrenia Mean (SD)	Control Mean (SD)	*t*	*df*	*p*
CTQ Total	43.33 (14.68)	48.83 (16.50)	-0.845	25	.406
CTQ Abuse Total	26.22 (7.05)	30.33 (12.30)	-0.935	25	.364

CTQ Neglect Total	17.11 (9.05)	18.50 (6.08)	-0.475	25	.639
CTQ Emotional Abuse	12.11 (3.86)	12.67 (3.34)	-0.387	25	.702
CTQ Physical Abuse	6.00 (2.34)	9.39 (5.19)	-2.334	25	.028*
CTQ Sexual Abuse	8.11 (3.48)	8.27 (6.43)	-0.72	25	.943
CTQ Emotional Neglect	7.89 (5.42)	9.72 (5.20)	-0.852	25	.402
CTQ Physical Neglect	9.22 (4.06)	8.78 (2.39)	0.360	25	.722

Table 4. Group differences in Childhood Trauma in Males

	Schizophrenia Mean (SD)	Control Mean (SD)	t	df	p
CTQ Total	44.71 (11.39)	38.33 (8.40)	1.870	37	.069
CTQ Abuse Total	25.88 (8.21)	23.93 (5.44)	0.809	37	.423
CTQ Neglect Total	18.83 (5.05)	14.40 (4.26)	2.825	37	.008*
CTQ Emotional Abuse	11.96 (3.59)	11.53 (3.68)	0.356	37	.724
CTQ Physical Abuse	8.21 (4.95)	7.27 (2.52)	0.681	37	.500
CTQ Sexual Abuse	5.71 (3.26)	5.13 (0.52)	0.674	37	.505
CTQ Emotional Neglect	9.88 (4.49)	6.87 (2.39)	2.726	37	.010*
CTQ Physical Neglect	8.96 (1.49)	7.53 (2.45)	2.034	37	.055

Table 5. Gender Differences in Childhood Trauma in Schizophrenia Participants

	Female Mean (SD)	Male Mean (SD)	Percentage of any affirmative response (F/M)	t	df	p
CTQ Total	43.33 (14.68)	44.71 (11.39)	100/100	-0.285	31	.777
CTQ Abuse Total	26.22 (7.05)	25.88 (8.21)	100/100	0.112	31	.911

	Female Mean (SD)	Male Mean (SD)	Percentage of any affirmative response (F/M)	t	df	p
CTQ Neglect Total	17.11 (9.05)	18.83 (5.05)	78/100	-0.696	31	.492
CTQ Emotional Abuse	12.11 (3.86)	11.96 (3.59)	100/100	0.107	31	.916
CTQ Physical Abuse	6.00 (2.34)	8.21 (4.95)	22/58	-1.276	31	.212
CTQ Sexual Abuse	8.11 (3.48)	5.71 (3.26)	56/8	1.851	31	.074
CTQ Emotional Neglect	7.89 (5.42)	9.88 (4.49)	33/88	-1.071	31	.292
CTQ Physical Neglect	9.22 (4.06)	8.96 (1.49)	78/92	0.278	31	.783

Table 6. Gender Differences in Childhood Trauma in Control Participants

	Female Mean (SD)	Male Mean (SD)	Percentage of any affirmative response (F/M)	t	df	p
CTQ Total	48.83 (16.50)	38.33 (8.40)	100/100	2.358	31	.026*
CTQ Abuse Total	30.33 (12.30)	23.93 (5.44)	100/100	1.988	31	.058
CTQ Neglect Total	18.50 (6.08)	14.40 (4.26)	95/73	2.199	31	.036*
CTQ Emotional Abuse	12.67 (3.34)	11.53 (3.68)	100/100	0.926	31	.361
CTQ Physical Abuse	9.39 (5.19)	7.27 (2.52)	67/60	1.531	31	.138
CTQ Sexual Abuse	8.27 (6.43)	5.13 (0.52)	56/67	2.066	31	.054
CTQ Emotional Neglect	9.72 (5.20)	6.87 (2.39)	78/53	2.082	31	.048*
CTQ Physical Neglect	8.78 (2.39)	7.53 (2.45)	83/60	1.474	31	.151

Aim 2: Between-Groups Comparison of Behavioral Measures of Response Inhibition

Motor execution. Response times did not differ significantly between groups on correctly performed GO trials (stop-signal probability of 0%) with both groups performing close

to the target response time of 800 ms (schizophrenia participants $M = 795$ ms, $SD = 37$ ms,

control participants $M = 793$ ms, $SD = 41$ ms; $t(65) = 0.153$; $p = 0.879$). Number of correct

responses on GO trials also did not differ between groups (schizophrenia participants $M = 78.68$,

$SD = 9.60$, control participants $M = 81.12$, $SD = 2.61$; $t(65) = -1.413$; $p = 0.162$). These results

indicate that participants in both groups were able to accurately perform the baseline task.

Reactive inhibition. Reactive inhibition speed (SSRT) did not differ significantly

between groups (schizophrenia participants $M = 300$ ms, $SD = 30$ ms, control participants $M =$

293 ms, $SD = 22$ ms; $t(65) = 1.126$; $p = 0.264$). Mean stop signal delay (SSD) also did not vary

between groups (schizophrenia participants $M = 296$ ms, $SD = 42$ ms, control participants $M =$

286 ms, $SD = 43$ ms; $t(65) = .972$; $p = 0.335$), another indication of similar reactive inhibition

processes between groups. Covarying for gender did not yield significant differences between

groups for either SSRT or SSD.

Proactive inhibition. Proactive inhibition is the effect of stop-signal probability on the

stop signal reaction time. If proactive inhibition processes are intact, reaction time is expected to

lengthen with increased stop signal probability. Difference in proactive inhibition between

groups was examined using a two-way repeated measures ANOVA on stop signal reaction time

with group and stop signal probability as factors. Proactive inhibition differed significantly

between groups (Figure 5; $F(2, 67) = 6.817$; $p = 0.002$). The schizophrenia group showed less

increased reaction time as a function of increased stop signal probability, as compared to

controls, indicating less proactive inhibition. Adding gender as a covariate did not change the

significance of the results.

Figure 5. Behavioral Measure of Proactive Control in Schizophrenia and Control Participants
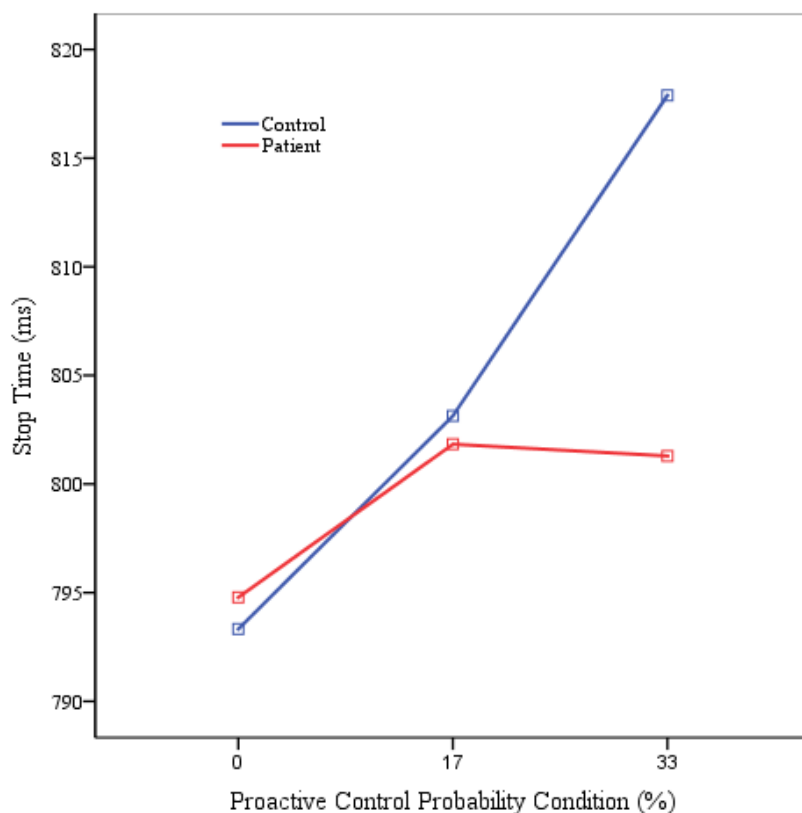
Aim 3: Between-Groups Comparisons of Neuroimaging Measures of Response Inhibition

Motor execution. One-way ANCOVA was performed to determine if there were group difference in motor cortex ROI activation during the baseline motor execution task, GO trials with a 0% probability of a STOP signal, as compared to the rest. Gender was included as a covariate. There was no significant difference between groups in motor cortex activation during the baseline motor task ($F(1, 57) = 0.094$, $p = 0.760$).

Reactive inhibition. One-way ANCOVA was performed to determine group differences in combined ROI activation during reactive inhibition, including gender as a covariate. ROIs included in the combined ROI for reactive inhibition were: 1) left putamen; 2) right putamen; 3) left middle occipital gyrus; 4) right middle occipital gyrus; 5) left pre/postcentral gyrus; 6) right

precuneus; and 7) right supramarginal gyrus. There was no significant difference between groups in reactive inhibition activation (Figure 6; $F(1, 58) = 0.266$, $p = 0.608$). Analyses of separate reactive inhibition ROI also yielded no significant differences between groups (Table 7).

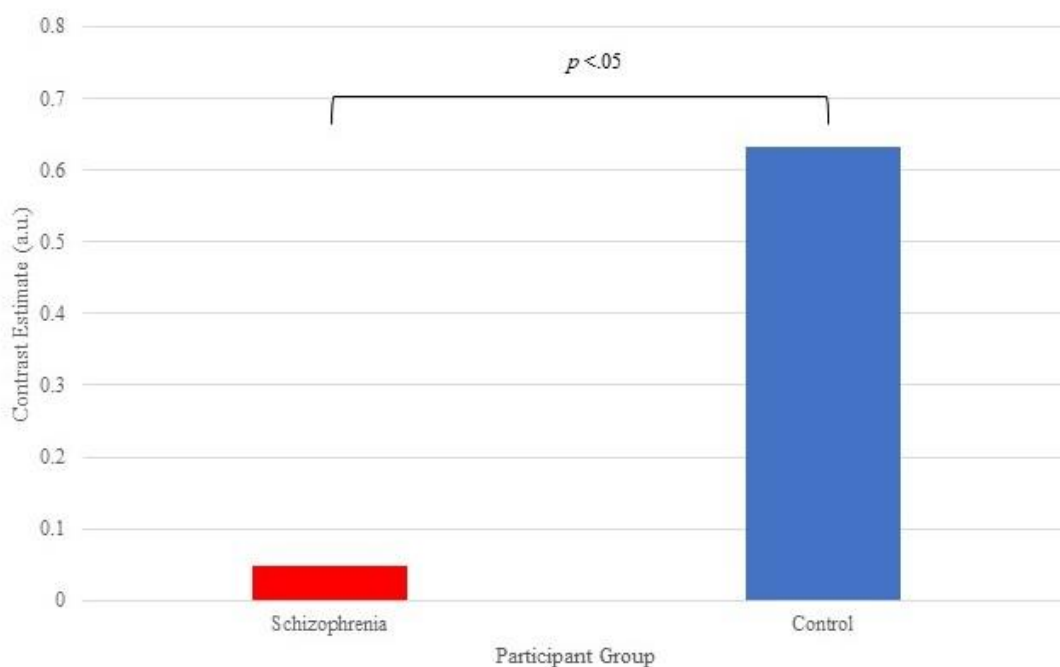Figure 6. Group Comparison of Combined Reactive Inhibition ROIs

Table 7. Group Comparison of Separate Reactive Inhibition ROIs

	Schizophrenia Mean (SD)	Control Mean (SD)	N (SZ, control)	t	df	p
Left Putamen	0.39 (0.66)	0.56 (0.66)	33/32	-0.965	60	.780
Right Putamen	0.30 (0.62)	0.26 (0.60)	32/30	0.281	63	.338
Left Middle Occipital Gyrus	0.31 (1.34)	0.11 (1.06)	32/30	0.629	60	.532
Right Middle Occipital Gyrus	0.35 (1.09)	0.27 (1.07)	32/32	0.265	62	.792
Left Pre/Postcentral Gyrus	0.07 (.89)	0.46 (0.80)	33/32	0.634	63	.529
Right Precuneus	0.04 (.061)	0.19 (0.65)	33/32	-0.938	63	.352

Right Supramarginal Gyrus	0.19 (0.67)	0.21 (0.83)	33/33	-0.138	64	.891

Proactive inhibition. One-way ANCOVA was performed to determine group differences in combined ROI activation during proactive inhibition, including gender as a covariate. ROIs included in the combined ROI for proactive inhibition were: 1) right striatum; 2) right inferior frontal cortex, extending into the precentral gyrus; 3) left middle frontal gyrus; 4) left temporoparietal junction; 5) left superior parietal gyrus, extending into the angular gyrus; 6) right superior parietal gyrus, extending into the angular gyrus; 7) right temporoparietal junction; 8) left precuneus; 9) anterior cingulate gyrus, extending into the superior frontal gyrus; 10) right superior frontal gyrus; 11) left superior frontal gyrus; 12) left inferior frontal gyrus; and 13) right anterior insula. Groups differed significantly in proactive inhibition activation (Figure 7; $F(1, 57) = 4.615$, $p = 0.036$). Analyses of each separate ROI did not reveal any significant differences between groups (Table 8).

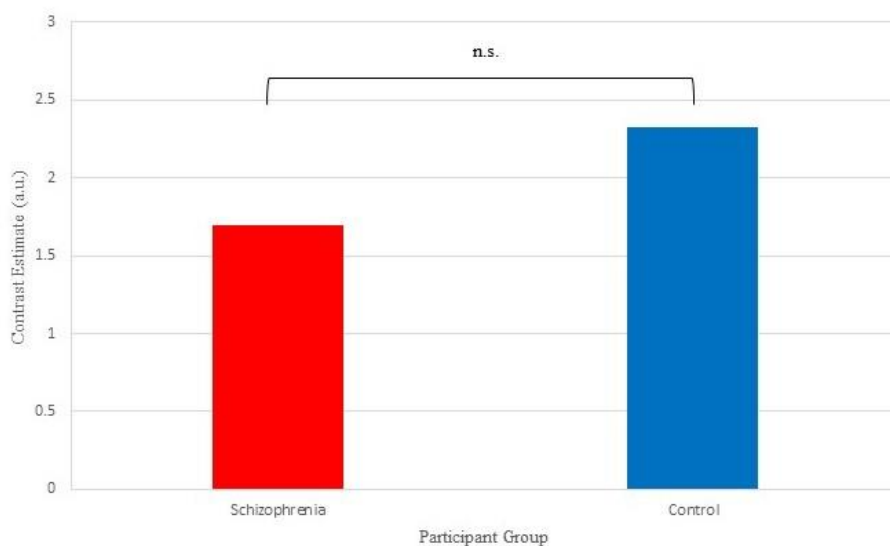Figure 7. Group Comparison of Combined Proactive Inhibition ROIs

Table 8. Group Comparison of Separate Proactive Inhibition ROIs

	Schizophrenia Mean (SD)	Control Mean (SD)	N (SZ, control)	t	df	p
Right Striatum	0.05 (1.17)	0.12 (0.76)	32/30	-0.261	60	.795
Right Inferior Frontal Cortex	0.20 (1.75)	0.55 (1.35)	34/33	-0.900	65	.371
Left Middle Frontal Gyrus	-0.20 (1.68)	0.35 (1.83)	32/32	-1.275	62	.207
Left Temporoparietal Junction	0.20 (1.28)	0.38 (1.37)	33/32	-0.544	63	.589
Left superior Parietal Gyrus	0.25 (1.06)	0.17 (1.13)	33/32	0.325	63	.746
Right Superior Parietal Gyrus	0.46 (1.79)	0.74 (1.52)	33/32	-.689	63	.493
Right Temporoparietal Junction	0.27 (2.03)	1.09 (1.81)	34/32	-1.722	64	.090
Left	0.12 (2.57)	0.43 (1.87)	33/31	.358	62	.587

Precuneus						
Anterior Cingulate Gyrus	0.12 (1.29)	0.12 (1.00)	34/33	-.002	65	.998
Right Superior Frontal Gyrus	-1.05 (1.29)	0.43 (1.38)	33/33	.998	64	.108
Left Superior Frontal Gyrus	-0.06 (1.23)	0.16 (1.36)	33/31	-.719	62	.475
Left Inferior Frontal Cortex	0.12 (1.18)	0.39 (1.53)	33/31	-1.129	62	.263
Right Anterior Insula	0.23 (1.66)	0.30 (1.31)	33/32	-.190	63	.850

Aim 4: Behavioral Measure of Proactive Inhibition as Mediators Between Childhood Trauma and Schizophrenia Symptoms

Bivariate regression analysis was used to test the first assumption of the mediation model, that CTQ total score is a significant predictor of positive symptoms in the schizophrenia group, as measured by the PANSS positive symptom subscale. Results indicated that CTQ total is not a significant predictor of PANSS positive symptoms ($\beta = .107$, $t(33) = .599$, $p = .554$). As a significant association between CTQ and PANSS positive symptoms is required for the mediation model (Baron & Kenny, 1986), it was not possible to test the rest of the mediation model.

Aim 5: Neuroimaging Measure of Proactive Inhibition as Mediator Between Childhood Trauma and Schizophrenia Symptoms

As CTQ total was not a significant predictor of PANSS positive symptoms, it was not possible to test further mediation models.

Discussion

In the current study, I examined childhood trauma (CHT) and response inhibition in South African individuals with schizophrenia. The main aim of this study was to test response inhibition as a partial mediator in the association between CHT and positive symptoms in schizophrenia. In addition, I expected to replicate past findings of higher incidence of CHT in people with schizophrenia and past findings of impaired inhibitory control in people with schizophrenia.

Aim 1: Between-Groups Comparison of Childhood Trauma

In Aim 1, I hypothesized that I would find higher levels of CHT in the schizophrenia sample, as has been frequently found in people with schizophrenia (Anda, Tietjen, Schulman, Felitti, & Croft, 2010; MacMillan, 1998; Merrick & Brown, 1999; Mulvihill, 2005). Contrary to expectations, I did not find higher rates of childhood trauma, nor more types of trauma, in the schizophrenia participants as compared to controls.

The lack of differences in rates of CHT and numbers of different types of trauma is in contrast to most previous research finding higher levels of CHT (Bonoldi et al., 2013; Gibson, Alloy, & Ellman, 2016; Kessler et al., 2010) and more types of trauma (Read, Agar, Argule, & Aderhold, 2003; Read, Os, Morrison, & Ross, 2005; Whitfield, Dube, Felitti, & Anda, 2005) in people with schizophrenia. One previous study has examined CHT rates in South African samples of people with schizophrenia, finding no group differences (Kilian et al., 2017). However, this paper analyzed a larger subset of the same broader sample as the current study; thus, it would be expected to find similar results. One additional study examined a history of traumatic experiences in young adults with schizophrenia in South Africa, finding significantly

higher positive symptoms in people with a history of sexual assault or history of witnessing a violent act (Burns, Jhazbhay, Esterhuizen, & Emsley, 2011). This study assessed for lifetime traumatic events, rather than only childhood trauma, though average age of participants was young ($M = 25.8$, $SD = 8.1$).

The lack of group differences in my sample may be due in part to overall high rates of adverse childhood experiences in South Africa as compared to Western countries, leading to a restriction of range of CTQ scores, and less detectible differences between groups. For all age groups combined, South Africa has the highest rate of rape for any country not at war (Wood & Jewkes, 1997) with approximately 40% of reported rapes involving victims under the age of 18 (Jewkes et al., 2009). South Africans also experience a high rate of violence, on average. The rate of mortality due to violent crime in South Africa is over 2.5 times the global average (Doolan, Ehrlick, & Myer, 2007).

In a meta-analysis of CHT in 41 countries across the world, most studies reported rates of 10 to 20% in females and less than 10% in males (Pereda et al., 2009). In a large ($N = 2,782$) rural community sample of young South Africans ages 15-26, both male and female respondents reported high levels of all abuse and neglect categories on a culturally adapted version of the CTQ (Jewkes et al., 2010). Rates of abuse subcategories for female and male participants included: emotional abuse, 54.7% and 56.4%; physical abuse, 89.3% and 94.4%; sexual abuse, 39.1% and 16.7%; emotional neglect, 41.6% and 39.6%; and physical neglect, 65.8% and 46.8%. In the control sample of the current study, rates of abuse and neglect were higher than these rates in all subcategories for both genders, with the exception of physical abuse. This indicates that my control sample may have had particularly high rates of childhood abuse and neglect, even for a

South African sample.

Higher levels of trauma at a young age in people with schizophrenia may have been more apparent in the research of Burns and colleagues (2011) for several reasons. First, Burns et al. (2011) had more participants as compared to this study, affording them greater statistical power. Second, the sample they used was from the eastern region of South Arica (KwaZulu-Natal), which has overall lower rates of violence as compared to the broader Cape Town area from which my sample was collected (Burton et al., 2004). This may have allowed for more variation in their sample. Third, Burns et al. (2011) used a different measure of assessing for CHT, which included questions about the participant witnessing violence and experiencing racism and discrimination, potentially impactful categories that are not included in the CTQ. In particular, the experience of discrimination has been linked to negative mental health outcomes, included psychosis (Read et al., 2005; Ucok & Bikmaz, 2007). Finally, the schizophrenia sample in Burns et al. (2011) included only psychiatric inpatients tested within 24 hours of admission, who had presumable higher levels of psychiatric symptoms at the time of testing as compared the outpatients in the current study's schizophrenia sample, though PANSS scores were not reported. As PANSS scores reflect current, and not lifetime, symptoms of schizophrenia, associations between CHT and PANSS scores may be more apparent in the acute phases of schizophrenia.

Psychological resilience is another factor that could influence the association between CHT and schizophrenia. Psychological resilience is the ability to endure and even thrive during life challenges (Fletcher & Sarkar, 2013). Possession of resilience factors can mitigate the negative long-term consequences of CHT (Thompson, Arnkof, & Glass, 2011). One prominent resiliency factor is religiosity (Kim & Esquivel, 2011) or spirituality (Peres, Moreiera-Almeida,

Nasello, & Koenig. The South African population has high levels of spirituality and religiosity on average, as compared to many Western samples (Rule, 2007). A belief in higher powers and the ability to create a meaningful narrative surrounding negative life events may play a role in mitigating long-term negative effects of CHT, including increased susceptibility to schizophrenia. It may be the case that resilience factors, such as spirituality and religiosity, that are prominent in South Africa may decrease the effect of CHT on the development of schizophrenia.

CHT and gender between and within groups. To better understand the lack of group differences in CHT, I examined gender differences between and within groups.

The finding of higher rates of physical abuse in control females as compared to schizophrenia females is in contrast to past findings in Western samples (Fisher et al., 2010; Fisher et al., 2014; Read et al., 2005). This may be due to the overall high level of CHT in the control sample, particularly in female controls. The finding that males in the schizophrenia group had higher levels of emotional and physical neglect as compared with controls is consistent with past research (McCabe, Maloney, Stain, Loughland, & Carr, 2012; Vogel et al., 2011). Childhood neglect has been specifically linked to negative symptoms (Vogel et al., 2011; Cicero & Kerns, 2010) and disorganization symptoms (Cancel et al., 2015), though I did not find this association in the current study.

The finding of no difference in CHT subcategories between females and males with schizophrenia is in contrast to most previous research findings showing higher levels of at least sexual abuse in females with schizophrenia (Bonoldi et al., 2013; Yildirim et al., 2014). Past research has suggested that childhood abuse may be more highly associated with an increased

risk of schizophrenia in females as compared to males (Bebbington et al., 2011; Gayer-Anderson et al., 2015; Fisher et al., 2009; Kelly et al., 2016). In particular, within people experiencing schizophrenia, females with a history of abuse have higher levels of positive symptoms as compared to males (Misiak et al., 2016; Thompson et al., 2010). The low number of females in the schizophrenia sample in the current study makes it difficult to interpret a lack of difference in reported CHT between males and females in the schizophrenia group.

Higher levels of CHT in females as compared to males in the control sample is consistent with previous research throughout diverse regions of the world (Choquet, Darves-Bornoz, Ledoux, Manfredi, & Hassler, 1997; Harrison, Fulkerson, & Beebe (year); Molnar, Buka, & Kessler, 2001). However, it is notable that in South African samples it is not always the case that females report higher levels of sexual abuse, as one study from the Northern Province indicated no significant gender differences in rates of childhood sexual abuse (Madu & Peltzer, 2001). It may be the case that female children are more protected from childhood sexual abuse than males in some specific cultures (Li et al., 2015) and that males may be less likely to report sexual abuse (Dhaliwal, Gauzas, Anotonowicz, & Ross, 1996).

Aim 2: Between-Groups Comparison of Behavioral Measure of Response Inhibition

I predicted that the schizophrenia group would perform worse than controls on the behavioral measures of proactive inhibition of the SSAT, but not the reactive inhibition measure. Consistent with my predictions, the schizophrenia group showed significantly reduced proactive inhibition as compared to the control group. In addition, this is the first study to replicate findings of reduced proactive inhibition in people with schizophrenia in a sub-Saharan African sample.

My findings are congruent with findings from other studies separately examining reactive and proactive inhibition in people with schizophrenia (Lesh et al., 2013; Zandbelt et al., 2011). Dissociation between reactive and proactive inhibition processes in schizophrenia, as demonstrated in the current study, may explain previous mixed findings of response inhibition deficit in schizophrenia. Most studies of response inhibition in schizophrenia have used tasks that recruit both reactive and proactive inhibitory processes (van Belle, Vink, Durston, & Zandbelt 2014). The results of these studies have been mixed, with some reporting reduced response inhibition in schizophrenia (Kaladjian, Jeanningros, Azorin, Anton, & Mazzola-Pomietto, 2011; Raemaekers et al., 2002), and others finding no difference compared to controls (Badcock, Michie, Johnson, & Crombrinck, 2002; Bellgrove et al., 2005; Rubia et al., 2001). Studies using tasks that rely heavily on proactive inhibition have consistently found people with schizophrenia to be impaired as compared to controls (Edwards et al., 2010; Mayer et al., 2016).

To further ensure that my results were comparable to past results, I compared the average SSRTs with other studies. In this study, the SSRTs of participants were as follows: schizophrenia participants $M = 300$ ms, $SD = 30$ ms, control participants $M = 292$ ms, $SD = 21$ ms. While previous studies using the SSAT in schizophrenia did not reported exact mean SSRTs (Vink et al., 2014; Zandbelt, van Buuren, Kahn, & Vink, 2011), figures provided in these studies indicate that the SSRTs in the current study are comparable to previous similar studies. Vink et al. (2014) indicated a range of mean SSRTs from 300 ms to 380 ms for individuals in their sample, based on graphs. Van Buuren et al. (2011) indicated that the majority of their participants had mean SSRTs from 300 ms to 350 ms.

Aim 3: Between-Groups Comparisons of Neuroimaging Measure of Response Inhibition

I predicted that the schizophrenia group would show reduced brain activation in areas of the brain associated with proactive inhibition, as compared to controls. I expected that brain activation associated with reactive inhibition would not differ between the schizophrenia and control groups. Consistent with these predictions, I found reduced neuronal activation in combined proactive inhibition ROIs as compared to controls and no group differences in combined reactive inhibition ROIs. In contrast to my expectations, however, I did not find group differences in individual proactive inhibition ROIs.

The finding of overall reduced activation in the schizophrenia group in all proactive inhibition ROIs combined is consistent with previous research (Lesh et al., 2013; Zandbelt et al., 2011). However, the lack of group difference in individual proactive inhibition ROIs is in contrast to previous work (Zandbelt et al., 2011). The results partially replicate previous findings of decreased activation in regions of the brain associated with proactive inhibition in people with schizophrenia.

The lack of group differences in individual ROIs compared to previous research may be in part due to variation in ROIs identified as being associated with proactive inhibition, as the neural underpinnings of proactive inhibition are not yet agreed upon. Proactive inhibition has been most consistently associated with the striatum and inferior frontal cortex (Jahfari, Stinear, Claffey, Verbruggen, & Aron, 2010; Vink et al., 2005; Zandbelt & Vink, 2010). However, there is not a complete consensus on additional brain areas involved in proactive inhibition, with some studies also reporting recruitment of the temporoparietal junction, superior parietal lobe, premotor cortex, and putamen (van Belle, Vink, Durston, & Zandbelt, 2014; Zandbelt et al., 2011), and sensorimotor cortex (Mayer et al., 2016). As well, the striatum and inferior frontal

cortex are complex structures and previous research is not consistent on which exact brain coordinates within these structures serve as the best ROIs for proactive inhibition (Zandbelt, Bloemendaal, Neggers, Kah, & Vink, 2013). It is difficult to completely dissociate proactive inhibition processes from reactive inhibition as these processes use overlapping neural networks and likely take place during overlapping time periods (Cullinera, Fuentemilla, Brignani, Cucurell, & Miniussi, 2014). Finally, while reactive inhibition tasks such as the SSAT do primarily require inhibitory processes, they necessarily also recruit other cognitive processes, such as error detection (Zandbelt et al., 2013), working memory (Braver, 2012), and attention (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010).

Similar to the behavioral task findings, the combined proactive inhibition ROI results provide some evidence of a specific deficit in proactive inhibition in people with schizophrenia. These findings support the role of impairment in the frontostriatal pathways in the pathogenesis of schizophrenia (Robbins, 1990). Abnormal dopaminergic and glutaminergic transmission in frontostriatal pathways may also underlie other observed cognitive dysfunctions in schizophrenia, such as reward processing (Moghaddam & Javitt, 2012; Radua et al., 2015; Strauss, Waltz, & Gold, 2014) and psychological symptoms of schizophrenia, particularly disorganization (Lin et al., 2017). Importantly, dysfunction in frontostriatal pathways may serve as an early marker for the development of schizophrenia (Bellgrove et al., 2006; Morey et al., 2005). However, as the individual proactive inhibition ROIs did not differ between groups, the overall fMRI findings of this dissertation were should be interpreted with caution.

Aims 4 and 5: Behavioral and Neuroimaging Measures of Proactive Inhibition as Mediators Between Childhood Trauma and Schizophrenia Symptoms

In Aims 4 and 5, I predicted that the behavioral and neuroimaging measures of proactive inhibition would mediate the relationship between severity of CHT and positive symptoms in the schizophrenia sample. I was not able to test the mediation model due to a lack of association between CHT and positive symptoms of schizophrenia.

The lack of association between CHT and positive symptoms is in contrast to several previous studies (Alemany et al., 2014; Ucok & Bikmaz, 2007; Wang et al., 2013). In particular, these results are contrary to previous research findings that South African young adults with schizophrenia scored an average of five points higher on the PANSS positive symptom scale if they had a history of sexual assault or witnessing a violent event (Burns, Jhazbhay, Esterhuizen, & Emsley, 2011). One possible explanation for this lack of association is the low number of females in the schizophrenia group. If the link between CHT and schizophrenia is particularly strong in females, as discussed above, the low number of females in this sample may have weakened the overall association between CHT and positive symptoms.

Limitations and future directions

Sample size. One major limitation of the current study was a small sample size, making it difficult to discern whether statistically insignificant findings are due to low statistical power or a true lack of association between variables or difference between groups. In particular, the low number of females in the schizophrenia group caused statistically significant imbalance in gender between the control and schizophrenia groups.

Notably, the current sample size of 33 and 34 in each group is generally considered acceptable for fMRI studies. Previous work using statistical methods and ROIs similar to the current project have reported sample sizes of 17 and 18 in patient and control groups,

respectively (du Plessis et al., 2015), and 24 subjects in both patient and control groups (Zandbelt et al., 2011). FMRI data is expensive to collect, contributing in part to a convention of allowing lower sample sizes in fMRI studies. Many experts acknowledge low sample sizes as a non-ideal but practical limitation of fMRI research (Desmond & Glover, 2002). However, some have scrutinized the acceptance of low sample sizes in fMRI, noting that it has led to under-powered studies (Button et al., 2013; Zandbelt et al., 2008).

Measurement and conceptualization of CHT. There were several limitations in the measurement of CHT in this study. First, the CTQ assesses for events that may be interpreted as traumatic by some but does not assess for actual psychological distress associated with potentially traumatic childhood events. In most models of the link between CHT and schizophrenia, it is assumed that the prolonged distress associated with adverse experiences is the means by which CHT can contribute to the development of schizophrenia (Kraan et al., 2015; Velikonja Fisher, Mason, & Johnson, 2015). Reactions to adverse life events can vary (Hinnant, Philbrook, Erath, & El-Sheikh, 2018), particularly for people with schizophrenia (Myin-Germeys, Delespaul, & van Os, 2005). It may be particularly important to assess for distress associated with aversive early life experiences, as there is evidence that a pre-existing stress sensitivity may be a risk factor in people with schizophrenia (Walker & Diforio, 1997). If people who later develop schizophrenia are more likely to experience adverse life events as distressing, it may be the case that, while there were equal levels of overall CHT in the schizophrenia and control samples, the schizophrenia participants could have experienced more subjective distress associated with these events. Future studies may address this limitation by using measure that assess for level of distress associated with childhood abuse and neglect. This may be done by

using a measure that explicitly asks if the respondent felt that the event was distressing (e.g.,

Attribution About Abuse Inventory; Feiring, Taska, & Chen, 2002) or by assessing for post-

traumatic psychological symptoms associated with the event, such as flashbacks, avoidance of

memories, and dysfunctional cognitive schemas about self or others (e.g., Child PTSD Symptom

Scale; Foa, Treadwell, Johnson, & Feeny, 2001; UCLA PTSD Reaction Index; Pynoos,

Rodriguez, Steinberg, Stuber, & Frederick, 1998). Of these two methods, it may be most

effective to ask about post-traumatic symptoms, as people are not always explicitly aware of the

impact of abuse and neglect on their level of current psychological distress (Pignon et al, 2019).

A second limitation of the study was that reports of CHT were not corroborated outside

of the participant's own memories of childhood events. Corroboration of CHT can be

challenging, as it typically involves comparing the participant's reports of CHT against the

reports of family members. A lack of agreement between the reports of family members and the

participant could be due to a number of reasons, including family members not knowing about

abuse or neglect of the participant, family members not wishing to disclose sensitive information

about the participant, differing interpretations of events from the participant's childhood, and

possible exaggeration or fabrication on the part of the participant. According to past research,

exaggeration or fabrication of past traumatic events is uncommon in research settings (Dill, Chu,

Grob, & Eisen, 1991). Some may question the reliability of self-report in people with

schizophrenia, as people with psychotic disorders may suffer from delusions beliefs about their

past. Notably, there is no evidence that people with schizophrenia differ in the accuracy of their

reported past traumas compared with non-psychiatric controls (Goodman et al., 1999; Meyer et

al., 1996). In fact, there is evidence that in clinical settings, psychiatric patients, including people

with schizophrenia, likely under-report trauma history as compared with non-psychiatric patients

(Briere & Zaidi, 1989; Dill, Chu, Grob, & Eisen, 1991).

A third limitation of the current study was that I did not have data for the age at which

people experienced abuse and neglect. The age at which a person experiences trauma may

impact the degree to which it impairs their functioning, with earlier exposure leading to worse

functional outcomes in people with schizophrenia (Alameda et al., 2015). Future studies may

collect more information on the timing of traumas to better understand the psychosocial and

neurobiological pathways between trauma and psychosis, as well as to better inform targeted

treatment strategies.

A fourth limitation of the current study was the measurement of CHT in a South African

sample using a measure of CHT developed in a Western culture. Cultural factors can affect both

interpretation of questionnaire items and conceptualization of what constitutes abuse and neglect

(International Test Commission, 2010). For example, previous studies have noted that violence,

particularly physical punishment and sexual assault, may be more normalized in South Africa as

compared to many Western countries (Doolan, Ehrlicj, & Myer, 2007; Jewkes, Nduna, Jama-

Shai, Chirwa, & Dunkle, 2016). Questions such as "I believe that I was physically abused" and

"I believe I was sexually abused" from the CTQ may be interpreted differently by South

Africans as compared to someone in a region of the world with lower rates of violent crime and

sexual assault.

One solution to this issue could be to create new measures for assessing trauma within a

given culture. For example, a screening tool for childhood trauma in school-aged kids has been

developed for interpersonal trauma in South Africa (Collings, Valijee, & Penning, 2013). This

measure may be used as a starting point for culturally appropriate probes for adverse childhood experiences in South Africa, better accounting for how abuse and neglect are conceptualized in South African cultures. However, downsides to this approach are that it can take significant time and resources to develop new measures and using culture-specific measures makes it more difficult to directly compare CHT between cultures. Another possible solution is to culturally translate measures, in addition to linguistically translating (International Test Commission, 2010). For example, in one study the CTQ was adapted for use with South Africa Xhosa youth by discussing the meaning, cultural significance, and wording of individual items with research staff familiar with local culture and language (Jewkes et al., 2010). Cultural translation of a measure allows for culturally appropriate phrasing of items, while not requiring development of an entirely new measure. It also allows for easier comparison of trauma between different populations of the world.

Finally, in order to best understand the diversity of adverse life experiences in different cultural settings, it may be particularly important to assess for a wider range of potentially traumatic experiences than is covered in the CTQ. For example, the CTQ does not assess for general exposure to community violence, discrimination, or accident causing injury or death. Use of additional measures, including the Traumatic Events Screening Inventory (TESI; Ippen et al., 2002) and Children's Exposure to Community Violence Survey (Richters & Martinez, 1993) may provide a more complete perspective on the impact of aversive early life events on later psychological functioning.

Response inhibition in schizophrenia. One major limitation in my response inhibition analyses was the lack of well-established regions of interest for proactive inhibition. Future

studies examining the neural correlates of proactive inhibition in non-psychiatric samples could provide more well-replicated ROIs for subsequent studies of proactive inhibition in schizophrenia.

Another limitation of the fMRI analysis was the use of combined ROIs as a proxy for analysis of reactive inhibition and proactive inhibition networks. While this technique has been used previously as a way to approximate the activation of a network of activity (e.g. Benke et al., 2006; Lewis, Talkington, Puce, Engel, & Frum, 2011; Wiebking et al., 2015), more advanced measure of network activation are preferred (Ginestet, Fournel, & Minnons, 2014).

Future studies may also aim to help translate the basic research on response inhibition into clinical interventions to improve these deficits. In particular, a better understanding of response inhibition in schizophrenia may have important implications for cognitive remediation interventions. Cognitive remediation interventions, behavioral training therapies that aim to improve cognitive deficits, have garnered interest as a means of reversing the significant cognitive deficits seen in people with schizophrenia (Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). Studies of cognitive remediation protocols assessing response inhibition have yielded mixed results. One limitation of the current body of research on remediation of response inhibition in people with schizophrenia is lack of specific tasks targeting response inhibition. A relatively large number of studies have examined executive functioning remediation in general ((Edwards, Barch, & Braver, 2010; Franck et al., 2013), but few have used tasks that specifically target response inhibition, such as the Go/No-Go Task or the Stop Signal Task. One study of these few studies used a spatial response inhibition task (Reeder, Smedley, Butt, Bogner, & Wykes, 2006). This study specifically targeted people with schizophrenia who were at least one

standard deviation below the norm in executive functioning. These participants then underwent

40 hour-long cognitive training sessions with a protocol including domains of attention, working

memory, executive functioning. As is typical of cognitive remediation protocols, the tasks were

repetitive and provided scaffolded strategies to increase cognitive efficiency and accuracy.

Response inhibition was assessed at baseline and after treatment. Participants showed

improvement on verbal long-term memory, visuospatial memory, and verbal working memory,

but not response inhibition. A similar earlier study by the same group also found no

improvement in response inhibition in the treatment group as compared to the control group but

noted that improvements in response inhibition were associate with lowering of the negative

symptoms of schizophrenia (Reeder, Newton, Frangou, & Wykes, 2004). Another study using a

range of cognitive tasks that targeted memory, attention, and response inhibition found

improvement in tasks that loaded on response inhibition (Kurtz, Seltzer, Shagan, Thime, &

Wexler, 2008).

Notably, improvements in task-based cognitive performance do not always generalize to

improvements in psychological symptoms and functional outcomes, such as social and

occupational skills (Wykes & Huddy, 2009). Future versions of cognitive remediation targeting

proactive inhibition may benefit from adding a component of "bridging" techniques, in which

cognitive strategies learned in a task-based clinical setting are explicitly generalized to real-life

scenarios outside of the clinic or lab (Bowie, McGurk, Mausbach, Patterson, & Harvey, 2012;

Eack et al., 2009). One version of this is to pair vocational training with cognitive remediation,

providing the patient with opportunity to apply improved cognitive strategies and skills to

learning new job skills (Wykes & Huddy, 2009). Explicitly bridging the connection between

basic cognitive skills and generalized life skills in cognitive remediation interventions is associated with better outcomes than task-based cognitive training alone (Kurtz, Mueser, Thime, Corbera, & Wexler, 2015; Lindermayer et al., 2018).

Conclusion

In the current study, I examined CHT and response inhibition in people with schizophrenia as compared to non-psychiatric controls. I did not find overall group differences on CHT. This may be explained by several factors, including high overall levels of CHT in the present South African sample and issues with the cultural appropriateness of the CHT assessment in this study. I did replicate past findings of impaired proactive inhibitory process in schizophrenia, using both behavioral and neuroimaging indices. These findings support a model of impaired frontostriatal integrity in people with schizophrenia.

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Appendix A

Memorandum of Understanding

1

Memorandum of Understanding between

Prof. Robin Emsley at the University of Stellenbosch, Stellenbosch, South Africa,

Dr. Stefan du Plessis at the University of Stellenbosch, Stellenbosch, South Africa,

and

Mallory Klaunig at the University of Hawaii at Manoa, Honolulu, Hawaii, United States

This Memorandum of Understanding (MOU) sets the terms and understanding between Dr. Stefan du Plessis and Mallory Klaunig to collaborate on the project, "Inhibitory Control as One Pathway Between Childhood Trauma and Positive Symptoms of Schizophrenia Spectrum Disorders"

Purpose
Mallory Klaunig will travel to Capetown, South Africa, to complete her dissertation project, "Inhibitory Control as One Pathway Between Childhood Trauma and Positive Symptoms of Schizophrenia Spectrum Disorders". Mallory Klaunig will reside in Capetown for 4-9 months in order to complete the aforementioned project, starting in September 2017. She will use neuroimaging, clinical, and cognitive task data from 40 subjects with first-episode psychosis and 40 non-psychiatric control subjects. The data include the: demographic information, Stop-Signal Anticipation Task behavioral and functional magnetic resonance imaging data, structural magnetic resonance imaging data, Positive and Negative Symptom Scale scores, and Childhood Trauma Questionnaire scores. These data have already been collected, have never been published in work similar to this project, and will be made available to Mallory.

Funding
Funding will not be provided from Stellenbosch for this project. Mallory is free to seek funds from outside sources to support travel and other expenses.

Duration
This MOU is at-will and may be modified by mutual consent of the signees. This MOU shall become effective upon signature and will remain in effect until modified or terminated by any one of the partners by mutual consent.

2

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Ethics Approval Letter

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Ethics Letter

11-July-2017

Ethics Reference #: N13/08/115

Title: Understanding the SHARED ROOTS of Neuropsychiatric Disorders and Modifiable Risk Factors for Cardiovascular Disease

Dear Prof Soraya Seedat,

Your request for extension/annual renewal of ethics approval dated 01 June 2017 refers.

The Health Research Ethics Committee reviewed and approved the annual progress report you submitted through an expedited review process.

The approval of the research project is extended for a further year.

Approval date: 11 July 2017

Expiry date: 10 July 2018

Kindly be reminded to submit progress reports two (2) months before expiry date.

Where to submit any documentation

Kindly submit **ONE HARD COPY** to Elvira Rohland, RDSD, Room 5007, Teaching Building, and **ONE ELECTRONIC COPY** to ethics@sun.ac.za .

Please remember to use your **protocol number (N13/08/115)** on any documents or correspondence with the HREC concerning your research protocol.

Federal Wide Assurance Number: 00001372
Institutional Review Board (IRB) Number: IRB0005240 for HREC1
Institutional Review Board (IRB) Number: IRB0005239 for HREC2
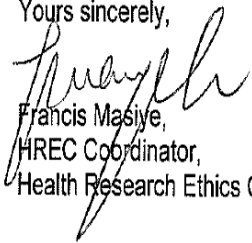
The Health Research Ethics Committee complies with the SA National Health Act No. 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki and the South African

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Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles, Structures and Processes 2015 (Departement of Health).

Yours sincerely,

Francis Masiye,
HREC Coordinator,
Health Research Ethics Committee 2.

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Health Research Ethics Committee

1 1 JUL 2017

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Appendix B

The Positive and Negative Syndrome Scale (PANSS)

POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS) RATING CRITERIA

GENERAL RATING INSTRUCTIONS

Data gathered from this assessment procedure are applied to the PANSS ratings. Each of the 30 items is accompanied by a specific definition as well as detailed anchoring criteria for all seven rating points. These seven points represent increasing levels of psychopathology, as follows:

1- absent

2- minimal

3- mild

4- moderate

5- moderate severe

6- severe

7- extreme

In assigning ratings, one first considers whether an item is at all present, as judging by its definition. If the item is absent, it is scored 1, whereas if it is present one must determine its severity by reference to the particular criteria from the anchoring points. The highest applicable rating point is always assigned, even if the patient meets criteria for lower points as well. In judging the level of severity, the rater must utilise a holistic perspective in deciding which anchoring point best characterises the patient's functioning and rate accordingly, whether or not all elements of the description are observed.

The rating points of 2 to 7 correspond to incremental levels of symptom severity:

- A rating of 2 (minimal) denotes questionable or subtle or suspected pathology, or it also may allude to the extreme end of the normal range.

- A rating of 3 (mild) is indicative of a symptom whose presence is clearly established but not pronounced and interferes little in day-to-day functioning.

- A rating of 4 (moderate) characterises a symptom which, though representing a serious problem, either occurs only occasionally or intrudes on daily life only to a moderate extent.

- A rating of 5 (moderate severe) indicates marked manifestations that distinctly impact on one's functioning but are not all-consuming and usually can be contained at will.

- A rating of 6 (severe) represents gross pathology that is present very frequently, proves highly disruptive to one's life, and often calls for direct supervision.

- A rating of 7 (extreme) refers to the most serious level of psychopathology, whereby the manifestations drastically interfere in most or all major life functions, typically necessitating close supervision and assistance in many areas.

Each item is rated in consultation with the definitions and criteria provided in this manual. The ratings are rendered on the PANSS rating form overleaf by encircling the appropriate number following each dimension.

PANSS RATING FORM

		absent	minimal	mild	moderate	moderate severe	severe	extreme
P1	Delusions	1	2	3	4	5	6	7
P2	Conceptual disorganisation	1	2	3	4	5	6	7
P3	Hallucinatory behaviour	1	2	3	4	5	6	7
P4	Excitement	1	2	3	4	5	6	7
P5	Grandiosity	1	2	3	4	5	6	7
P6	Suspiciousness/persecution	1	2	3	4	5	6	7
P7	Hostility	1	2	3	4	5	6	7
N1	Blunted affect	1	2	3	4	5	6	7
N2	Emotional withdrawal	1	2	3	4	5	6	7
N3	Poor rapport	1	2	3	4	5	6	7
N4	Passive/apathetic social withdrawal	1	2	3	4	5	6	7
N5	Difficulty in abstract thinking	1	2	3	4	5	6	7
N6	Lack of spontaneity & flow of conversation	1	2	3	4	5	6	7
N7	Stereotyped thinking	1	2	3	4	5	6	7
G1	Somatic concern	1	2	3	4	5	6	7
G2	Anxiety	1	2	3	4	5	6	7
G3	Guilt feelings	1	2	3	4	5	6	7
G4	Tension	1	2	3	4	5	6	7
G5	Mannerisms & posturing	1	2	3	4	5	6	7
G6	Depression	1	2	3	4	5	6	7
G7	Motor retardation	1	2	3	4	5	6	7
G8	Uncooperativeness	1	2	3	4	5	6	7
G9	Unusual thought content	1	2	3	4	5	6	7
G10	Disorientation	1	2	3	4	5	6	7
G11	Poor attention	1	2	3	4	5	6	7
G12	Lack of judgement & insight	1	2	3	4	5	6	7
G13	Disturbance of volition	1	2	3	4	5	6	7
G14	Poor impulse control	1	2	3	4	5	6	7
G15	Preoccupation	1	2	3	4	5	6	7
G16	Active social avoidance	1	2	3	4	5	6	7

Appendix C

Childhood Trauma Questionnaire (CTQ)

CTQ Name: _____ _____   *Ready Score*®
Answer Document

Age: _____ Sex: _____

When I was growing up ...	Never True	Rarely True	Sometimes True	Often True	Very Often True
1. I didn't have enough to eat.	●	●	●	●	●
2. I knew that there was someone to take care of me and protect me.	●	●	●	●	●
3. People in my family called me things like "stupid," "lazy," or "ugly."	●	●	●	●	●
4. My parents were too drunk or high to take care of the family.	●	●	●	●	●
5. There was someone in my family who helped me feel that I was important or special.	●	●	●	●	●
6. I had to wear dirty clothes.	●	●	●	●	●
7. I felt loved.	●	●	●	●	●
8. I thought that my parents wished I had never been born.	●	●	●	●	●
9. I got hit so hard by someone in my family that I had to see a doctor or go to the hospital.	●	●	●	●	●
10. There was nothing I wanted to change about my family.	●	●	●	●	●
11. People in my family hit me so hard that it left me with bruises or marks.	●	●	●	●	●
12. I was punished with a belt, a board, a cord, or some other hard object.	●	●	●	●	●
13. People in my family looked out for each other.	●	●	●	●	●
14. People in my family said hurtful or insulting things to me.	●	●	●	●	●
15. I believe that I was physically abused.	●	●	●	●	●
16. I had the perfect childhood.	●	●	●	●	●
17. I got hit or beaten so badly that it was noticed by someone like a teacher, neighbor, or doctor.	●	●	●	●	●
18. I felt that someone in my family hated me.	●	●	●	●	●
19. People in my family felt close to each other.	●	●	●	●	●
20. Someone tried to touch me in a sexual way, or tried to make me touch them.	●	●	●	●	●
21. Someone threatened to hurt me or tell lies about me unless I did something sexual with them.	●	●	●	●	●
22. I had the best family in the world.	●	●	●	●	●
23. Someone tried to make me do sexual things or watch sexual things.	●	●	●	●	●
24. Someone molested me.	●	●	●	●	●
25. I believe that I was emotionally abused.	●	●	●	●	●
26. There was someone to take me to the doctor if I needed it.	●	●	●	●	●
27. I believe that I was sexually abused.	●	●	●	●	●
28. My family was a source of strength and support.	●	●	●	●	●

CTQ Key:

Pink circle = physical neglect

Pink line = emotional neglect

Orange line = emotional abuse

Blue line = physical abuse

Yellow line = sexual abuse

Yellow tick = validity check